ABALOPARATIDE

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABALOPARATIDE</td>
<td>TYMLOS</td>
<td>44231</td>
<td></td>
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</tr>
</tbody>
</table>

The guideline named ABALOPARATIDE (Tymlos) requires that the patient has a diagnosis of postmenopausal osteoporosis and has not received a total of 24 months or more of parathyroid hormone therapy with Tymlos or Forteo. In addition, one of the following criteria must be met:

- High risk for fractures defined as ONE of the following:
  - History of osteoporotic (e.g., fragility, low trauma) fracture(s)
  - 2 or more risk factors for fracture (e.g., history of multiple recent low trauma fractures, BMD T-score less than or equal to -2.5, corticosteroid use, or use of GnRH analogs such as nafarelin, etc.)
  - No prior treatment for osteoporosis AND FRAX score ≥ 20% for any major fracture OR ≥ 3% for hip fracture
- Unable to use oral therapy (e.g., upper gastrointestinal [GI] problems - unable to tolerate oral medication, lower GI problems - unable to absorb oral medications, trouble remembering to take oral medications or coordinating an oral bisphosphonate with other oral medications or their daily routine)
- The patient has an adequate trial of, intolerance to, or a contraindication to bisphosphonates (e.g., Fosamax, Actonel, Boniva)

RATIONALE
To ensure safe and appropriate use of abaloparatide per approved indication and dosing and national treatment guidelines.

FDA APPROVED INDICATIONS
Indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Tymlos reduces the risk of vertebral fractures and nonvertebral fractures.

DOSAGE AND ADMINISTRATION
The recommended dosage of Tymlos is 80 mcg subcutaneously once daily. Cumulative use of Tymlos and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended. Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

REFERENCES

Created: 05/17
Effective: 03/09/18
Client Approval: 02/19/18
P&T Approval: N/A
NOTE: For requests for the SQ dosage form of Orencia, please see the ABATACEPT SQ Guideline.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named ABATACEPT - IV (Orencia - IV) requires a diagnosis of moderate to severe rheumatoid arthritis, moderate to severe juvenile idiopathic arthritis, or psoriatic arthritis. In addition, the following criteria must be met:

For patients with moderate to severe rheumatoid arthritis, approval requires all of the following:
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older
- Previous trial of TWO preferred self-administered immunomodulators: Actemra, Cimzia, Enbrel, Simponi, or Xeljanz

For patients with moderate to severe polyarticular juvenile idiopathic arthritis, approval requires all of the following:
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs) such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 6 years of age or older
- Previous trial of the preferred formulary TNF (tumor necrosis factor) inhibitor: Enbrel

For patients with psoriatic arthritis, approval requires all of the following:
- Therapy is prescribed by or given in consultation with a rheumatologist or dermatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older
- Previous trial of at least TWO of the following preferred self-administered immunomodulators: Cimzia, Cosentyx, Enbrel, Otezla, or Simponi

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ABATACEPT - IV

RENEWAL CRITERIA

The guideline named ABATACEPT - IV (ORENCIA - IV) renewal requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, or moderate to severe juvenile idiopathic arthritis for renewal. In addition, the following criteria must be met:

Renewal for the diagnosis of moderate to severe rheumatoid arthritis, approval requires:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy.

Renewal for the diagnosis of moderate to severe polyarticular juvenile idiopathic arthritis, approval requires:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy.

Renewal for the diagnosis of psoriatic arthritis, approval requires:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy.

RATIONALE
Ensure appropriate diagnostic, utilization and safety criteria are met for the management of requests for abatacept.

FDA APPROVED INDICATIONS
ABATACEPT (Orencia) is a selective T cell costimulation modulator indicated for:

Adult Rheumatoid Arthritis (RA)
Moderately to severely active RA in adults. Orencia may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)
Moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older. Orencia may be used as monotherapy or concomitantly with methotrexate. The safety and efficacy of subcutaneous Orencia injection has not been studied in patients under 18 years of age.

Adult Psoriatic Arthritis (PsA)
ORENCIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).

Important Limitations of Use
ABATACEPT (Orencia) should not be given concomitantly with TNF antagonists. Orencia is not recommended for use concomitantly with other biologic rheumatoid arthritis (RA) therapy, such as anakinra.

REFERENCES

Created: 02/18
Effective: 06/01/18
Client Approval: 04/10/18
P&T Approval: N/A
ABATACEPT - SQ

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABATACEPT - SQ</td>
<td>ORENCIA SQ</td>
<td></td>
<td>30289,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORENCIA CLICKJECT</td>
<td></td>
<td>41656</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: This criteria should be used only for the SQ dosage form of Orencia.

GUIDELINES FOR USE

Our guideline for **ABATACEPT - SQ** requires a diagnosis of moderate to severe rheumatoid arthritis (RA), moderate to severe polyarticular juvenile idiopathic arthritis (PJIA), or psoriatic arthritis (PsA). In addition, the following criteria must be met.

**For patients with moderate to severe rheumatoid arthritis, approval requires all of the following:**
- Therapy prescribed by or in consultation with a rheumatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- Patient is 18 years of age or older

**For patients with moderate to severe polyarticular juvenile idiopathic arthritis, approval requires all of the following:**
- Therapy prescribed by or given in consultation with a rheumatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- Patient is 2 years of age or older

**For patients with psoriatic arthritis, approval requires all of the following:**
- Therapy prescribed by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- Patient is 18 years of age or older

RENEWAL CRITERIA

Our guideline for the renewal of **ABATACEPT - SQ** requires a diagnosis of moderate to severe rheumatoid arthritis (RA), moderate to severe polyarticular juvenile idiopathic arthritis (PJIA), or psoriatic arthritis (PsA). In addition, the following criteria must be met.

**Renewal for the diagnosis of moderate to severe rheumatoid arthritis requires:**
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy.

**Renewal for the diagnosis of moderate to severe polyarticular juvenile idiopathic arthritis requires:**
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy.

**Renewal for the diagnosis of psoriatic arthritis requires:**
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy.

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RATIONALE
Ensure appropriate diagnostic, utilization and safety criteria are met for the management of requests for abatacept.

FDA APPROVED INDICATIONS
Orencia is a selective T cell costimulation modulator indicated for:

**Adult Rheumatoid Arthritis (RA)**
Moderately to severely active RA in adults. Orencia may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

**Polyarticular Juvenile Idiopathic Arthritis (PJIA)**
Moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 2 years of age and older. Orencia may be used as monotherapy or concomitantly with methotrexate. The safety and efficacy of Orencia ClickJect auto-injector for subcutaneous injection has not been studied in patients under 18 years of age.

**Psoriatic Arthritis (PsA)**
Psoriatic arthritis in adults. Orencia is used as monotherapy.

**Important Limitations of Use**
Orencia should not be given concomitantly with TNF antagonists. Orencia is not recommended for use concomitantly with other biologic rheumatoid arthritis therapy such as anakinra.

DOSAGE AND ADMINISTRATION

**Adult Rheumatoid Arthritis (RA)**
ORENcia 125 mg in prefilled syringes or in ORENCIA ClickJect™ autoinjector should be administered by subcutaneous injection once weekly and may be initiated with or without an intravenous loading dose. For patients initiating therapy with an intravenous loading dose, ORENCIA should be initiated with a single intravenous infusion (as per body weight categories listed in Table 1), followed by the first 125 mg subcutaneous injection administered within a day of the intravenous infusion. Patients transitioning from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

**Adult Psoriatic Arthritis (PsA)**
ORENcia SC 125 mg should be administered by subcutaneous injection once weekly without the need for an intravenous loading dose. Patients switching from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

**Polyarticular Juvenile Idiopathic Arthritis (PJIA)**
ORENcia for subcutaneous injection should be initiated without an intravenous loading dose and be administered utilizing the weight range-based dosing as specified in the Table below.

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ABATACEPT - SQ

DOSAGE AND ADMINISTRATION (CONTINUED)

The safety and efficacy of ORENCIA ClickJect autoinjector for subcutaneous injection has not been studied in patients under 18 years of age.

Dose of Ocrenica for subcutaneous administration in patients 2 years of age or older

<table>
<thead>
<tr>
<th>BODY WEIGHT OF PATIENT</th>
<th>DOSE (ONCE WEEKLY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to less than 25 kg</td>
<td>50 mg</td>
</tr>
<tr>
<td>25 to less than 50 kg</td>
<td>87.5 mg</td>
</tr>
<tr>
<td>50 kg or more</td>
<td>125 mg</td>
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</tbody>
</table>

REFERENCES


Created: 03/15
Effective: 06/18/18
Client Approval: 05/31/18
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named ABEMACICLIB (Verzenio) requires a diagnosis of advanced or metastatic breast cancer that is hormone receptor (HR+) positive and human epidermal growth factor 2 negative. In addition, ONE of the following criteria must be met:

- **The medication will be used in combination with fulvestrant and ALL of the following criteria are met:**
  - The patient is female
  - The patient has had disease progression following endocrine therapy
  - The patient has NOT experienced disease progression following prior CDK inhibitor therapy

- **The medication will be used as monotherapy and ALL of the following criteria are met:**
  - The patient is 18 years of age or older
  - The patient has had disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
  - The patient has NOT experienced disease progression following prior CDK inhibitor therapy

- **The medication will be used in combination with an aromatase inhibitor and ALL of the following criteria are met:**
  - The patient is a female and postmenopausal
  - The requested medication will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, or exemestane)
  - The patient has not received prior endocrine therapy for metastatic breast cancer (e.g., letrozole, anastrozole, tamoxifen, fulvestrant, exemestane)
  - The patient has NOT experienced disease progression following prior CDK inhibitor therapy

RATIONALE

Promote appropriate utilization of ABEMACICLIB (Verzenio) based on FDA approved indication and dosing.

FDA APPROVED INDICATIONS

VERZENIO is a kinase inhibitor indicated:

- In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy

- As monotherapy for the treatment of adult patients with HR positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

- In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer

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ABEMACICLIB

DOSAGE AND ADMINISTRATION
When used in combination with fulvestrant or an aromatase inhibitor, the recommended dose of VERZENIO is 150 mg taken orally twice daily. When given with VERZENIO, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29; and once monthly thereafter. Pre/perimenopausal women treated with the combination of VERZENIO plus fulvestrant should be treated with a gonadotropin-releasing hormone agonist according to current clinical practice standards.

When used as monotherapy, the recommended dose of VERZENIO is 200 mg taken orally twice daily. When given with VERZENIO, refer to the Full Prescribing Information for the recommended dose of the aromatase inhibitor being used.

Continue treatment until disease progression or unacceptable toxicity. VERZENIO may be taken with or without food. Instruct patients to take their doses of VERZENIO at approximately the same times every day. If the patient vomits after taking the dose, or misses a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time. VERZENIO tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

The recommended VERZENIO dose modifications for adverse reactions are provided in the table below.

*If further dose reduction below 50 mg twice daily is required, discontinue the treatment.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>VERZENIO Dose in Combination with Fulvestrant or an aromatase inhibitor</th>
<th>VERZENIO Dose for Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended starting dose</td>
<td>150 mg twice daily</td>
<td>200 mg twice daily</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>100 mg twice daily</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>50 mg twice daily</td>
<td>100 mg twice daily</td>
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<tr>
<td>Third dose reduction</td>
<td>Not applicable</td>
<td>50 mg twice daily*</td>
</tr>
</tbody>
</table>

Avoid concomitant use of the strong CYP3A inhibitor ketoconazole.

AVAILABLE STRENGTHS
Tablets: 50 mg, 100 mg, 150 mg, and 200 mg

REFERENCES
• Verzenio [Prescribing Information]. Indianapolis, IN. Eli Lilly and Company; February 2018.
GUIDELINES FOR USE

Approval requires a diagnosis of metastatic castration-resistant prostate cancer (CRPC) or metastatic high-risk castration-sensitive prostate cancer (CSPC). In addition, the requested medication must be used in combination with prednisone.

RATIONALE
To ensure appropriate use of Zytiga consistent with FDA approved indication.

FDA APPROVED INDICATIONS
Zytiga is indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer CRPC) and metastatic high-risk castration-sensitive prostate cancer (CSPC).

DOSAGE AND ADMINISTRATION
Metastatic castration-resistant prostate cancer: The recommended dose of Zytiga is 1,000 mg (two 500 mg tablets or four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily.

Metastatic high-risk castration-sensitive prostate cancer: The recommended dose of Zytiga is 1,000 mg (two 500 mg tablets or four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally once daily.

Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. ZYTIGA must be taken on an empty stomach, either one hour before or two hours after a meal [see Clinical Pharmacology (12.3)]. The tablets should be swallowed whole with water. Do not crush or chew tab.

If a strong CYP3A4 inducer must be co-administered, increase the Zytiga dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day).

REFERENCES

Created: 06/15
Effective: 04/15/19
Client Approval: 03/29/18
P&T Approval: 11/13
GUIDELINES FOR USE

The guideline named **YONSA (abiraterone, submicronized)** requires that the patient have a diagnosis of metastatic castration-resistant prostate cancer (CRPC). In addition, the requested medication must be used combination with methylprednisolone.

**RATIONALE**
Promote appropriate utilization of Yonsa based on FDA approved indication and dosing.

**DOSAGE**
The recommended dose of Yonsa is 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily.

Patients receiving Yonsa should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

**FDA APPROVED INDICATIONS**
Yonsa is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

**REFERENCES**
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline named ACALABRUTINIB (Calquence) requires a diagnosis of mantle cell lymphoma (MCL) and the following criterion must also be met:
- The patient has received at least one prior therapy for mantle cell lymphoma (MCL)

RATIONALE
To promote appropriate utilization of Calquence based on FDA approved indication.

FDA APPROVED INDICATIONS
Calquence is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOsing
The recommended dose of Calquence is 100 mg taken orally approximately every twelve hours until disease progression or unacceptable toxicity.

Patients should swallow capsule whole with water. Patients should not open, break or chew the capsules. Calquence may be taken with or without food. If a dose of Calquence is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules of Calquence should not be taken to make up for a missed dose.

REFERENCES

Created: 11/17
Effective: 01/20/18                   Client Approval: 11/29/17                   P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline for ADALIMUMAB (Humira) requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, moderate to severe polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, moderate to severe plaque psoriasis, moderately to severely active Crohn's disease, moderately to severely active ulcerative colitis, moderate to severe hidradenitis suppurativa or non-infectious intermediate, posterior and panuveitis. The following criteria must also be met:

For patients with moderate to severe rheumatoid arthritis, our guideline requires all of the following:
- Therapy initiated by or in consultation with a rheumatologist
- Previous trial with at least one DMARD (disease-modifying antirheumatic drug) agent: methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older
- Previous trial with 2 of the following preferred agents: Actemra SC, Cimzia, Enbrel, Simponi, Orencia SC, or Xeljanz/Xeljanz XR

For patients with moderate to severe polyarticular juvenile idiopathic arthritis, our guideline requires all of the following:
- Therapy initiated by or in consultation with a rheumatologist
- Previous trial with at least one DMARD (disease-modifying antirheumatic drug) agent: methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 2 years of age or older
- Documentation of patient's current weight
- Previous trial of Enbrel AND Orencia SC

For patients with psoriatic arthritis, our guideline requires all of the following:
- Therapy initiated by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least one DMARD (disease-modifying antirheumatic drug) agent: methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older
- Previous trial with 2 of the following preferred agents: Cimzia, Cosentyx, Enbrel, Simponi, Xeljanz/Xeljanz XR, Orencia SC, or Otezla

For patients with ankylosing spondylitis, our guideline requires all of the following:
- Therapy initiated by or in consultation with a rheumatologist
- 18 years of age or older
- Previous trial with 2 of the following preferred agents: Cimzia, Cosentyx, Enbrel, or Simponi

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INITIAL CRITERIA (CONTINUED)

For patients with moderate to severe plaque psoriasis, our guideline requires all of the following:
- Therapy initiated by or in consultation with a dermatologist
- Plaque psoriasis involves at least 10% body surface area (BSA) or psoriatic lesions affecting the face, hands, feet, or genital area
- Previous trial with one of the following conventional therapies: PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- 18 years of age or older
- Previous trial with 2 of the following preferred agents: Cosentyx, Enbrel, Cimzia, or Otezla

For patients with moderately to severely active Crohn's disease, our guideline requires all of the following:
- Therapy initiated by or in consultation with a gastroenterologist
- Previous trial with one or more conventional agents, such as corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
- 6 years of age or older
- For patients 18 years of age or older, a previous trial with Cimzia is required

For patients with moderately to severely active ulcerative colitis, our guideline requires all of the following:
- Therapy initiated by or in consultation with a gastroenterologist
- Previous trial with one or more conventional agents, such as corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
- 18 years of age or older
- Previous trial with Simponi

For patients with moderate to severe hidradenitis suppurativa, our guideline requires all of the following:
- Therapy initiated by or in consultation with a dermatologist
- 12 years of age or older

For patients with non-infectious intermediate, posterior and panuveitis, approval requires all of the following:
- Therapy initiated by or in consultation with an ophthalmologist
- 2 years of age or older
- Patient does not have isolated anterior uveitis

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RENEWAL CRITERIA

The guideline for ADALIMUMAB renewal requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, moderate to severe polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, moderate to severe plaque psoriasis, moderate to severe Crohn's disease, moderate to severe ulcerative colitis, moderate to severe hidradenitis suppurativa, or non-infectious intermediate, posterior and panuveitis. The following criteria must also be met.

Renewal for the diagnosis of moderate to severe rheumatoid arthritis requires:
Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy

For Humira weekly dosing requests for the diagnosis of rheumatoid arthritis, all of the following is required:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy
• Trial of at least a 3-month regimen of Humira 40mg every other week
• Concurrent methotrexate use or contraindication to methotrexate

Renewal for the diagnosis of moderate to severe polyarticular juvenile idiopathic arthritis requires:
Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy

Renewal for the diagnosis of psoriatic arthritis requires:
Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy

Renewal for the diagnosis of ankylosing spondylitis requires:
Documentation that the patient has experienced or maintained an improvement of at least 50% or 2 units (scale of 1-10) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) while on therapy

Renewal for the diagnosis of moderate to severe plaque psoriasis requires:
Documentation that the patient has achieved clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50% or more while on therapy

Renewal for the diagnosis of moderately to severely active Crohn's disease requires:
Documentation that the patient has achieved or maintained symptomatic improvement or a decrease in PCDAI (Pediatric Crohn's Disease Activity Index) of at least 15 points or decrease in CDAI (Crohn's Disease Activity Index) of at least 70 points while on therapy

Renewal for the diagnosis of moderately to severely active ulcerative colitis requires:
Documentation that the patient has achieved or maintained symptomatic improvement while on therapy

CONTINUED ON NEXT PAGE
ADALIMUMAB

RENEWAL CRITERIA (CONTINUED)

Renewal for the diagnosis of hidradenitis suppurativa:
Documentation of at least 50% reduction in total abscess and inflammatory nodule count while on therapy

Renewal for the diagnosis of non-infectious intermediate, posterior and panuveitis requires:
- Documentation that the patient has not experienced treatment failure while on therapy, defined as one of the following:
  - Development of new inflammatory chorioretinal or retinal vascular lesions
  - A 2-step increase from baseline in anterior chamber cell grade or vitreous haze grade
  - A worsening of best corrected visual acuity (BCVA) by at least 15 letters relative to best state achieved

RATIONALE
Ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for adalimumab.

FDA APPROVED INDICATIONS

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. Humira can be used alone or in combination with non-biologic DMARDs.

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

HUMIRA is indicated for reducing signs and symptoms, inducing, and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

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FDA APPROVED INDICATIONS (CONTINUED)

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adults and pediatric patients 2 years of age and older.

DOsing

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis
40mg every other week. Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40mg every week.

Juvenile Idiopathic Arthritis or Pediatric Uveitis
The recommended dose of HUMIRA for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis (JIA) or pediatric uveitis is based on weight as shown below:
10kg (22 lbs.) to <15kg (33 lbs.): 10mg every other week
15 kg (33 lbs.) to <30 kg (66 lbs.): 20mg every other week
≥30 kg (66 lbs.): 40mg every other week

Adult Crohn’s Disease and Ulcerative Colitis
Initial dose (Day 1) is 160mg (four 40mg injections in one day or two 40mg injections per day for two consecutive days), followed by 80mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40mg every other week.

Adult Hidradenitis Suppurativa
Initial dose (Day 1) is 160mg (four 40mg injections in one day or two 40mg injections per day for two consecutive days), followed by 80mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40mg every week.

Plaque Psoriasis or Uveitis
80mg initial dose followed by 40mg every other week starting one week after initial dose.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

**Pediatric Crohn's Disease**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage Schedule</th>
</tr>
</thead>
</table>
| 17 kg to <40 kg OR 37 lbs. to <88 lbs. | Day 1: 80mg x1 (Two 40mg injections in one day)  
|                       | Day 15: 40mg x1  
|                       | Day 29: 20mg every other week  |
| ≥40 kg OR ≥ 88 lbs.   | Day 1: 160mg x1 (Four 40mg injections in one day or two 40mg injections for 2 days)  
|                       | Day 15: 80mg x1  
|                       | Day 29: 40mg every other week  |

**DOSAGE FORMS AND STRENGTHS**

- **HUMIRA Pen Carton - 40 mg/0.8 mL**
- **HUMIRA Pen Carton - 40 mg/0.4 mL**
- **HUMIRA Pen 40 mg/0.8 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa**
- **HUMIRA Pen 40 mg/0.4 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa**
- **HUMIRA Pen 80 mg/0.8 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa**
- **HUMIRA Pen 40 mg/0.8 mL - Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package**
- **HUMIRA Pen 40 mg/0.4 mL - Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package**
- **HUMIRA Pen 80 mg/0.8 mL and 40 mg/0.4 mL - Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package**
- **Prefilled Syringe Carton - 40 mg/0.8 mL**
- **Prefilled Syringe Carton - 40 mg/0.4 mL**
- **Prefilled Syringe Carton - 20 mg/0.4 mL**
- **Prefilled Syringe Carton - 20 mg/0.2 mL**
- **Prefilled Syringe Carton - 10 mg/0.2 mL**
- **Prefilled Syringe Carton - 10 mg/0.1 mL**

CONTINUED ON NEXT PAGE
DOSAGE FORMS AND STRENGTHS (CONTINUED)

- HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn’s Disease Starter Package (6 count)
- HUMIRA Prefilled Syringe 80 mg/0.8 mL - Pediatric Crohn’s Disease Starter Package (3 count)
- HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn’s Disease Starter Package (3 count)
- HUMIRA Prefilled Syringe 80 mg/0.8 mL and 40 mg/0.4 mL - Pediatric Crohn’s Disease Starter Package (2 count)
- Single-Use Institutional Use Vial Carton - 40 mg/0.8 mL

REFERENCES
**AFATINIB**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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</thead>
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<tr>
<td>AFATINIB DIMALEATE</td>
<td>GILOTRIF</td>
<td>40478</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GUIDELINES FOR USE**

Approval requires a diagnosis of non-small cell lung cancer (NSCLC) and one of the following:
- The patient has metastatic NSCLC that has progressed after platinum-based chemotherapy.
- The medication is being requested as first line treatment for tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

**RATIONALE**

Promote appropriate utilization of **AFATINIB (Gilotrif)** based on its FDA approved indications.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS

• Gilotrif is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of Gilotrif have not been established in patients whose tumors have other EGFR mutations.

• Gilotrif is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

The recommended dose of Gilotrif is 40 mg orally once daily until disease progression or no longer tolerated by the patient. Take Gilotrif at least 1 hour before or 2 hours after a meal. Do not take a missed dose within 12 hours of the next dose.

Withhold Gilotrif for any drug-related adverse reactions of:

• National Cancer Institute Common Terminology Criteria for Adverse Events Grade 3 or higher
• Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking anti-diarrheal medication
• Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable
• Renal dysfunction of Grade 2 or higher

Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinstall Gilotrif at a reduced dose, i.e., 10 mg per day less than the dose at which the adverse reaction occurred.

Permanently discontinue Gilotrif for:

• Life-threatening bullous, blistering, or exfoliative skin lesions
• Confirmed interstitial lung disease (ILD)
• Severe drug-induced hepatic impairment
• Persistent ulcerative keratitis
• Symptomatic left ventricular dysfunction
• Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

REFERENCES

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Our guideline for ALECTINIB (Alecensa) requires a diagnosis of metastatic non-small cell lung cancer (NSCLC) AND the patient is positive for anaplastic lymphoma kinase (ALK) oncogene as detected by an FDA approved test.

RATIONALE
Promote appropriate utilization of ALECTINIB (Alecensa) based on its FDA approved indication.

FDA APPROVED INDICATIONS
Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

DOSAGE
The recommended dose of Alecensa is 600 mg orally twice daily with food. Alecensa therapy is continued until disease progression or unacceptable toxicity.

The dose of Alecensa can be modified if certain adverse reactions or laboratory abnormalities occur (e.g., elevated hepatic transaminases, bradycardia, elevated CPK). The dose should be reduced first to 450 mg twice daily, then to 300 mg twice daily, and discontinued if intolerability persists thereafter. If treatment-related ILD/pneumonitis, elevated ALT or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN in the absence of cholestasis or hemolysis, grade 4 renal impairment, or life-threatening bradycardia occurs, Alecensa should be permanently discontinued.

The contents of the capsule should not be opened or dissolved. If a dose is missed or vomiting occurs after taking a dose, the next dose should be taken at the scheduled time.

REFERENCES

Created: 01/16
Effective: 11/01/18
Client Approval: 09/24/18
P&T Approval: N/A
ALEMTUZUMAB

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<thead>
<tr>
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<td>LEMTRADA</td>
<td></td>
<td>36182</td>
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</tr>
</tbody>
</table>

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named ALEMTUZUMAB (Lemtrada) requires that the patient has a relapsing form of multiple sclerosis and that the patient has tried at least TWO of the following preferred MS agents: Aubagio, Avonex, Copaxone, Gilenya, Rebif, or Tecfidera. Please note that other MS agents may also require prior authorization.

RENEWAL CRITERIA

The guideline named ALEMTUZUMAB (Lemtrada) renewal requires that the patient have a relapsing form of multiple sclerosis. Approval also requires that at least 12 months has elapsed since receiving the first course of Lemtrada. Patients are limited to two Lemtrada courses of therapy in a lifetime.

RATIONALE
To ensure appropriate utilization of LEMTRADA.

FDA APPROVED INDICATIONS

LEMTRADA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

The efficacy of Lemtrada was evaluated in two studies, known in the literature as CARE-MS I and CARE-MS II studies, and referred to in the prescribing information as Study 2 and 1, respectively. Both studies were 2-year randomized, open-label, rater-blinded, active comparator (interferon 576 beta-1a 44 micrograms administered subcutaneously three times a week) controlled study in patients with RRMS. Patients had to have at least 2 relapses during the 2 years prior to trial entry and at least 1 relapse during the year prior to trial entry. Subjects randomized to Lemtrada received 12mg, once daily, as an infusion for 5 days for the first treatment course and then 1 year later received a 12 mg, once daily, as an infusion for 3 days for the 2nd course of treatment. In Study 1, both co-primary endpoints were statistically significantly lower for Lemtrada than for Rebif. In Study 2, the annualized relapse rate was statistically significantly lower for Lemtrada than for Rebif. There was no significant difference between Lemtrada and Rebif for the time to confirmed disability progression. Neither study showed a difference for the MRI outcome measure of change in T2 lesion volume.

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FDA APPROVED INDICATIONS (CONTINUED)

DOSING
Lemtrada is administered by intravenous infusion over 4 hours and for 2 annual treatment courses. The first course is 12mg/day for 5 consecutive days. The second course, which follows 12 months after the 1st course, is 12mg/day for 3 consecutive days. Patients should be pre-medicated with high dose corticosteroids (1000mg methylprednisolone or equivalent) immediately prior to receiving the Lemtrada infusion for the first 3 days of each treatment course. It is also recommended that patients be treated with anti-viral prophylaxis for herpetic viral infections on the first day of each treatment course and continue for a minimum of two months following treatment or until CD4+ lymphocyte count is ≥ 200 cells per microliter. Lemtrada should be administered in a setting with personnel and equipment to manage any serious infusion reaction or anaphylaxis.

REFERENCES

Created: 02/18
Effective: 06/01/18
Client Approval: 04/10/18
P&T Approval: N/A
GUIDELINES FOR USE
INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline for ALIROCUMAB (Praluent) requires a diagnosis of established cardiovascular disease (e.g., history of myocardial infarction or other acute coronary syndrome, coronary or other revascularization procedure, transient ischemic attack, ischemic stroke, atherosclerotic peripheral arterial disease, coronary atherosclerosis, renal atherosclerosis, aortic aneurysm secondary to atherosclerosis, carotid plaque with 50% or more stenosis) OR primary hyperlipidemia (e.g., heterozygous familial hypercholesterolemia (HeFH)). The following criteria must also be met:

- The patient is 18 years of age or older
- Prescribed by or given in consultation with a cardiologist, endocrinologist, or lipidologist
- The patient has an LDL-cholesterol level greater than 70 mg/dL
- Patient must not have a diagnosis of homozygous familial hypercholesterolemia (HoFH)

For patients with primary hyperlipidemia (heterozygous familial hypercholesterolemia (HeFH)), diagnosis must be determined by meeting ONE of the following criteria:

- Simon Broome diagnostic criteria for HeFH (definite)
- Dutch Lipid Network criteria for HeFH with a score of at least 6

For statin tolerant patients, approval also requires:

- Prior to Praluent, the patient must be taking maximal LDL-lowering drug treatment for at least 6 months that includes Zetia (ezetimibe) and ONE of the following drugs:
  - A high intensity statin (e.g., atorvastatin 40-80mg or rosuvastatin 20-40mg), OR
  - A maximally tolerated dose of any statin given that the patient has previously failed high-intensity statin, and has documentation regarding length of previous trials of statins and reasons why each agent could not be tolerated
- Patient must continue therapy with the maximally tolerated statin while using Praluent.

For statin intolerant patients, approval also requires ALL of the following:

- Prior to Praluent, the patient was being treated consistently for at least 6 months with maximal lipid-lowering therapy with another lipid-lowering agent (e.g., ezetimibe, bile acid sequestrant, niacin) (as documented by chart notes or claims history)
- The patient has ONE of the following:
  - An absolute contraindication to statin therapy (e.g., active decompensated liver disease, nursing female, pregnancy or plans to become pregnant, hypersensitivity reaction)
  - A complete statin intolerance as defined by severe and intolerable adverse effects (e.g., creatine kinase elevation greater than or equal to 10 times the upper limit of normal, liver function test elevation greater than or equal to 3 times the upper limit of normal, rhabdomyolysis, severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group) that have occurred with trials of at least two separate statins and have improved with the discontinuation of each statin

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE
RENEWAL CRITERIA

Our guideline for ALIROCUMAB (Praluent) renewal requires that the patient has had at least 12 weeks of therapy, is adherent to both statin therapy and Praluent during the regimen (unless statin intolerant), has no prescription claims for Repatha, Juxtapid, and/or Kynamro after the date of Praluent approval and first claim, and an LDL reduction while on therapy as noted below.

For the diagnosis of heterozygous familial hypercholesterolemia, approval requires a LDL reduction of at least 35% from baseline, at or after 12 weeks of alirocumab therapy.

For the diagnosis of atherosclerotic cardiovascular disease, approval requires an LDL reduction of at least 40% from baseline, at or after 12 weeks of alirocumab therapy.

For statin intolerant patients, approval also requires ALL of the following:

- The patient is adherent to both Praluent and another lipid-lowering agent (e.g., ezetimibe, bile acid sequestrant, niacin)
- The patient has ONE of the following:
  - The patient has an absolute contraindication to statin therapy (e.g., active decompensated liver disease, nursing female, pregnancy or plans to become pregnant, hypersensitivity reaction)
  - The patient has complete statin intolerance as defined by severe and intolerable adverse effects (e.g., creatine kinase elevation greater than or equal to 10 times the upper limit of normal, liver function test elevation greater than or equal to 3 times the upper limit of normal, rhabdomyolysis, severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group) that have occurred with trials of at least two separate statins and have improved with the discontinuation of each statin

RATIONALE
Promote appropriate utilization of Praluent based on FDA approved indication.

FDA APPROVED INDICATIONS
Praluent is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol.

DOSAGE
The recommended starting dose for Praluent is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks.

Measure LDL-C levels within 4 to 8 weeks of initiating or titrating Praluent, to assess response and adjust the dose, if needed.

CONTINUED ON NEXT PAGE
ALIROCUMAB

FDA APPROVED INDICATIONS (CONTINUED)

OTHER INFORMATION

Efficacy

The efficacy of Praluent was evaluated in five multi-center, double-blind, placebo-controlled trials which enrolled 3499 patients (36% of patients had heterozygous familial hypercholesterolemia [HeFH] and 54% had clinical atherosclerotic cardiovascular disease without a diagnosis of FH). The diagnosis of HeFH was made by either genotyping or clinical criteria (using the Simon Broome or WHO/Dutch Lipid Network Criteria). All patients were receiving a maximally tolerated dose of a statin, with or without other lipid-modifying therapies. Three studies (FH I, FH II, and ODYSSEY COMBO I) used an initial dose of 75mg every 2 weeks (Q2W) followed by criteria-based up-titration to 150mg Q2W at week 12 for patients who did not achieve their pre-defined target LDL-C at week 8. The majority of patients (57-83%) did not require up-titration. The other two studies (ODYSSEY LONG TERM and ODYSSEY HIGH FH) only used a 150mg Q2W dose. The FH I, FH II, and ODYSSEY HIGH FH were conducted exclusively in patients with HeFH.

All trials used a primary endpoint of mean percent change in LDL-C from baseline that was measured at week 24 (all trials were at least 52 weeks in duration). For the primary endpoint, results for the absolute treatment effect are as follows:

Table 1: Praluent clinical trials- primary endpoint and results for the absolute treatment effect

<table>
<thead>
<tr>
<th>Study</th>
<th>Praluent dosing</th>
<th>Absolute treatment effect of Praluent (difference between placebo and Praluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY LONG TERM (Study 1)</td>
<td>Praluent 150mg Q2W</td>
<td>-58% (95% CI: -61%, -56%; p-value &lt;0.0001)</td>
</tr>
<tr>
<td>ODYSSEY COMBO I (Study 2)</td>
<td>Praluent 75mg or 150mg Q2W</td>
<td>-43% (95% CI: -50%, -35%; p-value &lt;0.0001)</td>
</tr>
<tr>
<td>FH I (Study 3) &amp; FH II (Study 4)</td>
<td>Praluent 75mg or 150mg Q2W</td>
<td>-54% (95% CI: -59%, -50%; p-value &lt;0.0001)</td>
</tr>
<tr>
<td>ODYSSEY HIGH FH (Study 5)</td>
<td>Praluent 150mg Q2W</td>
<td>-36% (95% CI: -49%, -24%; p-value &lt;0.0001)</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
ALIROCUMAB

FDA APPROVED INDICATIONS (CONTINUED)

OTHER INFORMATION

Efficacy

Table 2: ODYSSEY LONG TERM Study - Effects of alirocumab on LDL-lowering, secondary lipid variables, and rates of adjudicated cardiovascular events.

<table>
<thead>
<tr>
<th>Change in LDL-C</th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percentage change in calculated LDL-C from baseline to week 24</td>
<td>-61%</td>
<td>0.8%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean percentage change in calculated LDL-C from baseline to week 78</td>
<td>-52.4%</td>
<td>3.6%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean absolute LDL-C level at week 24</td>
<td>48mg/dL</td>
<td>119mg/dL</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients meeting LDL-C goal of &lt;70mg/dL at week 24</td>
<td>79.3%</td>
<td>8.0%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Non-LDL lipid end points, percentage change (secondary lipid variables)

| Change in non-HDL cholesterol from baseline to week 24 | -51.6% +/- 0.6 | 0.7% +/- 0.9 | p<0.001 |
| Change in Apo lipoprotein B from baseline to week 24  | -52.8% +/- 0.7 | 1.2% +/- 1.0 | p<0.001 |
| Change in total cholesterol from baseline to week 24  | -37.8% +/- 0.5 | -0.3% +/- 0.7 | p<0.001 |
| Change in lipoprotein(a) from baseline to week 24     | -29.3% +/- 0.7 | -3.7% +/- 1.0 | p<0.001 |
| Change in fasting triglycerides from baseline to week 24 | -15.6% +/- 0.8 | 1.8% +/- 1.2 | p<0.001 |
| Change in HDL cholesterol from baseline to week 24    | 4.0% +/- 0.4  | -0.6% +/- 0.5 | p<0.001 |
| Change in Apolipoprotein A1 from baseline to week 24  | 4.0% +/- 0.4  | 1.2% +/- 0.6  | p<0.001 |

Cardiovascular adverse events

| Positively adjudicated cardiovascular events | 4.6% | 5.1% | 0.68 |
| Adjudicated major cardiovascular events in post-hoc analysis | 1.7% | 3.3% | 0.02 |

SAFETY

The only contraindication for Praluent is for patients with a history of serious hypersensitivity to the product itself. Serious allergic events have been reported with Praluent treatment and may include pruritus, rash, urticaria, hypersensitivity vasculitis, and/or hypersensitivity reactions requiring hospitalization. Allergic reactions were reported in 8.6% of patients treated with Praluent versus 7.8% of patients in the placebo group. Allergic reactions were cited as the top reason for discontinuing Praluent (0.6% of Praluent discontinuations versus 0.2% in the placebo group) due to adverse drug reactions (ADRs).

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

SAFETY
The most common adverse effects of Praluent (occurring in 5% or greater of clinical trial participants and more frequently than placebo) are injection site reactions, influenza, and nasopharyngitis. Injection site reactions are more likely to occur in patients who develop anti-drug antibodies (ADA). The development of ADA occurred in 4.8% of Praluent patients (versus 0.6% for control). Patients with anti-drug antibodies had a higher incidence of injection site reactions (10.2%) compared with patients who did not develop anti-drug antibodies (5.9%). Development of neutralizing antibodies occurred in 1.2% of patients treated with Praluent; no patients in the control group developed neutralizing antibodies. Of patients who developed neutralizing antibodies, 0.3% both tested positive for neutralizing antibodies and experienced a prolonged loss of efficacy. The long term consequences of continued treatment of Praluent while neutralizing antibodies are present is not known.

Table 3: Praluent adverse reactions (from Praluent prescribing information)

<table>
<thead>
<tr>
<th></th>
<th>Praluent (n=2476)</th>
<th>Placebo (n=1276)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common adverse reactions (reported in at least 2% of participants receiving Praluent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>7.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Influenza</td>
<td>5.7%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.7%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4.3%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.2%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>3.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3.0%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Cough</td>
<td>2.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Contusion</td>
<td>2.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>2.1%</td>
<td>1.6%</td>
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<tr>
<td><strong>Less common adverse effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>8.6%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Neurocognitive Events</td>
<td>0.8%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Confusion or Memory impairment</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Liver Enzyme Abnormalities</td>
<td>2.5%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Analysis of both placebo-controlled and active-controlled trials showed that 796 patients receiving Praluent had LDL levels less than 25mg/dL and 288 patients had LDL levels less than 15mg/dL. Adverse effects of very low LDL levels were not identified in Praluent clinical trials, but the long-term consequences of very low LDL levels are not known at this time.

CONTINUED ON NEXT PAGE
ALIROCUMAB

FDA APPROVED INDICATIONS (CONTINUED)

SAFETY
Praluent has not been studied in human pregnancy and lactation studies. Based on the human data from other human monoclonal antibodies, it is unlikely to cross the placenta in the first trimester; however, it is likely to cross the placenta in increasing amounts in the second and third trimester. There is no information regarding the presence of Praluent in human milk, the effects on the breastfed infant, or the effects on milk production. However, published data involving human IgG suggests that substantial amounts of IgG antibodies do not reach the infant’s circulation.

No dose adjustment is required in patients with mild or moderate renal or hepatic impairment. No data is available regarding use during severe renal or hepatic impairment. No differences in safety and efficacy were seen between geriatric and younger adults. Safety and efficacy has not been established in pediatric patients.

REFERENCES

• J Am Coll Cardiol. Nov 2018; DOI: 10.1016/j.jacc.2018.11.003
ALISKIREN AND ALISKIREN COMBINATION AGENTS

<table>
<thead>
<tr>
<th>Generic</th>
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<td>AMTURNIDE</td>
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<td>ALISKIREN/HYDROCHLOROTHIAZIDE</td>
<td>TEKTURNA HCT</td>
<td>99310, 99311, 99312, 99313</td>
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<tr>
<td>ALISKIREN/VALSARTAN</td>
<td>VALTURNA</td>
<td>27642, 27643</td>
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</tbody>
</table>

GUIDELINES FOR USE

Our guideline for approval requires that the patient does not have a diagnosis of diabetes mellitus or is not currently taking an angiotensin converting enzyme inhibitor (ACE) or an angiotensin receptor blocker (ARB) medication.

ALISKIREN AND ALISKIREN COMBINATION AGENTS

RATIONALE
To Promote use of Aliskiren in accordance with the fda safety warning and package insert contraindications.

FDA APPROVED INDICATIONS
Tekturna, Tekamlo, Amturnide, and Tekturna HCT are indicated to treat hypertension.

OTHER INFORMATION
On April 20, 2012 the U.S. Food and Drug Administration (FDA) released a safety announcement regarding medications containing aliskiren when used in combination with angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blocker (ARB) therapy in diabetics or those with renal impairment.

A randomized, double-blind, placebo controlled, parallel-group clinical trial (Aliskiren Trial in Type 2 diabetes using Cardio-renal Endpoints (ALTITUDE)) examined aliskiren 300mg daily versus placebo in 8,606 high risk patients with type 2 diabetes already taking baseline ACE or ARB therapy. The trial was terminated in December 2011 due to increased adverse events in the group taking aliskiren. A higher incidence of certain adverse events was found in the aliskiren group versus the placebo group. Individuals in the aliskiren group were also at a slightly higher risk for death or stroke. However, at this time, the FDA has not reached a final conclusion regarding whether a link exists between aliskiren-containing drugs and death or stroke.

<table>
<thead>
<tr>
<th>Adverse events in the ALTITUDE clinical trial</th>
<th>Aliskiren group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in renal function</td>
<td>12.4%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>18.6%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>36.9%</td>
<td>27.1%</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>2.7%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
Currently marketed medications containing aliskiren include Tekturna (aliskiren), Tekturna HCT (aliskiren/hctz), Amturnide (aliskiren/amlodipine/hctz), Tekamlo (aliskiren/amlodipine), and Valturna (aliskiren/valsartan). At this time, Novartis has planned to voluntarily withdraw Valturna from the market in July 2012. The labeling of other aliskiren-containing medications has been changed to reflect a contraindication for combination use of aliskiren with ARB or ACE inhibitors in patients with diabetes, and this combination should be avoided in patients with renal impairment (GFR<60mL/min).

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15

P&T Approval: 05/12
ALLERGEN EXTRACT-MIXED GRASS POLLEN

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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<tr>
<td>GR POL-ORC/SW</td>
<td>ORALAIR</td>
<td>39918</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

Our guideline for **ALLERGEN EXTRACT-MIXED GRASS POLLEN** requires a diagnosis of moderate to severe grass pollen-induced allergic rhinitis and a positive skin prick test and/or a positive titre to specific IgE antibodies for any of the five grass species included in Oralair; product must be prescribed or recommended by an allergist, immunologist, or other physician experienced in the diagnosis and treatment of allergic diseases; trial and failure of **two** of the following: oral antihistamine, intranasal antihistamine, intranasal corticosteroid, or leukotriene inhibitor; trial and failure of subcutaneous allergen immunotherapy; age of at least 10 years old; and a current claim or prescription for auto-injectable epinephrine.

RATIONALE

Promote appropriate utilization of Oralair based on FDA approved indication, dosage, and guidelines adopted from ARIA (Allergic Rhinitis and its Impact on Asthma) as well as the AAAAI (American Academy of Allergy, Asthma & Immunology) Practice Parameter on Allergen Immunotherapy.

Oralair is the first allergen-specific immunotherapy agent with FDA approval for sublingual use in the United States. The approval of oral allergen immunotherapy for allergic rhinitis provides a convenient and safe alternative to customary allergy shots. Oralair improves symptoms of allergic rhinoconjunctivitis and reduces use of rescue medication in adults and children. Allergen immunotherapy should be considered in patients who have persistent and moderate to severe symptoms despite pharmacotherapy, patients who experience intolerable side effects to medications, and those desiring to limit cost burden associated with chronic medication use. According to ARIA guidelines, persistent symptoms are defined as symptoms presenting at least 4 days a week or for at least 4 weeks, and moderate to severe symptoms include one or more of the following items: troublesome symptoms, sleep disturbance, impairment of daily activities, or impairment of school or work.

Side effects of Oralair are considered mild, with the majority of adverse events involving oral pruritus (25.1%) and throat irritation (22.0%) in adults. There were no reports of death or anaphylaxis during clinical trials.

Oralair has a black block warning that cites the following: Oralair can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema; Do not administer Oralair to patients with severe, unstable or uncontrolled asthma; Observe patients in the office for at least 30 minutes following the initial dose; Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use; Oralair may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction; Oralair may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

CONTINUED ON NEXT PAGE
DOSAGE
For adults 18 through 65 years of age, the dose is 300 IR daily.
For children and adolescents 10 through 17 years of age, the dose is increased over the first three days
(day 1 = 1 x 100 IR, day 2 = 2 x 100 IR, day 3 = 1 x 300 IR).

FDA APPROVED INDICATIONS
Oralair (5-Grass Pollen Allergy Extract Sublingual tablet containing Sweet Vernal, Orchard, Perennial
Rye, Timothy and Kentucky Blue Grass) is indicated for the treatment of grass pollen-induced allergic
rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific
IgE antibodies for any of the five grass species contained in Oralair, in people ages 10 through 65
years.

REFERENCES
2010;126:466–476
• GREER Laboratories, Inc. Oralair Package Insert. Lenoir, NC. January 2015
American Academy of Allergy, Asthma & Immunology. December 2010.
GUIDELINES FOR USE

Our guideline for **ALLERGEN EXTRACT-SHORT RAGWEED POLLEN** requires a diagnosis of moderate to severe short ragweed pollen-induced allergic rhinitis and a positive skin prick test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen; product must be prescribed or recommended by an allergist, immunologist, or other physician experienced in the diagnosis and treatment of allergic diseases; trial and failure of **two** of the following: oral antihistamine, intranasal antihistamine, intranasal corticosteroid, or leukotriene inhibitor; trial and failure of subcutaneous allergen immunotherapy; age of at least 18 years old; and a current claim or prescription for auto-injectable epinephrine.

RATIONALE

Promote appropriate utilization of Ragwitek based on FDA approved indication, dosage, and guidelines adopted from ARIA (Allergic Rhinitis and its Impact on Asthma) as well as the AAAAI (American Academy of Allergy, Asthma & Immunology) Practice Parameter on Allergen Immunotherapy.

Ragwitek is a ragweed allergen-specific immunotherapy agent with FDA approval for sublingual use. The approval of oral allergen immunotherapy for allergic rhinitis provides a convenient and safe alternative to customary allergy shots. Ragwitek improves symptoms of allergic rhinoconjunctivitis and reduces use of rescue medication in adults. Allergen immunotherapy should be considered in patients who have persistent and moderate to severe symptoms despite pharmacotherapy, patients who experience intolerable side effects to medications, and those desiring to limit cost burden associated with chronic medication use. According to ARIA guidelines, persistent symptoms are defined as symptoms presenting at least 4 days a week or for at least 4 weeks, and moderate to severe symptoms include one or more of the following items: troublesome symptoms, sleep disturbance, impairment of daily activities, or impairment of school or work.

Side effects are considered mild, with the majority of adverse events involving throat irritation (16.6% Ragwitek, 3.3% placebo), oral pruritus (10.9% Ragwitek, 2.0% placebo), ear pruritus (10.4% Ragwitek, 1.1% placebo), and oral paresthesia (10.1% Ragwitek, 4.0% placebo). One subject (1/1057, 0.1%) who received Ragwitek experienced anaphylaxis which led to discontinuation from the trial. The subject fully recovered after treatment with epinephrine, antihistamines, and oral corticosteroids. There were no reports of death during clinical trials.
ALLERGEN EXTRACT-SHORT RAGWEED POLLEN

RATIONALE (CONTINUED)

Ragwitek has a black block warning that cites the following: Ragwitek can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction; Do not administer Ragwitek to patients with severe, unstable or uncontrolled asthma; Observe patients in the office for at least 30 minutes following the initial dose; Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use; Ragwitek may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction; Ragwitek may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

DOSAGE

For adults 18 through 65 years of age, the dose is 1 tablet (12 Amb a 1-U) daily.

FDA APPROVED INDICATIONS

Ragwitek (short ragweed pollen extract) approved and indicated for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by a positive skin prick test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen in adults 18 years through 65 years of age.

REFERENCES

GUIDELINES FOR USE

Our guideline for **ALLERGEN EXTRACT-TIMOTHY GRASS POLLEN** requires a diagnosis of moderate to severe grass pollen-induced allergic rhinitis and a positive skin prick test and/or a positive titre to specific IgE antibodies for Timothy grass or cross-reactive grass pollens; product must be prescribed or recommended by an allergist, immunologist, or other physician experienced in the diagnosis and treatment of allergic diseases; trial and failure of **two** of the following: oral antihistamine, intranasal antihistamine, intranasal corticosteroid, or leukotriene inhibitor; trial and failure of subcutaneous allergen immunotherapy; age of at least 5 years old; and a current claim or prescription for auto-injectable epinephrine.

RATIONALE

Promote appropriate utilization of Grastek based on FDA approved indication, dosage, and guidelines adopted from ARIA (Allergic Rhinitis and its Impact on Asthma) as well as the AAAAI (American Academy of Allergy, Asthma & Immunology) Practice Parameter on Allergen Immunotherapy.

Grastek is a grass allergen-specific immunotherapy agent with FDA approval for sublingual use. The approval of oral allergen immunotherapy for allergic rhinitis provides a convenient and safe alternative to customary allergy shots. Grastek improves symptoms of allergic rhinoconjunctivitis and reduces use of rescue medication in adults and children. Allergen immunotherapy should be considered in patients who have persistent and moderate to severe symptoms despite pharmacotherapy, patients who experience intolerable side effects to medications, and those desiring to limit cost burden associated with chronic medication use. According to ARIA guidelines, persistent symptoms are defined as symptoms presenting at least 4 days a week or for at least 4 weeks, and moderate to severe symptoms include of one or more of the following items: troublesome symptoms, sleep disturbance, impairment of daily activities, or impairment of school or work.

Side effects are considered mild, with the majority of adverse events involving oral pruritus (26.7% Grastek, 3.5% placebo), throat irritation (22.6% Grastek, 2.8% placebo), ear pruritus (12.5% Grastek, 1.1% placebo), and mouth edema (11.1% Grastek, 0.8% placebo). There were no reports of death or anaphylaxis during clinical trials.

Grastek has a black block warning that cites the following: Grastek can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema; Do not administer Grastek to patients with severe, unstable or uncontrolled asthma; Observe patients in the office for at least 30 minutes following the initial dose; Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use; Grastek may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction; Grastek may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.
ALLERGEN EXTRACT-TIMOTHY GRASS POLLEN

DOSAGE
For children and adults 5 to 65 years of age, the dose is 1 tablet (2800 BAU) daily.

FDA APPROVED INDICATIONS
Grastek (Timothy grass pollen extract) approved and indicated for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens, in people ages 5 through 65 years.

REFERENCES
GUIDELINES FOR USE

The guideline named ALPELISIB (Piqray) requires a diagnosis of advanced or metastatic breast cancer that is hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative. In addition, the following criteria must be met:

- The patient is a postmenopausal female or male
- Piqray will be used in combination with Faslodex (fulvestrant)
- The patient has presence of PIK3CA-mutation as detected by an FDA-approved test
- The patient has experienced disease progression on or after an endocrine-based regimen

RATIONALE
To ensure the appropriate use of ALPELISIB according to diagnosis.

INDICATION
Piqray is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

DOSING
The recommended dose is 300 mg ALPELISIB (Piqray) (two 150 mg film-coated tablets) taken orally, once daily, with food.
When given with ALPELISIB, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter. Refer to the Full Prescribing Information for fulvestrant.

CONTINUED ON NEXT PAGE
ALPELISIB

DOSING (CONTINUED)

Table 1: Dose adjustment due to adverse reactions (ARs)

<table>
<thead>
<tr>
<th>ALPELISIB (Piqray)</th>
<th>Dose and Schedule</th>
<th>Number and Strength of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>300 mg once daily</td>
<td>Two 150 mg tablet</td>
</tr>
<tr>
<td>First-dose reduction</td>
<td>250 mg once daily</td>
<td>One 200 mg tablet and one 50 mg tablet</td>
</tr>
<tr>
<td>Second-dose reduction</td>
<td>200 mg once daily</td>
<td>One 200 mg tablet</td>
</tr>
</tbody>
</table>

*For pancreatitis patient, only one dose reduction is permitted
**Discontinue ALPELISIB (Piqray), if further dose reduction below 200 mg once daily is required.

Table 2: Dose Modification and Management for Hyperglycemia

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose (FPG)/Blood Glucose Values</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 FPG &gt; ULN-160 mg/dL or &gt; ULN-8.9 mmol/L</td>
<td>No ALPELISIB dose adjustment required. Initiate or intensify anti-diabetic treatment.</td>
</tr>
<tr>
<td>Grade 2 FPG &gt; 160-250 mg/dL or &gt; 8.9-13.9 mmol/L</td>
<td>No ALPELISIB dose adjustment required. Initiate or further intensify anti-diabetic treatment. If FPG does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 21 days under appropriate antidiabetic treatment, reduce PIQRAY dose by 1 dose level and follow FPG value specific recommendations.</td>
</tr>
<tr>
<td>Grade 3 &gt; 250-500 mg/dL or &gt; 13.9-27.8 mmol/L</td>
<td>Initiate or intensify oral anti-diabetic treatment and consider additional anti-diabetic medications for 1-2 days until hyperglycemia improves. Administer intravenous hydration and consider appropriate treatment (e.g., intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). If FPG decreases to ≤ 160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, resume PIQRAY at 1 lower dose level. If FPG does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate antidiabetic treatment, consultation with a physician with expertise in the treatment of hyperglycemia is recommended. If FPG does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 21 days following appropriate antidiabetic treatment, permanently discontinue PIQRAY treatment.</td>
</tr>
<tr>
<td>Grade 4 &gt; 500 mg/dL or ≥ 27.8 mmol/L</td>
<td>Interrupt ALPELISIB. Initiate or intensify appropriate anti-diabetic treatment2 (administer intravenous hydration and</td>
</tr>
</tbody>
</table>
consider appropriate treatment (e.g., intervention for electrolyte/ketoacidosis/hyperosmolar disturbances)), re-check FPG within 24 hours and as clinically indicated.
If FPG decreases to $\leq 500 \text{ mg/dL or } 27.8 \text{ mmol/L}$, follow FPG value specific recommendations for Grade 3.
If FPG is confirmed at $> 500 \text{ mg/dL or } 27.8 \text{ mmol/L}$, permanently discontinue PIQRAY treatment.

### Table 3: Dose Modification and Management for Rash

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (&lt; 10% body surface area (BSA) with active skin toxicity)</td>
<td>No ALPELISIB dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine to manage symptoms</td>
</tr>
<tr>
<td>Grade 2 (10-30% BSA with active skin toxicity)</td>
<td>No ALPELISIB dose adjustment required. Initiate or intensify topical corticosteroid and oral antihistamine treatment. Consider low dose systemic corticosteroid treatment.</td>
</tr>
<tr>
<td>Grade 3 (e.g., severe rash not responsive to medical management) (&gt; 30% BSA with active skin toxicity)</td>
<td>Interrupt ALPELISIB. Initiate or intensify topical/systemic corticosteroid and oral antihistamine treatment. Once improved to $\leq$ Grade 1, resume PIQRAY at the same dose level for first occurrence of rash, or at next lower dose level in case of second occurrence.</td>
</tr>
<tr>
<td>Grade 4 (e.g., severe bullous, blistering or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)</td>
<td>Permanently discontinue ALPELISIB.</td>
</tr>
</tbody>
</table>

*For all grades of rash, consider consultation with a dermatologist.

**Antihistamines administered prior to rash onset may decrease incidence and severity of rash

CONTINUED ON NEXT PAGE
ALPELISIB

DOSING (CONTINUED)

Table 4: Dose Modification and Management for Diarrhea

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>No ALPELISIB dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt ALPELISIB dose until recovery to Grade ( \leq 1 ), then resume ALPELISIB at same dose level.</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt ALPELISIB dose until recovery to Grade ( \leq 1 ), then resume ALPELISIB at the next lower dose level.</td>
</tr>
</tbody>
</table>

Table 5: Dose Modification and Management for Other Toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>No ALPELISIB dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Interrupt ALPELISIB dose until recovery to Grade ( \leq 1 ), then resume ALPELISIB at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue ALPELISIB.</td>
</tr>
</tbody>
</table>

*For Grade 2 and 3 pancreatitis, interrupt ALPELISIB dose until recovery to Grade \( < 2 \) and resume at next lower dose level. Only one dose reduction is permitted. If toxicity reoccurs, permanently discontinue PIQRAY treatment.

**For Grade 2 total bilirubin elevation, interrupt ALPELISIB dose until recovery to Grade \( \leq 1 \) and resume at the same dose if resolved in \( \leq 14 \) days or resume at the next lower dose level if resolved in > 14 days.

REFERENCES

Our guideline for Alpha1-proteinase inhibitor requires a diagnosis of emphysema, serum Alpha1-antitrypsin level less than 11mmols/L or less than 80mg/dL by radial immunodiffusion or less than 50mg/dL by nephelometry, and that the patient does not have an IgA deficiency with antibodies against IgA.

**RATIOALE**
Ensure appropriate use of Alpha1-proteinase inhibitor.

**FDA APPROVED INDICATIONS**
Alpha1-Proteinase Inhibitors are indicated for chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of Alpha1-proteinase inhibitor (Alpha1-PI), also known as alpha1-antitrypsin (AAT) deficiency.

The effect of augmentation therapy with any Alpha1-PI product on pulmonary exacerbations and on the progression of emphysema in Alpha1-PI deficiency has not been demonstrated in randomized, controlled clinical trials.

Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with Alpha1-PI are not available.

Alpha1-PI are not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been established.

**REFERENCES**
**AMANTADINE ER**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
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<tr>
<td>AMANTADINE ER</td>
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<td>44471</td>
<td>ROUTE = ORAL</td>
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<tr>
<td></td>
<td></td>
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<td>44473</td>
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</table>

**GUIDELINES FOR USE**

Our guideline named **OSMOLEX ER** requires that the patient have a diagnosis of Parkinson's disease or, in adult patients, drug-induced extrapyramidal symptoms. In addition, the patient must have history of amantadine IR in the previous 120 days (verified in prescription claims history or in submitted chart notes).

**RATIONALE**
Promote appropriate utilization of Osmolex ER based on FDA approved indication and dosing.

**DOSAGE**
The recommended dose of Osmolex ER is 1 extended-release tablet by mouth daily (do not chew, crush, or divide) in the morning, beginning at a dose of 129 mg per day. Dosing may be increased once weekly to a maximum of 322 mg daily (administered as a 129 mg and 193 mg tablet).

**FDA APPROVED INDICATIONS**
Osmolex ER is indicated for the treatment of:
- Parkinson's disease
- Drug-induced extrapyramidal reactions in adult patient

**REFERENCES**

Created: 06/18  
Effective: 08/20/18  
Client Approval: 07/06/18  
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA

The guideline named AMIFAMPRIDINE (Firdapse) requires a diagnosis of Lambert-Eaton myasthenic syndrome (LEMS). In addition, the following criteria must be met:

- The patient is 18 years of age or older
- Therapy is prescribed by or in consultation with a neurologist or hematologist-oncologist
- Diagnosis is confirmed by electrodiagnostic studies and/or voltage-gated calcium channel (VGCC) antibody testing AND clinical triad of muscle weakness, autonomic dysfunction, and decreased tendon reflexes.

RENEWAL CRITERIA

The guideline named AMIFAMPRIDINE (Firdapse) requires a diagnosis of Lambert-Eaton myasthenic syndrome (LEMS). In addition, the following criterion must be met:

- Physician attests to the improvement or stabilization in muscle weakness compared to baseline.

RATIONALE

For further information, please refer to the Prescribing Information for Firdapse.

REFERENCES

ANABOLIC STEROIDS

<table>
<thead>
<tr>
<th>Generic</th>
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<td>01409</td>
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<td>OXANDRIN</td>
<td>01412</td>
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</table>

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

ANADROL:

Our guideline for ANABOLIC STEROIDS-ANADROL requires one of the following diagnoses: anemia or cachexia associated with AIDS. Additional guideline requirements apply.

For the diagnosis of anemia, approval requires:
- Anemia caused by one of the following conditions: acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and the hypoplastic anemias, or Fanconi's anemia
- Patient does not have any of the following contraindications to anabolic steroid therapy:
  - Known or suspected carcinoma of the prostate or breast in male patients
  - Known or suspected carcinoma of the breast in females with hypercalcemia
  - Known or suspected nephrosis (the nephrotic phase of nephritis)
  - Known or suspected hypercalcemia
  - Severe hepatic dysfunction
- Patient will be monitored for peliosis hepatis, liver cell tumors and blood lipid changes

For the diagnosis of cachexia associated with AIDS, approval requires:
- Patient on anti-retroviral therapy
- Documented viral load (with date) of less than 200 copies per mL within the past 3 months
- Prescribed by or in consultation with one of the following specialist: Gastroenterologist, Nutritional Support Specialist (SBS) or Infectious Disease Specialist
- One of the following criteria must be met:
  - 10% unintentional weight loss over 12 months, or
  - 7.5% unintentional weight loss over 6 months, or
  - 5% body cell mass (BCM) loss within 6 months, or
  - BCM less than 35% (men) and a body mass index (BMI) less than 27 kg per meter squared, or
  - BCM less than 23% (women) of total body weight and a body mass index (BMI) less than 27 kg per meter squared, or
  - BMI less than 18.5 kg per meter squared
- Patient does not have any of the following contraindications to anabolic steroid therapy:
  - Known or suspected carcinoma of the prostate or breast in male patients
  - Known or suspected carcinoma of the breast in females with hypercalcemia
  - Known or suspected nephrosis (the nephrotic phase of nephritis)
  - Known or suspected hypercalcemia
  - Severe hepatic dysfunction
- Patient will be monitored for peliosis hepatis, liver cell tumors and blood lipid changes

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INITIAL CRITERIA - OXANDRIN

OXANDRIN:

Our guideline for **ANABOLIC STEROIDS-OXANDRIN** requires one of the following diagnoses: weight loss, protein catabolism associated with prolonged administration of corticosteroids, bone pain accompanying osteoporosis, cachexia associated with AIDS, or Turner's Syndrome. Additional guideline requirements apply.

**For the diagnosis of weight loss, approval requires:**
- Weight loss due to one of the following conditions: extensive surgery, chronic infections, or severe trauma
- Use as adjunctive therapy to promote weight gain
- Patient does not have any of the following contraindications to anabolic steroid therapy:
  - Known or suspected carcinoma of the prostate or breast in male patients
  - Known or suspected carcinoma of the breast in females with hypercalcemia
  - Known or suspected nephrosis (the nephrotic phase of nephritis)
  - Known or suspected hypercalcemia
  - Severe hepatic dysfunction
- Patient will be monitored for peliosis hepatis, liver cell tumors and blood lipid changes

**For the diagnosis of protein catabolism associated with prolonged administration of corticosteroids, bone pain accompanying osteoporosis, or Turner's Syndrome, approval requires:**
- Patient does not have any of the following contraindications to anabolic steroid therapy:
  - Known or suspected carcinoma of the prostate or breast in male patients
  - Known or suspected carcinoma of the breast in females with hypercalcemia
  - Known or suspected nephrosis (the nephrotic phase of nephritis)
  - Known or suspected hypercalcemia
  - Severe hepatic dysfunction
- Patient will be monitored for peliosis hepatis, liver cell tumors and blood lipid changes

**For the diagnosis of cachexia associated with AIDS, approval requires:**
- Patient on anti-retroviral therapy
- Documented viral load (with date) of less than 200 copies per mL within the past 3 months
- Prescribed by or in consultation with one of the following specialist: gastroenterologist, nutritional support specialist (SBS) or infectious disease specialist
- One of the following criteria must be met:
  - 10% unintentional weight loss over 12 months, or
  - 7.5% unintentional weight loss over 6 months, or
  - 5% body cell mass (BCM) loss within 6 months, or
  - In men: BCM < 35% of total body weight and body mass index (BMI) < 27 kg/m(2), or
  - In women: BCM < 23% of total body weight and BMI < 27 kg/m(2), or
  - BMI < 18.5 kg/m(2)

CONTINUED ON NEXT PAGE
INITIAL CRITERIA - OXANDRIN (CONTINUED)

- Patient does not have any of the following contraindications to anabolic steroid therapy:
  - Known or suspected carcinoma of the prostate or breast in male patients
  - Known or suspected carcinoma of the breast in females with hypercalcemia
  - Known or suspected nephrosis (the nephrotic phase of nephritis)
  - Known or suspected hypercalcemia
  - Severe hepatic dysfunction
- Patient will be monitored for peliosis hepatis, liver cell tumors and blood lipid changes

RENEWAL CRITERIA

OXANDRIN and ANADROL

Our guideline for ANABOLIC STEROIDS renewal requires the diagnosis of cachexia associated with AIDS. The following criteria must also be met:

- Patient is on anti-retroviral therapy
- Patient's viral load is less than 200 copies per mL within the past 3 months
- Patient has responded to therapy as measured by at least a 10% increase in weight from baseline (current weight must have been measured within the last 4 weeks, document date of measurement)
- Patient has not received more than 24 weeks of therapy in a calendar year

ANABOLIC STEROIDS

RATIONALE
To cover oxandrolone or oxymetholone for FDA approved indications and the following compendia indication: HIV wasting syndrome or HIV related cachexia.

FDA APPROVED INDICATIONS
Anadrol®-50 Tablets is indicated in the treatment of anemias caused by deficient red cell production. Acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and the hypoplastic anemias due to the administration of myelotoxic drugs often respond. Anadrol®-50 Tablets should not replace other supportive measures such as transfusion, correction of iron, folic acid, vitamin B12 or pyridoxine deficiency, antibacterial therapy and the appropriate use of corticosteroids. Oxandrin is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis

Compendia uses include (but not limited):

- Anadrol-50 (oxymetholone): Cachexia associated with AIDS & Fanconi's Anemia
- Oxandrin (oxandrolone): Cachexia associated with AIDS & Turner’s Syndrome

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ANABOLIC STEROIDS

DOSAGE

**Anadrol-50**
The recommended daily dose in children and adults is 1-5 mg/kg of body weight per day. The usual effective dose is 1-2 mg/kg/day but higher doses may be required, and the dose should be individualized. Response is not often immediate, and a minimum trial of three to six months should be given. Following remission, some patients may be maintained without the drug; others may be maintained on an established lower daily dosage. A continued maintenance dose is usually necessary in patients with congenital aplastic anemia.

**Oxandrin**
Therapy with anabolic steroids is adjunctive to and not a replacement for conventional therapy. The duration of therapy with Oxandrin (oxandrolone) will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent.

Adults: The response of individuals to anabolic steroids varies. The daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses. The desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.
Children: For children the total daily dosage of Oxandrin is ≤0.1 mg per kilogram body weight or ≤0.045 mg per pound of body weight. This may be repeated intermittently as indicated.
Geriatric Use: Recommended dose for geriatric patients is 5 mg bid.

CONTINUED ON NEXT PAGE
ANABOLIC STEROIDS

REFERENCES

ANAKINRA

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INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ANAKINRA requires a diagnosis of moderate to severe rheumatoid arthritis or a diagnosis of Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Cryopyrin-Associated Periodic Syndromes (CAPS). Additional guideline requirements apply.

For patients with moderate to severe rheumatoid arthritis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older
- Previous trial with 2 preferred agents: Cimzia, Enbrel, Simponi, Actemra SC, Orencia SC, or Xeljanz

RENEWAL CRITERIA

Our guideline for the renewal of ANAKINRA requires a diagnosis of moderate to severe rheumatoid arthritis or a diagnosis of Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Cryopyrin-Associated Periodic Syndromes (CAPS). Additional guideline requirements apply.

Renewal for the diagnosis of moderate to severe rheumatoid arthritis requires:
- Documentation that the patient has experienced or maintained a 20% improvement in tender or swollen joint count while on therapy.

Renewal for the diagnosis of Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Cryopyrin-Associated Periodic Syndromes (CAPS) requires:
- Documentation that the patient has experienced or maintained symptomatic improvement while on therapy.

CONTINUED ON NEXT PAGE
ANAKINRA

RATIONALE
Ensure appropriate diagnostic, utilization, and safety criteria.

FDA APPROVED INDICATIONS
Rheumatoid Arthritis (RA)
- Reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs (DMARDs)
Cryopyrin-Associated Periodic Syndromes (CAPS)
- Treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

REFERENCES

Created: 03/15
Effective: 09/18/17
Client Approval: 08/29/17
P&T Approval: 06/15
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GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline named ANTIPSYCHOTICS does not allow the use of the requested medication under the age of 18 (exceptions: age 10 for Latuda, age 12 for perphenazine). See Appendix 2 for age limitations.

Our guideline named ANTIPSYCHOTICS does not allow the use of the requested medication at quantities above those listed in Appendix 2.

Our guideline named ANTIPSYCHOTICS allows for low dose atypical antipsychotics use for patients with a mental health diagnosis such as bipolar disorder, schizophrenia, psychosis, or major depressive disorder.

Our guideline for ANTIPSYCHOTICS for patients with claims suggesting therapeutic duplication requires that the medications are being cross-tapered or that the medication in history is being discontinued. Therapeutic duplication will be allowed for patients who meet the following criteria:

- Patients with a diagnosis of psychosis within the past two years; both antipsychotics involved in the therapeutic duplication are prescribed by or in consultation with a psychiatrist; history of at least 4 weeks of single-agent therapy at an adequate dose for 2 different antipsychotics in the past 2 years; and history of at least 4 weeks of therapy with clozapine in the past 2 years (unless patient has contraindication, allergy, or intolerance to clozapine)
- Patients with a diagnosis of bipolar affective disorder, unspecified episodic mood disorder, or depressed mood disorder within the past two years; both antipsychotics involved in the therapeutic duplication are prescribed by or in consultation with a psychiatrist; and history of at least 4 weeks of single-agent therapy at an adequate dose for 2 different antipsychotics in the past 2 years

RENEWAL CRITERIA

Our guideline for ANTIPSYCHOTIC renewal for patients with claims suggesting therapeutic duplication requires that there is history of paid claims for the requested antipsychotic for 90 of the past 120 days.

RATIONALE

To promote prudent prescribing of atypical antipsychotics and antipsychotic duplicate therapies.

A look back period of 120 days will be utilized to identify patients new to therapy with an antipsychotic.

A look back period of 60 days will be utilized to identify potential therapeutic duplication.

CONTINUED ON NEXT PAGE
### APPENDIX 1: Antipsychotic Minimum Effective Doses for Mental Health Diagnoses

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<td>aripiprazole</td>
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<td>asenapine</td>
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<td>brexpiprazole</td>
<td>2 mg/ day; 1 mg/ day for depression</td>
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<td>1.5 mg/ day</td>
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<td>loperidone</td>
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<td>lurasidone</td>
<td>20 mg/ day</td>
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### APPENDIX 2: Antipsychotic Age Limits and Quantity Limits

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<td>ARISTADA</td>
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<td>43488</td>
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<td>44941</td>
<td>ARIPIPRAZOLE LAUROXIL, SUBMICRONIZED</td>
<td>ARISTADA INITIO</td>
<td>SUSR</td>
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<td>40683</td>
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Created: 07/16
Effective: 07/29/19
Client Approval: 07/02/19
P&T Approval: N/A
APALUTAMIDE

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GUIDELINES FOR USE

The guideline named APALUTAMIDE (Erleada) requires a diagnosis of non-metastatic castration-resistant prostate cancer.

RATIONALE

To promote appropriate utilization of ERLEADA based on FDA approved indication and dosing.

FDA APPROVED INDICATION

Erleada is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

DOSAGE & ADMINISTRATION

Erleada 240 mg (four 60 mg tablets) administered orally once daily. Swallow tablets whole. Erleada can be taken with or without food.

Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

REFERENCES


Created: 04/18
Effective: 05/21/18
Client Approval: 04/02/18
P&T Approval: N/A
MDwise MANAGED MEDICAID
PRIOR AUTHORIZATION GUIDELINES

APOMORPHINE

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GUIDELINES FOR USE

Our guideline for approval requires concurrent use of other medications for the treatment of Parkinson’s disease such as carbidopa/levodopa (Sinemet, Sinemet CR, Parcopa), carbidopa/levodopa/entacapone (Stalevo), pramipexole (Mirapex), ropinirole (Requip), rotigotine (Neupro), entacapone (Comtan), selegiline (Eldepryl, Zelapar), or rasagiline (Azilect).

RATIONALE

Ensure appropriate use of Apokyn.

Max dose for acute intermittent treatment of hypomobility “off” episodes in Parkinson’s disease: 0.2 to 0.6mL (2 to 6mg) SC as needed for “off” episodes; MAX 1 dose/episode; not more than 5 doses or MAX 2mLs (20mg) per day.

FDA APPROVED INDICATION

Indicated for the acute, intermittent treatment of hypomobility, “off” episodes (“end of dose wearing off” and unpredictable “on/off” episodes) associated with advanced Parkinson’s disease. Apokyn has been studied as an adjunct to other medications.

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/12
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for APREMILAST requires a diagnosis of psoriatic arthritis or moderate to severe plaque psoriasis, or oral ulcers associated with Behçet’s disease. In addition, the following criteria must be met:

For patients with psoriatic arthritis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older

For patients with moderate to severe plaque psoriasis, our guideline requires:
- Therapy initiated by or in consultation with a dermatologist
- Plaque psoriasis involves at least 10% body surface area (BSA) or psoriatic lesions affecting the hands, feet, or genital area
- Previous trial with at least one or more forms of preferred therapies such as PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- The patient is 18 years of age or older

For the diagnosis of oral ulcers associated with Behçet’s disease, approval requires:
- The patient is 18 years of age or older

RENEWAL CRITERIA

Our guideline for the renewal of APREMILAST requires a diagnosis of psoriatic arthritis or moderate to severe plaque psoriasis. The following criteria must also be met.

Renewal for the diagnosis of psoriatic arthritis requires:
- Documentation that the patient has experienced or maintained a 20% improvement in tender or swollen joint count while on therapy

Renewal for the diagnosis of moderate to severe plaque psoriasis requires:
- Documentation that the patient has achieved clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50% or more.

CONTINUED ON NEXT PAGE
APREMILAST

RATIONALE
To ensure appropriate diagnostic, utilization and safety criteria are used for the management of prior authorization requests for apremilast.

FDA APPROVED INDICATIONS
Otezla is an inhibitor of phosphodiesterase 4 (PDE4) indicated for the treatment of:
- Adult patients with active psoriatic arthritis
- Patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- Adult patients with oral ulcers associated with Behçet’s Disease

DOSAGE
The recommended initial dosage titration of Otezla from Day 1 to Day 5 is shown in Table 1. Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy. Otezla can be administered without regard to meals. Do not crush, split, or chew the tablets.

In patients with severe renal impairment (creatinine clearance (CLcr) of less than 30 mL per minute estimated by the Cockcroft–Gault equation), Otezla dosage should be reduced to 30 mg once daily. For initial dosage titration in this group, it is recommended that Otezla be titrated using only the AM schedule listed in Table 1 (skip PM doses).

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6 &amp; thereafter</th>
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</thead>
<tbody>
<tr>
<td>AM 10 mg</td>
<td>AM 10 mg</td>
<td>PM 10 mg</td>
<td>AM 20 mg</td>
<td>PM 20 mg</td>
<td>AM 30 mg</td>
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REFERENCES

Created: 03/15
Effective: 11/01/19
Client Approval: 10/17/19
P&T Approval: 06/15
INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ASFOTASE ALFA (Strensiq) requires a documented diagnosis of perinatal/infantile-onset hypophosphatasia (HPP) or juvenile-onset hypophosphatasia (HPP). Additional guideline requirements apply.

For patients with perinatal/infantile-onset hypophosphatasia (HPP), all of the following criteria must be met:

• Prescribed by or in consultation with an endocrinologist
• Patient was 6 months of age or younger at hypophosphatasia (HPP) onset
• Positive for a tissue non-specific alkaline phosphatase (TNSALP) (ALPL) gene mutation as confirmed by genetic testing OR meets at least TWO of the following criteria:
  o Serum alkaline phosphatase (ALP) level below that of normal range for patient age
  o Serum pyridoxal-5'-phosphate (PLP) levels elevated AND patient has not received vitamin B6 supplementation in the previous week
  o Urine phosphoethanolamine (PEA) level above that of normal range for patient age
  o Radiographic evidence of hypophosphatasia (HPP) (e.g., flared and frayed metaphyses, osteopenia, widened growth plates, areas of radiolucency or sclerosis)
  o Presence of two or more of the following:
    ▪ Rachitic chest deformity
    ▪ Craniosynostosis (premature closure of skull bones)
    ▪ Delay in skeletal growth resulting in delay of motor development
    ▪ History of vitamin B6 dependent seizures
    ▪ Nephrocalcinosis or history of elevated serum calcium
    ▪ History or presence of non-traumatic postnatal fracture and delayed fracture healing

For patients with juvenile-onset hypophosphatasia (HPP), all of the following criteria must be met:

• Prescribed by or in consultation with an endocrinologist
• Patient was 18 years of age or younger at hypophosphatasia (HPP) onset
• Positive for a tissue non-specific alkaline phosphatase (TNSALP) (ALPL) gene mutation as confirmed by genetic testing OR meets at least TWO of the following criteria:
  o Serum alkaline phosphatase (ALP) level below that of normal range for patient age
  o Serum pyridoxal-5'-phosphate (PLP) levels elevated AND patient has not received vitamin B6 supplementation in the previous week
  o Urine phosphoethanolamine (PEA) level above that of normal range for patient age
  o Radiographic evidence of hypophosphatasia (HPP) (e.g., flared and frayed metaphyses, osteopenia, osteomalacia, widened growth plates, areas of radiolucency or sclerosis)

(Initial denial text continued on next page)
INITIAL CRITERIA (CONTINUED)

- Presence of two or more of the following:
  - Rachitic deformities (rachitic chest, bowed legs, knock-knees)
  - Premature loss of primary teeth prior to 5 years of age
  - Delay in skeletal growth resulting in delay of motor development
  - History or presence of non-traumatic fractures or delayed fracture healing

Strensiq will not be approved for the following patients:
- Patients currently receiving treatment with a bisphosphonate [e.g., Boniva (ibandronate), Fosamax (alendronate), Actonel (risedronate)]
- Patients with serum calcium or phosphate levels below the normal range
- Patients with a treatable form of rickets

RENEWAL CRITERIA

Our guideline for ASFOTASE ALFA (Strensiq) renewal requires that the patient has experienced an improvement in the skeletal characteristics of hypophosphatasia (HPP) (e.g., improvement of the irregularity of the provisional zone of calcification, physeal widening, metaphyseal flaring, radiolucencies, patchy osteosclerosis, ratio of mid-diaphyseal cortex to bone thickness, gracile bones, bone formation and fractures).

RATIONALE

To ensure appropriate use of Strensiq consistent with FDA approved indication.

Strensiq (asfotase alfa) is the first therapy approved for the treatment of hypophosphatasia (HPP), a genetic, ultra-rare metabolic disorder. HPP is caused by a mutation in the tissue non-specific alkaline phosphatase (TNSALP) gene, which results in defective bone mineralization. Its prevalence is estimated to be less than 20 patients per one million in the general population and it is estimated to affect approximately one in 100,000 live births. HPP can affect people of all ages and the forms of HPP are classified primarily by the age of onset of symptoms and diagnosis. The clinical manifestations vary widely, ranging from stillbirth without mineralized bone to skeletal abnormalities due to softened bones. In perinatal HPP (onset in-utero), signs of HPP manifest in utero and may cause stillbirth or neonatal death shortly after birth.

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

Patients with infantile HPP (onset prior to 6 months of age) often appear normal at birth but typically present with skeletal abnormalities and failure to thrive within the first 6 months of life. Mortality, usually due to pulmonary complications, has been reported to be as high as 50% within the first year of life. Juvenile or childhood HPP (onset ≥6 months to <18 years), is often first recognized when there is premature loss of the deciduous teeth, and radiographs reveal skeletal defects. First signs of HPP may also present later in life (onset ≥18 years of age); however, some adult patients report a history of early tooth loss or rickets during childhood. In adult HPP, hypomineralization manifests as osteomalacia. Manifestations of the disease can be severe and debilitating, often requiring multiple surgeries, multiple pain medications, and the use of supportive devices to perform activities of daily living.

Current treatment of HPP has been directed toward the management of specific symptoms and complications. The approval of Strensiq is the turning point for patients with HPP for which there is no cure. This biological agent targets the bone and replaces the deficient TNSALP enzyme, thereby preventing or reversing the complications of a defective mineralization process.

FDA APPROVED INDICATION

Strensiq is approved for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

DOSAGE

Perinatal/Infantile-Onset hypophosphatasia (HPP)
Recommended dosage regimen is 2mg/kg administered subcutaneously three times per week, or 1mg/kg six times per week. Injection site reactions may limit the tolerability of the six times per week regimen. The dosage may be increased to 3mg/kg three times per week for insufficient efficacy.

Juvenile-Onset hypophosphatasia (HPP)
Recommended dosage regimen is 2mg/kg administered subcutaneously three times per week, or 1mg/kg six times per week. Injection site reactions may limit the tolerability of the six times per week regimen.

Please refer to prescribing information for tables of weight-based dosing by treatment regimen.

Strensiq is available as single-use vials in the following strengths: 18mg/0.45ml, 28mg/0.7ml, 40mg/ml, 80mg/0.8ml. The vials must be stored in the original carton until time of use under refrigerated conditions and protected from light. Once removed from refrigeration, Strensiq should be administered within 1 hour.
ASFOTASE ALFA

FDA APPROVED INDICATION (CONTINUED)

AVAILABLE STRENGTHS:
- 18mg/0.45ml single-use vial
- 28mg/0.7ml single-use vial
- 40mg/ml single-use vial
- 80mg/0.8ml single-use vial

REFERENCES
GUIDELINES FOR USE

Our guideline for ASPIRIN ER requires a diagnosis of chronic coronary artery disease, (e.g. a history of MI or unstable angina), or a history of an ischemic stroke or transient ischemic attack (TIA). In addition, the following criteria must also be met:

• Patient has previously tried aspirin over-the-counter (OTC)
• Durlaza is not being used for acute treatment of myocardial infarction or before percutaneous coronary intervention

RATIONALE

Promote appropriate utilization of Durlaza based on FDA approved indication and cost-effectiveness.

DURLAZA is a nonsteroidal anti-inflammatory drug indicated to reduce the risk of death and myocardial infarction (MI) in patients with chronic coronary artery disease, such as patients with a history of MI or unstable angina pectoris or with chronic stable angina and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack.

Limitation of Use: Use immediate-release aspirin, not DURLAZA in situations where a rapid onset of action is required (such as acute treatment of myocardial infarction or before percutaneous coronary intervention).

Durlaza is a 162.5mg extended release formulation of aspirin. Aspirin is available in multiple strengths as an over the counter (OTC) product. There were no new studies on the safety and efficacy of Durlaza performed. The platelet inhibitory effects of aspirin last for the life of the circulating platelets, which is ~10 days, thus an extended release formulation of aspirin has not been demonstrated to be superior to previously available OTC aspirin.

DOSAGE
The recommended dose is 162.5 mg per day with a full glass of water at the same time each day.

FDA APPROVED INDICATION
DURLAZA is a nonsteroidal anti-inflammatory drug indicated to reduce the risk of death and myocardial infarction (MI) in patients with chronic coronary artery disease, such as patients with a history of MI or unstable angina pectoris or with chronic stable angina and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack.

Limitation of Use: Use immediate-release aspirin, not DURLAZA in situations where a rapid onset of action is required (such as acute treatment of myocardial infarction or before percutaneous coronary intervention).
ASPIRIN ER

REFERENCES


Created: 01/16
Effective: 06/01/16
Client Approval: 04/18/16
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named **ASPIRIN-OMEPRAZOLE (Yosprala)** requires an indication of secondary prevention of cardiovascular or cerebrovascular events and has **ONE** of the following diagnoses: ischemic stroke, transient ischemia of the brain due to fibrin platelet emboli, previous myocardial infarction, unstable angina pectoris, chronic stable angina pectoris, or previous revascularization procedures (i.e., coronary artery bypass graft, percutaneous transluminal coronary angioplasty). In addition, the following criteria must also be met:

- The patient has a risk of developing aspirin associated gastric ulcers due to age (55 years or older) **AND** documented history of gastric ulcers
- The patient has tried both aspirin over-the-counter (OTC) **AND** generic proton pump inhibitors (e.g., omeprazole, lansoprazole, pantoprazole, rabeprazole)

RATIONAL
Promote appropriate utilization of **Yosprala** based on FDA approved indication and dosing.

FDA APPROVED INDICATIONS
Indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.

The aspirin component is indicated for:
- Reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli,
- Reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris,
- Reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris,
- Use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated.

The omeprazole component of Yosprala is indicated for decreasing the risk of developing aspirin associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55) or documented history of gastric ulcers.

Limitations of Use:
- Not for use as the initial dose of aspirin therapy during onset of acute coronary syndrome, acute myocardial infarction or before percutaneous coronary intervention.
- Has not been shown to reduce the risk of gastrointestinal bleeding due to aspirin.
- Yosprala is not interchangeable with the individual components of aspirin and omeprazole.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE
The recommended dosage is one tablet daily.

Yosprala is available in combinations that contain 81 mg or 325 mg of aspirin. Generally, 81 mg of aspirin has been accepted as an effective dose for secondary cardiovascular prevention. Providers should consider the need for 325 mg and refer to current clinical practice guidelines.

REFERENCES
AXITINIB

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<th>HICL</th>
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GUIDELINES FOR USE

Approval requires a diagnosis of advanced renal cell carcinoma (RCC) and a trial of at least one systemic therapy for the treatment of RCC such as Avastin (bevacizumab) in combination with interferon, Nexavar (sorafenib), Torisel (temsirolimus), Sutent (sunitinib), or Votrient (pazopanib), all of which may require prior authorization. Additionally Avastin may be covered under the medical benefit rather than the pharmacy benefit.

RATIONALE

Ensure appropriate utilization of Inlyta based on FDA approved indication and NCCN guidelines.

Inlyta (axitinib) is a receptor tyrosine kinase inhibitor shown to have activity against vascular endothelial growth factor receptors 1, 2, and 3. National Comprehensive Cancer Network (NCCN) category 1 options for first line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma include sunitinib, bevacizumab with interferon-alfa, pazopanib, and temsirolimus. NCCN lists sorafenib as a category 2A option.

Approval of Inlyta was based on a randomized, open-label, multicenter Phase 3 study comparing progression-free survival (PFS) of patients with advanced RCC whose disease had progressed on or after treatment with 1 prior systemic therapy, including sunitinib, bevacizumab, temsirolimus, or cytokine-containing regimens. Other endpoints included objective response rate (ORR) and overall survival (OS) 99% of study subjects had clear cell histology. Patients were randomized to receive Inlyta or sorafenib. There was a statistically significant advantage for Inlyta over sorafenib for the endpoint of PFS (6.7 vs. 4.7 months, respectively, P < 0.0001). There was no statistically significant difference between the arms in OS.

The most common (≥ 20%) adverse reactions are diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight loss, vomiting, asthenia, and constipation. Please reference the prescribing information for a complete list of warnings and precautions.

Dosage: The starting dose is 5 mg orally twice daily. Administer dose approximately 12 hours apart with or without food. Dose may be increased to 7mg twice daily and further increased to 10mg twice daily for patients who tolerate Inlyta for at least two consecutive weeks. In the pivotal trial, the dosage of 10mg twice daily was not associated with an improved outcome over the 5mg twice daily dosage. If a strong CYP3A4/5 inhibitor is required or for patients with moderate hepatic impairment, the dose may be decreased to 3mg twice daily and further reduced to 2mg twice daily.

FDA APPROVED INDICATION

Inlyta is indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

CONTINUED ON NEXT PAGE
REFERENCES


Created: 06/15
Effective: 07/01/17
Client Approval: 05/01/17
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for approval requires a diagnosis of cystic fibrosis, patient age of at least 7 years, and lung infection with a Gram negative species.

AZTREONAM INHALED

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RATIONALE

Promote appropriate utilization of Cayston based on FDA approved indication.

Dosage: One ampule three times daily in repeated cycles of 28 days on drug followed by 28 days off drug.

FDA APPROVED INDICATION

Cayston is indicated to improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*. Safety and effectiveness have not been established in pediatric patients below the age of 7 years, patients with FEV₁ <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 05/12
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named BARICITINIB (Olumiant) requires a diagnosis of moderate to severe rheumatoid arthritis. In addition, the following criteria must also be met:

- Therapy is prescribed by or given in consultation with a rheumatologist
- The patient has had a previous trial of at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older
- The patient has had a previous trial of any TWO of the following formulary preferred immunomodulators: Cimzia, Enbrel, Oreneca SC, Simponi, Xeljanz/Xeljanz XR, OR Actemra SC.

The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition or prior prescription history for drugs that require prior authorization.

RENEWAL CRITERIA

The guideline named BARICITINIB (Olumiant) requires a diagnosis of moderate to severe rheumatoid arthritis and that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy.

RATIONALE

To ensure appropriate use of Olumiant consistent with its FDA approved indication and dosing.

FDA APPROVED INDICATION

Olumiant is a Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Limitation of Use: Use of Olumiant in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

DOSAGE FORMS AND STRENGTHS

Olumiant is available as 2 mg oral tablets.

DOSAGE AND ADMINISTRATION

The recommended dose of Olumiant is 2 mg orally once daily. Olumiant may be used as monotherapy or in combination with methotrexate or other DMARDs.

REFERENCES


Created: 06/18
Effective: 08/20/18
Client Approval: 07/06/18
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for approval requires that Sirturo only be used in the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB), in adults (18 years of age or older), and used in combination with at least three other antibiotics to which the patient's MDR-TB isolate has been shown to be susceptible.

RATIONALE
To ensure appropriate use aligned with FDA approved indication.

The recommended dosage of Sirturo is 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks. Sirturo should be administered by directly observed therapy (DOT). Sirturo should be swallowed whole and administered with food and water. No dosage adjustment is necessary in patients with mild to moderate renal or hepatic impairment.

Sirturo should only be used in combination with at least 3 other antibiotics to which the patient's MDR-TB isolate has been shown to be susceptible in vitro. If in vitro testing results are not available, treatment may be initiated with Sirturo in combination with at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible.

The term multi-drug resistant tuberculosis (MDR-TB) refers to an isolate of M. tuberculosis that is resistant to at least isoniazid and rifampin, and possibly additional agents. Treatment of suspected MDR-TB should be guided by drug susceptibility testing whenever possible. Susceptibility data is often not available (at least initially), and empiric therapy must be used. Empiric regimens for patients in areas with a known high prevalence of MDR-TB (or for patients with a new diagnosis of TB following contact with an individual known to have MDR-TB) should include first-line agents plus any additional drugs necessary to ensure a combination regimen containing at least four drugs which are active against the most prevalent drug-resistant strains. In general, treatment of MDR-TB should include a fluoroquinolone (levofloxacin 1000mg daily is favored by the WHO MDR-TB treatment guidelines) and an injectable agent (in many countries, kanamycin [dosed at 15mg/kg/daily IV or IM] is the first-choice injectable agent since it is relatively inexpensive and readily available). There is no role for the use of more than one fluoroquinolone or injectable agent. Subsequently, if needed, ethionamide, cycloserine, and aminosalicylic acid may be added to complete the regimen such that it consists of at least four active drugs. Alternative agents should be added only when the preceding drugs are not sufficient.

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

Treatment failure refers to failure of cultures to become negative during the course of treatment, or reappearance of positive cultures after the cultures convert to negative during treatment. Treatment failure implies resistance to all of the drugs being administered at the time when failure is diagnosed. The relatively poor response of drug resistant TB to treatment is likely a function of the relatively weak potency of the drugs used rather than the inherent properties of the microbe.

The FDA approval of Sirturo was based on two studies.

Study 1
The placebo-controlled, double-blind, randomized trial enrolled 160 newly diagnosed patients with multi-drug resistant pulmonary Mycobacterium tuberculosis. Subjects were randomized to receive treatment with either Sirturo or placebo, both added to other drugs used to treat MDR-TB. Sirturo was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times per week for the following 22 weeks. After the 24-week Sirturo or placebo treatment phase, subjects continued to receive their other drugs used to treat MDR-TB until a total treatment duration of 18 to 24 months. Time to sputum culture conversion was measured as the interval between the first dose of the study drug and the date of the first two consecutive negative sputum cultures collected. The Sirturo treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 24. Treatment success was reached by 77.6% of the Sirturo arm versus 57.6% of the placebo arm at Week 24 (p=0.014). At Week 72 success was reached by 70.1% and 56.1% of the respective arms. Median time to culture conversion was 83 days for the Sirturo treatment group compared to 125 days for the placebo treatment group.

Study 2
This placebo controlled study was designed similarly to Study 1 except that Sirturo or placebo was given for only 8 weeks instead of 24 weeks. A total of 47 subjects were treated. The Sirturo treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 8. At Weeks 8 and 24, the differences in culture conversion proportions were 38.9% (p-value: 0.004) and 15.7% (p-value: 0.32) respectively.

Sirturo has two boxed warnings. The first warns of an increased risk of death seen in those treated with Sirturo (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%). The imbalance in deaths is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, or severity of disease could be observed. It is recommended that Sirturo only be used when an effective treatment regimen cannot otherwise be provided. The second warning states that QT prolongation can occur with Sirturo. Concomitant use with other drugs that prolong the QT interval is discouraged as this may cause additive QT prolongation. Sirturo should be discontinued if significant ventricular arrhythmia or a QTc interval > 500 ms develops.

CONTINUED ON NEXT PAGE
BEDAQUILINE FUMARATE

RATIONALE (CONTINUED)

The most common adverse reactions reported in ≥10% of patients treated with Sirturo are nausea, arthralgia, and headache. Additional adverse events reported in ≥10% of patients treated with Sirturo and with a higher frequency than the placebo treatment group are hemoptysis and chest pain. Hepatic-related adverse drug reactions have also been reported with use of Sirturo. As a result, liver function tests should be monitored.

The major CYP isoenzyme involved in the metabolism of bedaquiline is CYP3A4. Co-administration of Sirturo with strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions. Therefore, the use of strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided while on Sirturo, unless the benefit of treatment with the drug combination outweighs the risk. Alcohol should also be avoided throughout the treatment period.

Pregnancy Category B.

FDA APPROVED INDICATIONS

Sirturo is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Sirturo is reserved for use when an effective treatment regimen cannot otherwise be provided. Sirturo is not indicated for the treatment of latent, extra-pulmonary, or drug-sensitive tuberculosis.

REFERENCES

NOTE: For requests for the SQ dosage form of Benlysta, please see the BELIMUMAB SQ Guideline.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

The guideline named BELIMUMAB IV (Benlysta) requires that the patient has a diagnosis of autoantibody positive systemic lupus erythematosus (SLE) and ALL of the following criteria are met:

- The patient is 5 years of age or older
- The patient does NOT have severe active lupus nephritis or severe active central nervous system lupus
- The medication will NOT be used in combination with biologics (e.g., Rituxan) or intravenous cyclophosphamide
- The patient is currently receiving corticosteroids, antimalarials, NSAIDs, or immunosuppressants
- The patient has a Safety of Estrogens in Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of at least 6

RENEWAL CRITERIA

The guideline for BELIMUMAB IV (Benlysta) renewal requires that the patient have a diagnosis of autoantibody positive systemic lupus erythematosus (SLE) and has achieved or maintained at least a 4-point reduction in their Safety of Estrogens in Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score from baseline.

RATIONALE

Ensure appropriate utilization of Benlysta consistent with its FDA approved indication and dosing.

FDA APPROVED INDICATION

Benlysta is indicated for the treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy.

Limitations of Use: Not recommended for patient with severe active lupus nephritis or severe active central nervous system lupus or in combination with other biologics or intravenous cyclophosphamide.

CONTINUED ON NEXT PAGE
BELIMUMAB – IV

FDA APPROVED INDICATION (CONTINUED)

DOSAGE AND ADMINISTRATION
The intravenous formulation of Benlysta is supplied as 120mg/5mL and 400mg/20mL single-dose vials.

The recommended intravenous dosage regimen in adult and pediatric patients is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

REFERENCES

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

The guideline named BELIMUMAB (Benlysta SQ) requires that the patient has a diagnosis of autoantibody positive systemic lupus erythematosus (SLE) and ALL of the following criteria have been met:

- The patient is 18 years of age or older
- The patient does NOT have severe active lupus nephritis or severe active central nervous system lupus
- The medication will NOT be used in combination with biologics (e.g., Rituxan) or intravenous cyclophosphamide
- The patient is currently using corticosteroids, antimalarials, NSAIDs, or immunosuppressants
- The patient has a Safety of Estrogens in Erythematous National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of at least 6

RENEWAL CRITERIA

The guideline named BELIMUMAB (Benlysta SQ) renewal requires that the patient has a diagnosis of autoantibody positive systemic lupus erythematosus (SLE) and has achieved or maintained at least a 4-point reduction in their Safety of Estrogens in Erythematous National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score from baseline.

RATIONALE

Ensure appropriate utilization of Benlysta consistent with its FDA approved indication and dosing.

FDA Approved Indications
Benlysta is indicated for the treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy.

Limitations of Use: Not recommended for patient with severe active lupus nephritis or severe active central nervous system lupus or in combination with other biologics or intravenous cyclophosphamide.

DOSAGE AND ADMINISTRATION

The subcutaneous formulation of Benlysta is supplied as 200mg/mL syringes and auto-injectors. The recommended dose of Benlysta is 200mg SQ once weekly.

Subcutaneous dosing of Benlysta has not been evaluated and is not approved for patients younger than 18 years of age.

CONTINUED ON NEXT PAGE
BELIMUMAB - SQ

REFERENCES


Created: 08/17
Effective: 01/01/20
Client Approval: 12/09/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named BENRALIZUMAB (Fasenra) requires a diagnosis of severe eosinophilic asthma. In addition, the following criteria must be met:

- The medication was prescribed by or given in consultation with a physician specializing in allergic or pulmonary medicine
- The patient is 12 years of age or older
- The patient is currently adherent to a maximally tolerated dose of an inhaled corticosteroid AND at least one other maintenance medication (e.g., long-acting inhaled beta2-agonist, long-acting muscarinic antagonist, a leukotriene receptor antagonist, theophylline, or oral corticosteroid)
- The patient has a documented blood eosinophil level of 300 cells/mcL or more within the past 6 months
- The patient has experienced at least 2 or more asthma exacerbations within the past 12 months (exacerbation is defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 or more days)
- The patient has ONE of the following:
  - Asthma Control Test (ACT) score of less than 20
  - Asthma Control Questionnaire (ACQ) score of at least 1.5 or more
  - Asthma Therapy Assessment Questionnaire (ATAQ) score of at least 1 or more
- Fasenra will be used as add-on maintenance treatment
- The patient is not concurrently being treated with Xolair, Dupixent, or another anti-IL5 asthma biologic (e.g. Nucala, Cinqair)

RENEWAL CRITERIA

The guideline named BENRALIZUMAB (Fasenra) requires a diagnosis of severe eosinophilic asthma for renewal. In addition, the following criteria must also be met:

- The patient has experienced a reduction in asthma exacerbations (defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days) from baseline
- The patient has experienced an improvement in the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Asthma Therapy Assessment Questionnaire (ATAQ) score from baseline
- The patient has decreased their total daily oral corticosteroid dose from baseline if the patient was on a maintenance therapy with oral corticosteroids prior to initiation of Fasenra

CONTINUED ON NEXT PAGE
RATIONALE
Promote appropriate utilization of **BENRALIZUMAB** based on FDA approved indication and dosing.

DOSAGE AND ADMINISTRATION
The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

Fasenra should be administered by a healthcare professional.

FDA APPROVED INDICATION
Fasenra (benralizumab) is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa) indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Limitations of Use:
- Not for treatment of other eosinophilic conditions.
- Not for relief of acute bronchospasm or status asthmaticus.

REFERENCES
GUIDELINES FOR USE

Our guideline for approval requires a diagnosis of cutaneous T-cell lymphoma that is refractory to prior systemic therapy.

BEXAROTENE

RATIONALE
Promote appropriate utilization of Targretin based on FDA approved indication.

FDA APPROVED INDICATIONS
Targretin (bexarotene) capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

(Systemic therapy to treat CTCL may include gemcitabine, methotrexate, liposomal doxorubicin, Velcade, and other agents.)

OTHER INFORMATION
Capsules (weight-based dosing of 4 to 14 capsules per day).

Gel (applications may be titrated from every other day up to four times daily; typical application varies from twice daily up to four times daily).

Targretin capsules should be administered once daily with a meal. The initial dose is 300mg/m²/day. The dose may be increased up to 400mg/m²/day when there is no tumor response after 8 weeks.

In clinical trials oral Targretin was administered for up to 97 weeks and topical Targretin gel was administered for up to 172 weeks.


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OTHER INFORMATION (CONTINUED)

Targretin contains a **black box warning** that this product is a member of the retinoid class of drugs and should not be administered to pregnant women (Pregnancy Category X).

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/13
GUIDELINES FOR USE
The guideline named BINIMETINIB (Mektovi) requires a diagnosis of unresectable or metastatic melanoma. In addition, the following criteria must be met:
- The patient has BRAF V600E or V600K mutation as detected by an FDA-approved test
- The medication will be used in combination with Braftovi (encorafenib)

RATIONALE
To promote appropriate utilization of MEKTOVI based on FDA approved indication and dosing.

FDA APPROVED INDICATION
Mektovi is a kinase inhibitor indicated, in combination with Braftovi (encorafenib), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

DOSAGE & ADMINISTRATION
The recommended dosage of Mektovi is 45 mg orally taken twice daily, approximately 12 hours apart, in combination with Braftovi (encorafenib) until disease progression or unacceptable toxicity. Refer to the Braftovi (encorafenib) prescribing information for recommended Braftovi (encorafenib) dosing information.

Mektovi may be taken with or without food. Do not take a missed dose of Mektovi within 6 hours of the next dose of Mektovi. Do not take an additional dose if vomiting occurs after Mektovi administration but continue with the next scheduled dose.

REFERENCES

Created: 08/18  Effective: 10/22/18  Client Approval: 09/11/18  P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline named BOSUTINIB (Bosulif) requires that the requested medication is used for newly diagnosed, chronic phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) OR chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML). In addition, the patient must be at least 18 years old AND has had a Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) mutational analysis confirming that both the T315I and V299L mutations are not present. The following criteria must also be met.

For the diagnosis of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML), approval requires:
• Previous trial of or contraindication to Gleevec, Sprycel, or Tasigna.

RATIONALE

Ensure appropriate utilization of bosutinib based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS

Bosulif is a kinase inhibitor indicated for the treatment of adult patients with:
• Newly diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML). This indication is approved under accelerated approval based on molecular and cytogenetic response rates. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow up trial
• Chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy

DOSAGE AND ADMINISTRATION

Newly Diagnosed chronic phase Ph+ CML: The recommended dose of Bosulif is 400 mg orally once daily with food and continues until disease progression or patient intolerance.

Chronic Phase, Accelerated Phase, or Blast Phase Ph+ CML with resistance or intolerance to prior therapy: The recommended dose of Bosulif is 500 mg once daily with food and continues until disease progression or patient intolerance.

The tablet is to be swallowed whole and should not be broken or cut. Dose escalation to 600 mg once daily, by increments of 100 mg once daily, can be considered for patients who do not reach complete hematological response (CHR) by week 8 or have a complete cytogenetic response by week 12, and do not have grade 3 or higher adverse reactions while taking the recommended starting dosage.
FDA APPROVED INDICATIONS (CONTINUED)

If liver transaminases exceed 5x the institutional upper limit of normal (ULN), withhold treatment until recovery of liver transaminases reach a level of no more than 2.5x ULN, and resume at 400mg once daily. If recovery takes longer than 4 weeks or transaminase elevations of at least 3x ULN occur with bilirubin elevations of least 2x ULN, or alkaline phosphates less than 3x ULN, discontinue treatment.

In the presence of grade 3 - 4 diarrhea, withhold Bosulif until recovery to Grade less than or equal to 1, and may resume Bosulif at 400 mg once daily.

For other clinically significant, moderate, or severe non-hematological toxicity, withhold treatment until the toxicity has resolved, then may resume at a dose reduced by 100 mg once daily. If clinically appropriate, consider re-escalating the dose to the starting dose taken once daily. Doses less than 300 mg/day have been used in patients; however, efficacy has not been established. Consider dose reduction by 100 mg in the presence of neutropenia or thrombocytopenia.

For creatinine clearance 30 to 50 ml/min, consider dose reduction to 300 mg daily for newly diagnosed Ph+ CML and 400 mg daily for chronic, accelerated, or blast phase Ph+ CML. For creatinine clearance less than 30 ml/min, consider dose reduction to 200 mg daily for 300mg daily for newly diagnosed Ph+ CML and 300 mg daily for chronic, accelerated, or blast phase Ph+ CML. For mild, moderate, or severe hepatic impairment, consider dose reduction to 200 mg daily.

DOSEAGE STRENGTHS

- 100 mg tablets
- 400 mg tablets
- 500 mg tablets

REFERENCES

GUIDELINES FOR USE

BOTOX INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for BOTULINUM NEUROTOXIN (BOTOX) requires one of the following non-cosmetic conditions: treatment of overactive bladder (OAB) in adults, treatment of urinary incontinence in adults, prophylaxis of chronic migraine headaches in adults, treatment of upper or lower limb spasticity in adults, treatment of upper limb or lower spasticity in pediatric patients 2 to 17 years of age, treatment of cervical dystonia (spasmodic torticollis or involuntary contracting of the neck muscles) in adults, treatment of severe axillary hyperhidrosis (excessive underarm sweating) in adults, treatment of blepharospasm in patients age 12 years or greater, or treatment of strabismus (crossed-eye) in patients age 12 years or greater. This medication will not be approved for the improvement of appearance of glabellar lines in the face (e.g., wrinkles). Additional guideline requirements apply.

- For the treatment of overactive bladder (OAB), approval requires:
  - Age 18 years or greater
  - Documentation that the patient has had a previous trial of or contraindication to THREE of the following anticholinergic medications (chart notes required in the absence of electronic prescription claims history): Ditropan/Ditropan XL, Detrol/Detrol LA, Enablex, Gelnique, Myrbetriq, Oxytrol, Toviaz, VESIcare, or Sanctura

- For the treatment of urinary incontinence, approval requires:
  - Age 18 years or greater
  - Detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)]
  - Documentation that the patient has had a previous trial of or contraindication to THREE of the following anticholinergic medications (chart notes required in the absence of electronic prescription claims history): Ditropan/Ditropan XL, Detrol/Detrol LA, Enablex, Gelnique, Myrbetriq, Oxytrol, Toviaz, VESIcare, or Sanctura

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GUIDELINES FOR USE (CONTINUED)

BOTOX INITIAL CRITERIA

- For the prophylaxis of chronic migraine headaches, approval requires:
  - Age 18 years or greater
  - Documentation that the patient has had a previous trial of THREE of the following preventive migraine treatments (chart notes required in the absence of electronic prescription claims history):
    - beta-blocker (e.g., propranolol, nadolol)
    - candesartan
    - cyproheptadine
    - lisinopril
    - tricyclic antidepressant (e.g., amitriptyline, nortriptyline, doxepin)
    - topiramate
    - valproic acid/divalproex sodium
    - verapamil

BOTOX RENEWAL CRITERIA

Our guideline for the renewal of BOTULINUM NEUROTOXIN (BOTOX) requires one of the following non-cosmetic conditions: treatment of overactive bladder (OAB), treatment of urinary incontinence, prophylaxis of chronic migraine headaches, treatment of upper or lower limb spasticity, treatment of cervical dystonia (spasmodic torticollis or involuntary contracting of the neck muscles), treatment of severe axillary hyperhidrosis (excessive underarm sweating), treatment of blepharospasm (involuntary forcible closure of the eyelid), or for the treatment of strabismus (crossed-eye). This medication will not be approved for the improvement of appearance of glabellar lines in the face (e.g., wrinkles). Additional guideline requirements apply.

- Renewal for the treatment of overactive bladder (OAB) requires:
  - Documentation that the patient has experienced or maintained at least a 50% reduction in the number of daily urinary incontinent episodes

- Renewal for the treatment of urinary incontinence requires:
  - Documentation that the patient has experienced or maintained at least a 50% reduction in the number of daily urinary incontinent episodes

- Renewal for the prophylaxis of chronic migraine headaches requires:
  - Documentation (i.e., chart notes) that ONE of the following criteria has been met:
    - The patient has experienced a reduction in migraine or headache frequency of at least 2 days per month with Botox therapy
    - The patient has experienced a reduction in migraine severity with Botox therapy
    - The patient has experienced a reduction in migraine duration with Botox therapy

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GUIDELINES FOR USE (CONTINUED)

DYSPORT INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for **BOTULINUM NEUROTOXIN (DYSPORT)** requires a non-cosmetic diagnosis of cervical dystonia also called spasmodic torticollis (involuntary contracting of the neck muscles) in adults, upper limb spasticity in adults, or lower limb spasticity in patients age 2 years or greater. This medication will not be approved for the improvement of appearance of glabellar lines in the face (e.g., wrinkles).

DYSPORT RENEWAL CRITERIA

Our guideline for **BOTULINUM NEUROTOXIN (DYSPORT)** requires a non-cosmetic diagnosis of cervical dystonia also called spasmodic torticollis (involuntary contracting of the neck muscles), upper limb spasticity, or lower limb spasticity. This medication will not be approved for the improvement of the appearance of glabellar lines in the face (e.g., wrinkles).

MYOBLOC INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for **BOTULINUM NEUROTOXIN (MYOBLOC)** requires a non-cosmetic diagnosis of cervical dystonia also called spasmodic torticollis (involuntary contracting of the neck muscles) in adults. This medication will not be approved for the improvement of appearance of glabellar lines in the face (e.g., wrinkles).

MYOBLOC RENEWAL CRITERIA

Our guideline for the renewal of **BOTULINUM NEUROTOXIN (MYOBLOC)** requires a non-cosmetic diagnosis of cervical dystonia also called spasmodic torticollis (involuntary contracting of the neck muscles). This medication will not be approved for the improvement of appearance of glabellar lines in the face (e.g., wrinkles).

XEOMIN INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for **BOTULINUM NEUROTOXIN (XEOMIN)** requires a non-cosmetic diagnosis such as cervical dystonia (spasmodic torticollis or involuntary contracting of the neck muscles) in adults, blepharospasm (involuntary forcible closure of the eyelid) in adults, upper limb spasticity in adults, or chronic sialorrhea in adults. This medication will not be approved for the improvement of appearance of glabellar lines in the face (e.g., wrinkles). Additional guideline requirements apply.

- **For the diagnosis of blepharospasm**, approval requires a previous trial of Botox (onabotulinum toxin A). A prior authorization has been entered for Botox.

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GUIDELINES FOR USE (CONTINUED)

XEOMIN RENEWAL CRITERIA

Our guideline for renewal of BOTULINUM NEUROTOXIN (XEOMIN) requires a non-cosmetic diagnosis such as cervical dystonia (spasmodic torticollis or involuntary contracting of the neck muscles), blepharospasm (involuntary forcible closure of the eyelid), upper limb spasticity, or chronic sialorrhea. This medication will not be approved for the improvement of appearance of glabellar lines in the face (e.g., wrinkles).

RATIONALE
Ensure botulinum neurotoxin is used for non-cosmetic use.

FDA APPROVED INDICATIONS
BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:
• Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
• Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication
• Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer)
• Treatment of upper or lower limb spasticity in adult patients
• Treatment of upper limb or lower spasticity in pediatric patients 2 to 17 years of age
• Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain
• Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
• Treatment of blepharospasm associated with dystonia in patients ≥12 years of age
• Treatment of strabismus in patients ≥12 years of age

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BOTULINUM NEUROTOXIN

FDA APPROVED INDICATIONS (CONTINUED)

Important limitations:
Safety and effectiveness of Botox have not been established for:
• Prophylaxis of episodic migraine (14 headache days or fewer per month)
• Treatment of hyperhidrosis in body areas other than axillary

DYSPORT is indicated for:
• Treatment of adults with cervical dystonia in adults
• The temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age
• Treatment of spasticity in adults
• Treatment of lower limb spasticity in pediatric patients 2 years of age and older

MYOBLOC is indicated the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

XEOMIN is approved for:
• Chronic sialorrhea in adults
• Cervical dystonia in adults, to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients
• Blepharospasm in adults previously treated with onabotulinum toxin A
• Upper limb spasticity in adults
• Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults

REFERENCES
• Guinn, D. Hickenbottom, S. Lee MJ. Headache in pregnant and postpartum women. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed June 11, 2019

CONTINUED ON NEXT PAGE
BOTULINUM NEUROTOXIN

REFERENCES (CONTINUED)

GUIDELINES FOR USE

Our guideline for BRAND MEDICALLY NECESSARY MEDICATIONS requires that this product is only covered for patients that have tried a generically equivalent medication within the previous 6 months (verified in prescription claims history or in submitted chart notes) and are unable to use the generic equivalent due to allergic reaction or therapeutic failure. Approval for brand medications when a generic equivalent exists requires documentation of allergic reaction or therapeutic failure associated with the use of the generic equivalent by reporting to the FDA on a MedWatch Form. Your physician did not provide the required information and therefore your request was not approved. Brand medications will not be approved for patients who report lesser efficacy as compared to the equivalent generic medication unless it would be clinically inappropriate to address efficacy with dose adjustment. In addition, a past trial of the brand medication is required to confirm better efficacy of the brand medication over the generic equivalent.

RATIONALE

The intent of this prior authorization is to encourage the use of cost-effective generically equivalent medications before considering coverage of brand medications.

REFERENCES

GUIDELINES FOR USE

The guideline named BRIGATINIB (Alunbrig) requires a diagnosis of metastatic non-small cell lung cancer (NSCLC). In addition, the following criteria must be met:
- The patient is positive for anaplastic lymphoma kinase (ALK) fusion oncogene
- The patient has progressed or is intolerant to Xalkori (crizotinib)

RATIONALE

Promote appropriate utilization of BRIGATINIB based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS

Alunbrig is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION

The recommended dose of Alunbrig as treatment is 90 mg orally once daily for the first 7 days; if tolerated, increase to 180 mg orally once daily. May be taken with or without food.

Administer Alunbrig until disease progression or unacceptable toxicity.

If Alunbrig is interrupted for 14 days or longer for reasons other than adverse reactions, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

Alunbrig may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets.

If a dose of Alunbrig is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of Alunbrig at the scheduled time.

To manage adverse reactions, consider interruption of treatment or dose reduction. Recommended dose reductions are summarized in Table 1.

Table 1. Recommended Dose Adjustments

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dose Reduction Levels</th>
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<tbody>
<tr>
<td></td>
<td>First</td>
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<tr>
<td>90 mg once daily</td>
<td>60 mg once daily</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>180 mg once daily</td>
<td>120 mg once daily</td>
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</tbody>
</table>

Once reduced for adverse reactions, do not subsequently increase the dose of Alunbrig. Permanently discontinue Alunbrig if patients are unable to tolerate the 60 mg once daily dose.
DOSAGE FORMS AND STRENGTHS
Tablets: 180 mg, 90 mg, and 30 mg

REFERENCES

Created: 05/17
Effective: 02/23/18
Client Approval: 02/05/18
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named **BRODALUMAB (Siliq)** requires a diagnosis of moderate to severe plaque psoriasis (PsO). In addition, the following criteria must also be met:

- Therapy is prescribed by or in consultation with a dermatologist
- Plaque psoriasis involves at least 10% body surface area (BSA) OR psoriatic lesions affecting the hands, feet, or genital area
- Previous trial of one or more forms of conventional therapies, such as PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- The patient is 18 years of age or older
- The patient has been counseled on and expresses understanding of the risk of suicidal ideation and behavior
- Previous trial of **TWO** of the following preferred formulary agents: Cosentyx (secukinumab), Enbrel (etanercept), or Otezla (apremilast)

RENEWAL CRITERIA

The guideline named **BRODALUMAB (Siliq)** requires a diagnosis of moderate to severe plaque psoriasis (PsO) for renewal. The following criteria must also be met:

- Documentation that the patient has achieved or maintained clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50% or more
- The patient has not developed or reported worsening depressive symptoms or suicidal ideation and behaviors

RATIONALE

Ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for brodalumab.

FDA APPROVED INDICATIONS

Siliq is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

DOsing & ADMINISTRATION

The recommended Siliq dose is 210 mg administered by subcutaneous injection at Weeks 0, 1, and 2, followed by 210 mg every 2 weeks.

CONTINUED ON NEXT PAGE
BRODALUMAB

FDA APPROVED INDICATIONS (CONTINUED)

If an adequate response has not been achieved after 12 to 16 weeks of treatment with Siliq, consider discontinuing therapy. Continued treatment beyond 16 weeks in patients who have not achieved an adequate response is not likely to result in greater success.

REFERENCES


Created: 04/17
Effective: 06/17/17
Client Approval: 04/25/17
P&T Approval: N/A
BUPRENORPHINE ANALGESICS

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<td>39959</td>
<td>39965 39966 39967 39968 39969 39975</td>
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<td>ROUTE = BUCCAL</td>
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<td>ROUTE = TRANSDERM</td>
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GUIDELINES FOR USE

RENEWAL CRITERIA will apply in the following scenarios only:

○ For patients active with MDwise for 90 days or longer AND previous prior authorization approval for the same medication with the same strength AND recent paid pharmacy claims for the requested medication. Chart notes and/or cash pay for opioid use is not accepted.

○ For patients new to MDwise within the past 90 days AND chart notes are provided that document the patient is stable on the requested medication.

All other requests will be reviewed against the INITIAL CRITERIA.

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline for BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) for patients with past use of opioid dependency agents (i.e., buprenorphine/naloxone SL tablets/films or buprenorphine SL tablets) requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid analgesic will be authorized.

Our guideline for BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) does not permit concurrent use with carisoprodol-containing products.

CONTINUED ON NEXT PAGE
Our guideline named BUPRENORPHINE ANALGESICS, reviewed for BUTRANS 5MCG/HR, requires that the opioid is requested for the treatment of moderate to severe pain and that ALL of the following criteria are met:

- Your provider submitted documentation of trial and failure of one non-drug treatment for pain (for example, thermotherapy, cryotherapy, massage therapy, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), physical therapy) for 6 weeks duration within the previous 2 years unless contraindicated.
- You have tried and failed TWO non-opioid drug treatments prescribed for pain from different drug classes (for example, NSAIDs, acetaminophen, anticonvulsants, antidepressants) at maximum therapeutic doses within the previous 365 days unless contraindicated or not tolerated. Chart notes documenting doses and dates of therapy are required in the absence of electronic prescription claim history.
- You have a documented Opioid Risk Tool score of 8 or higher.

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

Our guideline for BUPRENORPHINE ANALGESICS (BUTRANS 7.5MCG/HR, 10MCG/HR, 15MCG/HR, OR 20MCG/HR) requires that all patients meet ALL of the following criteria:

- You have a diagnosis of severe pain.
- You meet the definition of opioid tolerance [defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid].
  o Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted. For patients active with MDwise less than 90 days, chart notes are required to verify previous opioid use for this criterion.
- You have had a trial of at least 30 days generic MS Contin in the previous 120 days [NOTE: This requirement does not apply for BUTRANS requests in patients who have difficulty swallowing.]
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals.

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for BUPRENORPHINE ANALGESICS (BELBUCA) requires that all patients meet ALL of the following criteria:

- You have a diagnosis of severe pain
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals
- **ONE** of the following:
  - You have had a 14-day trial of Butrans (buprenorphine transdermal system)
  - **BOTH** of the following:
    - You have had a trial of at least 30 days generic MS Contin in the previous 120 days *(NOTE: This requirement does not apply for BELBUCA requests in patients who have difficulty swallowing.)*
    - Documentation of a current daily MME dose greater than 80mg and the prescriber's belief that the maximum dose of Butrans (20mcg/hour) will not provide adequate analgesia.

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

Our guideline named BUPRENORPHINE ANALGESICS for concurrent use of more than one long-acting opioid requires patients to meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You experience refractory pain (pain that continues or returns) despite concurrent therapy with one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan. Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

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INITIAL CRITERIA (CONTINUED)

Our guideline for BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
- The diagnosis contributing to the need for opioid analgesic therapy and previous therapy attempted, including dates and doses of prior therapies (if applicable). For a diagnosis of moderate to severe cancer-related pain, pain related to sickle cell disease, or pain in patients receiving palliative care, no additional criteria applies.
  - For long-acting opioid therapy requested for chronic moderate to severe pain, ALL of the following are required:
    ➢ You meet the definition of opioid tolerance (defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydrocodone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose (a dose of one pain medication that is the same in pain-relieving effects to that of another pain medication) of another opioid). Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted.
    ➢ Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals
    ➢ For any long-acting opioid other than MS Contin, you have had a trial of at least 30 days generic MS Contin in the previous 120 days
- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT (Indiana controlled substance monitoring program)
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the risk of using benzodiazepines and opioid analgesics together at the same time

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INITIAL CRITERIA (CONTINUED)

Our guideline for BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) for patients with claims in history for antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RENEWAL CRITERIA

Our guideline for BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) does not permit concurrent use with carisoprodol-containing products.

Our guideline named BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) for renewal of buprenorphine analgesic therapy requires patients to meet ALL of the following criteria:

- Opioid therapy has resulted in a meaningful improvement in your pain and/or function
- Your doctor has developed an updated pain management plan with clear treatment goals
- A risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (for example, INSPECT)
- Adherence to prescribed opioid regimen has been periodically assessed (for example, urine drug screen, pill counts)

In addition, requests for renewal of concurrent use of (used at the same time with) more than one long-acting opioid requires patients to meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You experience refractory pain (pain that continues or returns) despite concurrent therapy with (used at the same time with) one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan. Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
Our guideline for renewal of BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
- The diagnosis contributing to the need for renewal of the requested opioid analgesic therapy
- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT (Indiana controlled substance monitoring program)
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the risk of using benzodiazepines and opioid analgesics together at the same time

Our guideline for BUPRENORPHINE ANALGESICS (BUTRANS AND BELBUCA) for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RATIONALE
To ensure opioid analgesics are used according to FDA approved indications with patient safety in mind, and to encourage the use of more cost-effective analgesics.

From 2000-2014, almost half a million people died due to drug overdose, with 2014 being the highest year for deaths on record. In that time, the number of opioids prescribed, as well as the number of opioid overdoses, has risen exponentially. At least half of all opioid overdose deaths involve a prescription opioid. Indiana was among the states that had a statistically significant increase of overdose deaths from 2013-2014.

CONTINUED ON NEXT PAGE
BUPRENORPHINE ANALGESICS

RATIONALE (CONTINUED)

According to recent research, the opioid epidemic has a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed opioids at double the rate of non-Medicaid patients, and are subsequently at much higher risk of prescription opioid overdose. Improving the way that opioids are prescribed can ensure safer and more effective pain treatment, and reduce the addiction, misuse, abuse, and overdose of these drugs. These guidelines are to ensure that the use of opioids is consistent with their FDA approved indications, and to initiate action combating the current opioid epidemic.

When buprenorphine is used for analgesia, individualized dosing should be used for each patient. The patient’s opioid tolerance, physical and mental status, and degree of analgesia desired should be considered when initiating patients on buprenorphine treatment. Higher than usual doses may be required when buprenorphine is used in a patient tolerant to opioids. Careful titration of buprenorphine in opioid-naïve patients is required until tolerance develops to some of the side effects. Monitor patients frequently for respiratory depression, particularly during the first 24 to 72 hours after initiation and dose escalation. Patients who experience breakthrough pain may require a dosage increase or a rescue medication.

Transdermal buprenorphine should be reserved for patients in whom alternative treatment options (non-opioids or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide enough management of pain. Butrans potencies of 7.5 mcg/hr and higher should only be used for opioid experienced patients. There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids.

CONTINUED ON NEXT PAGE
Rationale (continued)

### Buprenorphine Conversion Table

<table>
<thead>
<tr>
<th>Buprenorphine Product</th>
<th>Oral MME Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belbuca buccal film (mcg/hr)</td>
<td>0.03</td>
</tr>
<tr>
<td>Buprenorphine, tablet or film for opioid use disorder</td>
<td>30</td>
</tr>
<tr>
<td>Butrans transdermal patch (mcg/hr)</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Example: 900 mcg buprenorphine buccal film x (60 films/30 days) x 0.03 = 54 MME/day
Example: 5 mcg buprenorphine patch x (4 patches/28 days) x 12.6 = 9 MME/day

### Methadone Conversion Table

<table>
<thead>
<tr>
<th>Methadone daily dose (mg/day)</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0, &lt;= 20</td>
<td>4</td>
<td>20mg</td>
</tr>
<tr>
<td>&gt;20, &lt;= 40</td>
<td>8</td>
<td>7.5mg</td>
</tr>
<tr>
<td>&gt;40, &lt;= 60</td>
<td>10</td>
<td>6mg</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>5mg</td>
</tr>
</tbody>
</table>

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 25mcg transdermal fentanyl/hour, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid for a week or longer.

### Opioid Conversion Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butorphanol</td>
<td>7</td>
<td>8.5mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
<td>400mg</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>0.12</td>
<td>0.5mg (500mcg)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Hydromorphone HCl</td>
<td>4</td>
<td>15mg</td>
</tr>
<tr>
<td>Meperidine HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
<td>1.5</td>
<td>40mg</td>
</tr>
<tr>
<td>Oxymorphine HCl</td>
<td>3</td>
<td>20mg</td>
</tr>
<tr>
<td>Pentazocine HCl</td>
<td>0.37</td>
<td>162mg</td>
</tr>
<tr>
<td>Tapentadol HCl</td>
<td>0.4</td>
<td>150mg</td>
</tr>
<tr>
<td>Tramadol HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
</tbody>
</table>

Continued on next page
Rationale (Continued)

Opioid Usage in Chronic Pain Management

Per systematic review in the CDC Guideline for Prescribing Opioids for Chronic Pain, long-term (> 1 year) efficacy of opioids in management of chronic pain, function, or quality of life is not established. Most randomized controlled trials present effectiveness within 6 weeks or less. Conversely, significant risks of adverse events are present with chronic opioid therapy, including opioid abuse and dependence, social role withdrawal, and increased risk of CNS depression, and withdrawal emergencies.

The CDC also recommends re-evaluating and re-establishing treatment goals, including realistic expectation for pain and function, as well as discontinuation strategies when benefits do not outweigh risks. The guideline provides the following recommendations for opioid selection, dosage, duration, follow-up and discontinuation:

- Immediate-release (IR) opioids are preferred over extended-release (ER) forms.
- The lowest effective dosage is preferred with initial opioid use. Caution is warranted at any dose and reassessing benefits and risks is recommended for 50 morphine milligram equivalents (MME) daily or more. 90 MME daily or more should be avoided if possible.
- Within 1 to 4 weeks of therapy, clinicians should evaluate benefits and harms of using opioids to treat chronic pain. Therapy continuation should be evaluated every 3 months or sooner. If benefits do not outweigh harms to continue opioid therapy, other therapies should be optimized and opioid tapering/discontinuation should be considered and encouraged.

Assessing Risk and Addressing Harms of Opioid Use

- Prior to and throughout opioid therapy, adverse events should be evaluated periodically. Factors that increase risk for opioid overdose include history of overdose or substance use disorder, 50 MME daily or more, and concurrent benzodiazepine use.
- Prescription drug monitoring program (PDMP) data (e.g., RXINSPECT) are useful to monitor total opioid dosage. PDMP data is helpful for initial and periodic opioid usage evaluations.
- Prescribing opioids and benzodiazepines concurrently should be avoided.
- For patients with substance use disorder, evidence-based treatment (medication-assisted and behavioral therapy) is recommended.

Analysis performed by the US Department of Health and Human Services Center for Disease Control and Prevention (CDC) determined the risk of harm to individuals increases as their opioid dose increases and as their length of opioid therapy increases. For example:

- Individuals taking opioid doses > 50 morphine milligram equivalents (MMEs) per day had twice the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking opioid doses > 90 (MMEs) per day had 10 times the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking an opioid for > 3 months (even at low doses) had 15 times the risk of addiction to those taking opioids for < 3 months.

CONTINUED ON NEXT PAGE
RATIONALe (CONTINUED)
The Opioid Risk Tool (ORT) is a brief, self-report screening tool designed for use with adult patients in primary care settings to assess risk for opioid abuse among individuals prescribed opioids for treatment of chronic pain. Patients categorized as high-risk are at increased likelihood of future abusive drug-related behavior.

Opioid Risk Tool
This tool should be administered to patients upon an initial visit prior to beginning opioid therapy for pain management. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse.

Mark each box that applies:

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rx drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Personal history of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Rx drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Age between 16—45 years</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>History of preadolescent sexual abuse</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychological disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADD, OCD, bipolar, schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Scoring totals</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 1: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM

INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY
PRIOR AUTHORIZATION REQUEST FORM

Today’s Date

Note: This form must be completed by the prescribing provider.
**All sections must be completed or the request will be denied.**

<table>
<thead>
<tr>
<th>Patient's Medicaid #</th>
<th>Date of Birth</th>
<th>Patient’s Name</th>
<th>Prescriber’s Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber’s IN License #</td>
<td>Prescriber’s Specialty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriber’s NPI #</td>
<td>Prescriber’s Signature: <strong>Required below within attestation section.</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Return Fax # Return Phone #

PA is required for the following:
- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).

<table>
<thead>
<tr>
<th>Benzodiazepine Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### MDwise MANAGED MEDICAID
### PRIOR AUTHORIZATION GUIDELINES

<table>
<thead>
<tr>
<th>Opioid Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:

- Are you requesting PA for:  
  - Benzodiazepine Agent(s) □
  - Opioid Agent(s) □
  - Both □

- Is/are the other prescriber(s) aware of the request for concurrent therapy? □ Yes □ No
- Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? □ Yes □ No

### PA Requirements:

**Patient diagnosis/diagnoses for use of benzodiazepine therapy:**

Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you plan to continue benzodiazepine therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

**Patient diagnosis/diagnoses for use of opioid therapy:**

Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, ____________________________, hereby attest to the following:

(Prescriber Name)
• The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
• I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
• If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
• I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber Signature: ____________________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**

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REFERENCES


CONTINUED ON NEXT PAGE
REFERENCES (CONTINUED)

- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).
GUIDELINES FOR USE

** Please use the criteria for the specific drug requested **

PROBUPHINE:

Our guideline for **BUPRENORPHINE IMPLANT (PROBUPHINE)** requires patients to be 16 years of age or older; the physician meets all qualifications (Federal, State, Local) to prescribe buprenorphine or buprenorphine/naloxone; a diagnosis of opioid dependence; the patient has not been previously treated with Probuphine; the patient has achieved and sustained prolonged clinical stability on transmucosal buprenorphine; the patient is currently on a maintenance dose of 8 mg per day or less of a buprenorphine-containing sublingual tablet or its transmucosal buprenorphine product equivalent; the patient has been on the maintenance dose (8 mg per day or less of a buprenorphine-containing sublingual tablet or its transmucosal buprenorphine product equivalent) for three months or longer without any need for supplemental dosing or adjustments; and medical justification supports inability to continue to use oral (e.g., sublingual, buccal) formulations of buprenorphine.

SUBLOCADE:

Our guideline for **BUPRENORPHINE INJECTION (SUBLOCADE)** requires patients to be 18 years of age or older; the physician meets all qualifications (Federal, State, Local) to prescribe buprenorphine or buprenorphine/naloxone; a diagnosis of opioid dependence; the patient is currently on a maintenance dose of 8 to 24 mg per day of a buprenorphine-containing sublingual tablet or its transmucosal buprenorphine product equivalent for 7 days or longer; medical justification supports inability to continue to use oral (e.g., sublingual, buccal) formulations of buprenorphine; and dose does not exceed 300 mg buprenorphine per month.
RATIONAL

FDA APPROVED INDICATIONS

- Probuphine is a partial opioid agonist indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of buprenorphine-containing sublingual tablet or generic equivalent).
- Sublocade is a partial opioid agonist indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.

Probuphine and Sublocade should be used as part of a complete treatment program to include counseling and psychosocial support.

Probuphine and Sublocade are not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet or generic equivalent.

Use of these products is limited under the Drug Addiction Treatment Act.

DOSAGE AND ADMINISTRATION

- Probuphine implant
  - Four Probuphine implants are inserted subdermally in the upper arm for 6 months of treatment and are removed by the end of the sixth month.
  - Probuphine implants should not be used for additional treatment cycles after one insertion in each upper arm.
  - Probuphine implants must be inserted and removed by trained Healthcare Providers only.
  - Probuphine implants should be administered in patients who have achieved and sustained prolonged clinical stability on transmucosal buprenorphine.

- Sublocade injection
  - The recommended dose of Sublocade following induction and dose adjustment with transmucosal buprenorphine is 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly.
  - The maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use.
  - Only health care providers should prepare and administer Sublocade.
  - Sublocade is for abdominal subcutaneous injection only.
  - Administer Sublocade monthly with a minimum of 26 days between doses.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

Table 1: Brand/Generic Transmucosal Formulations Equivalent to Subutex or Suboxone SL Tablets Containing less than or equal to 8 mg of Buprenorphine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Transmucosal Formulation</th>
<th>Brand/Generic</th>
<th>Brand/ Generic Strength</th>
<th>Subutex/Suboxone SL Tablet Strength</th>
<th>Buprenorphine/Naloxone Equivalency</th>
</tr>
</thead>
<tbody>
<tr>
<td>buprenorphine HCl</td>
<td>Tablet, SL</td>
<td>generic</td>
<td>2 mg</td>
<td>2 mg (Subutex)</td>
<td>2 mg (Subutex)</td>
</tr>
<tr>
<td>buprenorphine HCl/naloxone HCl</td>
<td>Tablet, SL</td>
<td>generic</td>
<td>2 mg/0.5 mg</td>
<td>2 mg/0.5 mg (Suboxone)</td>
<td>2 mg/0.5 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 mg/2 mg</td>
<td>8 mg/2 mg (Suboxone)</td>
<td>8 mg/2 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zubsvol</td>
<td>1.4 mg/0.36 mg</td>
<td>2 mg/0.5 mg (Suboxone)</td>
<td>2 mg/0.5 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.9 mg/0.71 mg</td>
<td>4 mg/1 mg (Suboxone)</td>
<td>4 mg/1 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.7 mg/1.4 mg</td>
<td>8 mg/2 mg (Suboxone)</td>
<td>8 mg/2 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Film, buccal</td>
<td>2.1 mg/0.3 mg</td>
<td>4 mg/1 mg (Suboxone)</td>
<td>4 mg/1 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.2 mg/0.7 mg</td>
<td>8 mg/2 mg (Suboxone)</td>
<td>8 mg/2 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Film, SL or buccal</td>
<td>2 mg/0.5 mg</td>
<td>2 mg/0.5 mg (Suboxone)</td>
<td>2 mg/0.5 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg/1 mg</td>
<td>4 mg/1 mg (Suboxone)</td>
<td>4 mg/1 mg (Suboxone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 mg/2 mg</td>
<td>8 mg/2 mg (Suboxone)</td>
<td>8 mg/2 mg (Suboxone)</td>
</tr>
</tbody>
</table>

Table 2: Therapeutic Alternatives
This table provides a listing of alternative therapies for opioid dependence. Generic sublingual tablets are preferred.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>buprenorphine/naloxone (Suboxone) sublingual (SL) or buccal dissolving film, SL tablet</td>
<td>Maintenance: Target dose buprenorphine 16 mg/naloxone 4 mg once daily; dosage should be adjusted in increments or decrements of 2 mg/ 0.5 mg or 4 mg/1 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms; usual range: 4 mg/1 mg to 24 mg/6 mg per day</td>
<td>24 mg/6 mg per day</td>
</tr>
<tr>
<td>Bunavail® (buprenorphine/naloxone) buccal film</td>
<td>Maintenance: Target dose buprenorphine 8.4 mg/naloxone 1.4 mg once daily; dosage should be adjusted in increments or decrements of 2.1 mg/ 0.3 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms; usual range: 2.1 mg/0.3 mg to 12.6 mg/2.1 mg per day</td>
<td>12.6 mg/2.1 mg per day</td>
</tr>
<tr>
<td>Zubsolv® (buprenorphine/naloxone) SL tablet</td>
<td>Maintenance: Target dose buprenorphine 11.4 mg/naloxone 2.9 mg once daily; dosage should be adjusted in increments or decrements of 2.9 mg/ 0.71 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms; usual range: 2.9 mg/0.71 mg to 17.2 mg/4.2 mg per day</td>
<td>17.1 mg/4.2 mg per day</td>
</tr>
</tbody>
</table>
REFERENCES


Created: 05/18
Effective: 06/01/18
Client Approval: 05/04/18
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for **BUPRENORPHINE-NALOXONE** requires that Suboxone film, Zubsolv sublingual tablets, or Bunavail film may be approved for patients that have a hypersensitivity reaction to an inactive ingredient in generic buprenorphine/naloxone tablets if the hypersensitivity reaction is clearly documented in the patient's medical record. Suboxone film, Zubsolv sublingual tablets, or Bunavail film may also be approved for patients that have failed an adequate trial of generic buprenorphine/naloxone tablets (an adequate trial is defined as at least 28 days of treatment) in the previous 120 days (verified in prescription claims history or in submitted chart notes) and are unable to use generic buprenorphine/naloxone tablets due to therapeutic failure or adverse outcome. Approval for Suboxone Film, Zubsolv sublingual tablets, or Bunavail Film requires documentation of therapeutic failure or adverse outcome associated with the use of the generic buprenorphine/naloxone tablets and requires a copy of the MedWatch form submitted to the FDA. Suboxone film, Zubsolv sublingual tablets, or Bunavail film will not be approved for patients who report lesser efficacy with the generic buprenorphine/naloxone tablets unless it would be clinically inappropriate to address efficacy with dose adjustment. Please note that generic buprenorphine/naloxone SL tablets do not require prior authorization.

CONTINUED ON NEXT PAGE
BUPRENEORPHINE-NALOXONE

RATIONALE
The intent of this prior authorization criteria is to encourage the use of cost-effective preferred generic medications before considering coverage of brand medications.

NOTES
- GI upset or irritation is not generally considered an allergy or failed treatment. Patients should be referred to their physician or pharmacist for advice on dose adjustment, and/or other options to reduce GI upset/irritation.
- Common documented side effects attributed to buprenorphine/naloxone (e.g., headache, nausea, blurred vision, fatigue, muscle aches) are not considered an allergy and would be expected to occur at the same level in both generic and brand agents.
- Drug hypersensitivity symptoms may include skin rash, hives, itching, fever, swelling, shortness of breath, wheezing, runny nose, itchy and/or watery eyes, and in severe cases, anaphylaxis.

REFERENCE
GUIDELINES FOR USE

RENEWAL CRITERIA will apply in the following scenarios only:

- For patients active with MDwise for 90 days or longer AND previous prior authorization approval for the same medication with the same strength AND recent paid pharmacy claims for the requested medication. Chart notes and/or cash pay for opioid use is not accepted.
- For patients new to MDwise within the past 90 days AND chart notes are provided that document the patient is stable on the requested medication.

All other requests will be reviewed against the INITIAL CRITERIA.

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline for BUTALBITAL/CODEINE-CONTAINING AGENTS FOR HEADACHE for patients with past use of opioid dependency agents (such as, buprenorphine/naloxone SL tablets/films or buprenorphine SL tablets) requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid analgesic will be authorized.

Our guideline for BUTALBITAL/CODEINE-CONTAINING AGENTS FOR HEADACHE does not permit concurrent use with carisoprodol-containing products.

Our guideline for BUTALBITAL/CODEINE-CONTAINING AGENTS FOR HEADACHE requires a diagnosis of tension-type headaches (TTH). In addition, documentation of trial and failure of ALL of the following for TTH is required unless contraindicated:

- Acetaminophen
- Aspirin
- Non-steroidal anti-inflammatory agent (NSAID) (for example, ibuprofen, naproxen)
- Combination therapy of caffeine plus any one of the three aforementioned agents (for example, caffeine/acetaminophen, caffeine/aspirin, caffeine/NSAID)

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for BUTALBITAL/CODEINE-CONTAINING AGENTS FOR HEADACHE for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)

- A diagnosis of tension-type headache (TTH) and documentation of trial and failure of ALL of the following for TTH is required unless contraindicated:
  - Acetaminophen
  - Aspirin
  - Non-steroidal anti-inflammatory agent (NSAID) (for example, ibuprofen, naproxen)
  - Combination therapy of caffeine plus any one of the three aforementioned agents (for example, caffeine/acetaminophen, caffeine/aspirin, caffeine/NSAID)

- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT (Indiana controlled substance monitoring program)
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the risk of using benzodiazepines and opioid analgesics together at the same time

Our guideline for BUTALBITAL/CODEINE-CONTAINING AGENTS FOR HEADACHE for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE (CONTINUED)

Our guideline for BUTALBITAL/CODEINE-CONTAINING AGENTS FOR HEADACHE for concurrent use of more than one short-acting opioid requires that you meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You have a pain that is not responding to treatment despite concurrent (used at the same time) therapy with one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan.

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

RENEWAL CRITERIA

Our renewal guideline for BUTALBITAL/CODEINE-CONTAINING AGENTS FOR HEADACHE requires patients to meet ALL of the following criteria:

- Opioid therapy has resulted in a meaningful improvement in your pain and/or function
- Your prescriber has developed an updated pain management plan with clear treatment goals
- Risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (for example, INSPECT)
- Adherence to prescribed opioid regimen has been periodically assessed (for example, urine drug screen, pill counts)

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA

Our renewal guideline for BUTALBITAL/ CODEINE-CONTAINING AGENTS FOR HEADACHE for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
- A diagnosis of tension-type headache (TTH) and previous therapy attempted
- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the of using benzodiazepines and opioid analgesics together at the same time

Our guideline for BUTALBITAL/ CODEINE-CONTAINING AGENTS FOR HEADACHE for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

CONTINUED ON NEXT PAGE
Rationale
To ensure opioid analgesics are used according to FDA approved indications with patient safety in mind, and to encourage the use of more cost-effective analgesics.

From 2000-2014, almost half a million people died due to drug overdose, with 2014 being the highest year for deaths on record. In that time, the number of opioids prescribed, as well as the number of opioid overdoses, has risen exponentially. At least half of all opioid overdose deaths involve a prescription opioid. Indiana was among the states that had a statistically significant increase of overdose deaths from 2013-2014.

According to recent research, the opioid epidemic has a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed opioids at double the rate of non-Medicaid patients, and are subsequently at much higher risk of prescription opioid overdose.

Improving the way that opioids are prescribed can ensure safer and more effective pain treatment, and reduce the addiction, misuse, abuse, and overdose of these drugs. These guidelines are to ensure that the use of opioids is consistent with their FDA approved indications, and to initiate action combating the current opioid epidemic.

Assessing Risk and Addressing Harms of Opioid Use
• Prior to and throughout opioid therapy, adverse events should be evaluated periodically. Factors that increase risk for opioid overdose include history of overdose or substance use disorder, 50 MME daily or more, and concurrent benzodiazepine use.
• Prescription drug monitoring program (PDMP) data (e.g., RXINSPECT) are useful to monitor total opioid dosage. PDMP data is helpful for initial and periodic opioid usage evaluations.
• Prescribing opioids and benzodiazepines concurrently should be avoided.
• For patients with substance use disorder, evidence-based treatment (medication-assisted and behavioral therapy) is recommended.

Analysis performed by the US Department of Health and Human Services Center for Disease Control and Prevention (CDC) determined the risk of harm to individuals increases as their opioid dose increases and as their length of opioid therapy increases. For example:
• Individuals taking opioid doses > 50 morphine milligram equivalents (MMEs) per day had twice the risk of death from an overdose than those taking < 20 MMEs per day.
• Individuals taking opioid doses > 90 (MMEs) per day had 10 times the risk of death from an overdose than those taking < 20 MMEs per day.
• Individuals taking an opioid for > 3 months (even at low doses) had 15 times the risk of addiction to those taking opioids for < 3 months.

CONTINUED ON NEXT PAGE
APPENDIX 1: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM

INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY
PRIOR AUTHORIZATION REQUEST FORM

Today's Date

Note: This form must be completed by the prescribing provider.
**All sections must be completed or the request will be denied.**

<table>
<thead>
<tr>
<th>Patient’s Medicaid #</th>
<th>Date of Birth / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Name</td>
<td>Prescriber’s Name</td>
</tr>
<tr>
<td>Prescriber’s IN License #</td>
<td>Specialty</td>
</tr>
<tr>
<td>Prescriber’s NPI #</td>
<td>Prescriber's Signature: <strong>Required below within attestation section.</strong></td>
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<tr>
<td>Return Fax #</td>
<td>Return Phone #</td>
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PA is required for the following:
- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).

<table>
<thead>
<tr>
<th>Benzodiazepine Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
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</tbody>
</table>
### MDwise MANAGED MEDICAID
### PRIOR AUTHORIZATION GUIDELINES

<table>
<thead>
<tr>
<th>Opioid Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
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*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:
- Are you requesting PA for: Benzodiazepine Agent(s) ☐ Opioid Agent(s) ☐ Both ☐
- Is/are the other prescriber(s) aware of the request for concurrent therapy? ☐ Yes ☐ No
- Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? ☐ Yes ☐ No

### PA Requirements:

**Patient diagnosis/diagnoses for use of benzodiazepine therapy:**

**Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):**

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
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Do you plan to continue benzodiazepine therapy for this patient? ☐ Yes ☐ No
If no, please provide withdrawal plan:

**Patient diagnosis/diagnoses for use of opioid therapy:**

**Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):**

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
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</table>
MDwise MANAGED MEDICAID
PRIOR AUTHORIZATION GUIDELINES

Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, ____________________________________________, hereby attest to the following:

(Prescriber Name)

• The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
• I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
• If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
• I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber
Signature:____________________________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**

CONFIDENTIAL INFORMATION
This facsimile transmission (and attachments) may contain protected health information from the Indiana Health Coverage Programs (IHCP), which is intended only for the use of the individual or entity named in this transmission sheet. Any unintended recipient is hereby notified that the information is privileged and confidential, and any use, disclosure, or reproduction of this information is prohibited.
REFERENCES

- Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016; 65(1);1-49. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

CONTINUED ON NEXT PAGE
REFERENCES (CONTINUED)

- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).

Created: 09/19
Effective: 11/08/19
Client Approval: 10/14/19
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Our guideline for C1 ESTERASE INHIBITOR (Berinert, Cinryze, Haegarda, or Ruconest) requires a diagnosis of hereditary angioedema (HAE) and the requested agent must be prescribed by or given in consultation with a hematologist or allergist/immunologist.

RATIONALE

To ensure the appropriate use of Berinert, Cinryze, Haegarda, and Ruconest in patients with hereditary angioedema (HAE).

FDA APPROVED INDICATIONS

Berinert:
- Is a plasma-derived C1 esterase inhibitor (human) indicated for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema in adult and adolescent patients.
- The safety and efficacy of Berinert for prophylactic therapy have not been established.

Cinryze:
- Is a C1 inhibitor indicated for routine prophylaxis against angioedema in adolescent and adult patients with hereditary angioedema.

Haegarda:
- Is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

Ruconest:
- Is indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE).
- Limitation of use: Effectiveness was not established in HAE patients with laryngeal attacks.

DOSAGE

Berinert
The dose is 20 International Units (IU) per kg body weight by intravenous injection. Doses lower than 20 IU/kg body weight should not be administered. Each Berinert vial containing 500 IU of C1 esterase inhibitor as a lyophilized concentrate for reconstitution with 10 mL of Sterile Water for Injection.

Cinryze
A dose of 1,000 Units can be administered every 3 or 4 days for routine prophylaxis against angioedema attacks in HAE patients. Cinryze is administered at an injection rate of 1 mL per minute. To obtain the required dose, reconstitute two Cinryze vials with two vials Sterile Water for Injection, USP (5 mL each) using aseptic sterile technique.

Haegarda
Haegarda is intended for self-administration after reconstitution at a dose of 60 International Units (IU) per kg body weight by subcutaneous (S.C.) injection twice weekly (every 3 or 4 days). The patient or caregiver should be trained on how to administer Haegarda. Administer at room temperature within 8 hours after reconstitution. For subcutaneous use after reconstitution only.

Ruconest
The dose is 50 IU/kg for patients less than 84 kg, or 4200 IU for patients that weigh 84 kg or more. Each vial (2100 IU) should be reconstituted by adding 14mL of sterile water for injection to obtain a solution of 150 IU/mL. After reconstitution the dose can be administered as a slow intravenous injection over 5 minutes. If appropriately trained, patients may self-administer the dose as needed upon recognition of an HAE attack. No more than two doses should be administered within a 24- hour period, and no more than 4200 IU per dose should be administered.

REFERENCES
GUIDELINES FOR USE

COMETRIQ
The guideline for CABOZANTINIB S-MALATE (Cometriq) requires a diagnosis of progressive, metastatic medullary thyroid cancer (MTC).

CABOMETYX
The guideline for CABOZANTINIB S-MALATE (Cabometyx) requires a diagnosis of advanced renal cell carcinoma (RCC).

RATIONALE
Ensure appropriate utilization of Cometriq based on FDA approved indication.

FDA APPROVED INDICATIONS
Cometriq
- Is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).
- Cometriq has a boxed warning for increased occurrence of gastrointestinal perforations, fistula formation, and severe hemorrhage. Warnings and precautions include; thrombotic events, wound complications, hypertension, osteonecrosis of the jaw, palmar-planter erythrodysesthesia syndrome (PPES), proteinuria, and reversible posterior leukoencephalopathy syndrome (RPLS).
- Cometriq is available only through a limited distribution network.

Cabometyx
- Is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC)
- Unlike Cometriq, Cabometyx does not have a boxed warning for GI perforations and fistulas, nor severe hemorrhage; however those reactions are listed as warnings and precautions. Similar to Cometriq, Cabometyx also carries warnings and precautions for thrombotic events (e.g., myocardial infarction, cerebral infarction), hypertensive crisis and hypertension, palmar-planter erythrodysesthesia syndrome (PPES), reversible posterior leukoencephalopathy syndrome (RPLS), and embryo-fetal toxicity. Cabometyx also carries a warning for severe diarrhea.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Cometriq
The recommended daily dose of Cometriq is 140mg (one 80mg and three 20mg capsules). Patients should not to eat for at least 2 hours before and at least 1 hour after taking Cometriq. The daily dose of Cometriq should not exceed 180mg.

For patients who require treatment with a strong CYP3A4 inhibitor, reduce the daily Cometriq dose by 40 mg. Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor. For patients who require treatment with a strong CYP3A4 inducer, increase the daily Cometriq dose by 40mg as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer.

Dosage reduction recommended to 100mg and then 60mg in the presence of NCI CTCAE Grade 4 hematologic adverse reactions, Grade 3 or greater non-hematologic adverse reactions or intolerable Grade 2 adverse reactions. Continue treatment until disease progression or unacceptable toxicity occurs.

Cabometyx
The recommended dosage for Cabometyx is 60mg daily. Patients should not eat for at least 2 hours before and at least 1 hour after taking Cabometyx. Daily dose of Cabometyx should not exceed 80mg.

Patients concurrently taking a strong CYP3A4 inhibitor should reduce the dose by 20mg. In those concurrently taking a strong CYP3A4 inducer, the Cabometyx dose should be increased by 20mg.

In patients with mild to moderate hepatic impairment the starting dose of Cabometyx is 40 mg. Cabometyx therapy should be held at least 28 days prior to surgery, including dental surgery.

If the patient develops Grade 4 reactions, or Grade 2 or 3 reactions that cannot be managed with supportive care, the drug should be held until return to baseline or resolution to Grade 1. At that time, Cabometyx should be re-initiated at 20mg less than previous regimen. Those previously on 20mg should resume at 20mg if tolerated. Continue treatment until the patient no longer experiences clinical benefit or experiences unacceptable toxicity.

REFERENCES
GUIDELINES FOR USE

The guideline named CAPLACIZUMAB-YHDP (Cablivi) requires a diagnosis of acquired thrombotic thrombocytopenia purpura (aTTP). In addition, the following criteria must be met.

- The patient is 18 years of age or older
- The patient is continuing a regimen of Cablivi that was previously initiated as part of the FDA approved treatment regimen in combination with plasma exchange and immunosuppressive therapy

RATIONALE

For further information, please refer to the Prescribing Information for Cablivi.

INDICATION

CABLIVI is a von Willebrand factor (vWF)-directed antibody fragment indicated for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.

DOSAGE AND ADMINISTRATION

CABLIVI should be administered upon the initiation of plasma exchange therapy. The recommended dose of CABLIVI is as follows:

- First day of treatment: 11 mg bolus intravenous injection at least 15 minutes prior to plasma exchange followed by an 11 mg subcutaneous injection after completion of plasma exchange on day 1.
- Subsequent treatment during daily plasma exchange: 11 mg subcutaneous injection once daily following plasma exchange.
- Treatment after the plasma exchange period: 11 mg subcutaneous injection once daily for 30 days beyond the last plasma exchange.
- If after initial treatment course, sign(s) of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.
- Discontinue CABLIVI if the patient experiences more than 2 recurrences of aTTP, while on CABLIVI.

The first dose should be administered by a healthcare provider as a bolus intravenous injection. Administer subsequent doses subcutaneously in the abdomen.

REFERENCE


Created: 04/19
Effective: 05/20/19
Client Approval: 04/04/19
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires supervision by a rheumatologist; a diagnosis of Cryopyrin-Associated Periodic Syndromes (CAPS) such as Familial Cold Autoinflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS) and that the patient is at least 4 years of age; or a diagnosis of Active Systemic Juvenile Idiopathic Arthritis (SJIA) and that the patient is at least 2 years of age; or a diagnosis of Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), or Familial Mediterranean Fever (FMF).

RATIONALE

Ensure appropriate use for canakinumab.

Dosage

Cryopyrin-Associated Periodic Syndromes
150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight ≥ 15 kg and ≤ 40 kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. Administer subcutaneously every 8 weeks.

Systemic Juvenile Idiopathic Arthritis (SJIA)
4 mg/kg (with a maximum of 300 mg) for patients with a body weight ≥ 7.5 kg. Administer subcutaneously every 4 weeks.

Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF)
2 mg/kg for patients with a body weight ≤ 40 kg. If clinical response is not adequate, the dose can be increased to 4 mg/kg. Administer subcutaneously every 4 weeks.
150 mg for patients with a body weight > 40 kg. If clinical response is not adequate, the dose can be increased to 300 mg. Administer subcutaneously every 4 weeks.

FDA APPROVED INDICATIONS

Iloris is an interleukin-1β blocker indicated for the treatment of:

• Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:
  o Familial Cold Autoinflammatory Syndrome (FCAS)
  o Muckle-Wells Syndrome (MWS)
• Active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older
• Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)
• Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)
• Familial Mediterranean Fever (FMF)
REFERENCES


Created: 10/15
Effective: 06/17/17
Client Approval: 05/19/17
P&T Approval: 10/15
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline named CANNABIDIOL (Epidiolex) requires a diagnosis of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome. In addition, the following criteria must be met:

For the diagnosis of seizures associated with Dravet syndrome, approval requires:
- The patient is 2 years of age or older
- Therapy is prescribed by or in consultation with a neurologist
- The patient has had a trial of or contraindication to TWO of the following: clobazam (tablet or suspension), a valproic acid derivative product, or topiramate

For the diagnosis of seizures associated with Lennox-Gastaut syndrome, approval requires:
- The patient is 2 years of age or older
- Therapy is prescribed by or in consultation with a neurologist
- The patient has had a trial of or contraindication to clobazam (tablet or suspension) AND either topiramate or lamotrigine

RATIONAL
For further information please refer to the Prescribing Information for Epidiolex.

REFERENCES

Created: 12/18
Effective: 01/21/19
Client Approval: 12/20/18
P&T Approval: N/A
CAPECITABINE

<table>
<thead>
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<td>CAPECITABINE</td>
<td>XELODA</td>
<td>18385</td>
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GUIDELINES FOR USE

Our guideline for approval of CAPECITABINE requires a diagnosis of Stage III (Duke’s C) colon cancer; or a diagnosis of metastatic colorectal cancer (mCRC) and that is Xeloda being used in combination with oxaliplatin (CapeOX or XELOX regimen) or as a monotherapy; or a diagnosis of metastatic breast cancer and that Xeloda is being used as monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen or is being used in combination with docetaxel after failure of prior anthracycline-containing therapy. The required therapies may require a prior authorization and may be covered under the medical benefit.

CAPECITABINE

RATIONALE
To ensure appropriate use of Xeloda consistent with FDA approved indication and NCCN guidelines.

Xeloda (capecitabine) which is the pro-drug of 5-fluorouracil (5-FU), is administered orally with food. The daily dose is 2500mg/m² given in two divided doses approximately 12 hours apart at the end of a meal. Individual doses will vary by patient based on the body surface area. Xeloda is approved as first-line monotherapy for mCRC when treatment with fluoropyrimidine therapy alone is preferred and as adjuvant therapy for patients with Stage III (Duke’s C) colon cancer. It is also FDA approved for the treatment of breast cancer and has demonstrated efficacy in several other cancers.

Table 1 XELODA Dose Calculation According to Body Surface Area

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Total Daily Dose* (mg)</th>
<th>150 mg</th>
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<tr>
<td>≤ 1.25</td>
<td>3000</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1.26-1.37</td>
<td>3300</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>1.38-1.51</td>
<td>3600</td>
<td>2</td>
<td>3</td>
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<tr>
<td>1.52-1.65</td>
<td>4000</td>
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<td>4</td>
</tr>
<tr>
<td>1.66-1.77</td>
<td>4300</td>
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<td>4</td>
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<tr>
<td>1.78-1.91</td>
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<td>4</td>
</tr>
<tr>
<td>1.92-2.05</td>
<td>5000</td>
<td>0</td>
<td>5</td>
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<tr>
<td>2.06-2.17</td>
<td>5300</td>
<td>1</td>
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<tr>
<td>≥ 2.18</td>
<td>5600</td>
<td>2</td>
<td>5</td>
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</table>

*Total Daily Dose divided by 2 to allow equal morning and evening doses

CONTINUED ON NEXT PAGE
CAPECITABINE

RATIONALE (CONTINUED)

Surgical removal is the preferred treatment for early stage disease. Surgery is accompanied by adjuvant chemotherapy for patients with high-risk features or more extensive cancer involvement.

Primary treatment options for resectable synchronous metastases are:
- Chemotherapy (FOLFIRI, FOLFOX, or CapeOX) with or without Avastin
- Chemotherapy (FOLFIRI or FOLFOX) with or without Vectibix (KRAS wild-type patients only)
- Chemotherapy (FOLFIRI) with or without Erbitux (KRAS wild-type patients only)
- Staged resection
- Infusional IV 5-FU with radiation

Primary treatment options for unresectable metachronous metastases previously treated with adjuvant FOLFOX are:
- FOLFIRI with or without Avastin
- FOLFIRI with or without Zaltrap
- Irinotecan with or without Avastin
- Irinotecan with or without Zaltrap
- FOLFIRI or irinotecan with Erbitux or Vectibix (KRAS wild-type patients only)

Initial therapy options for treatment of mCRC in patients appropriate for intensive therapy are:
- FOLFOX, with or without Avastin
- FOLFOX, with or without Vectibix (KRAS wild-type patients only)
- CapeOX with or without Avastin
- FOLFIRI with or without Avastin
- FOLFIRI with our without Erbitux or Vectibix (KRAS wild-type patients only)
- 5-FU/leucovorin or Xeloda with or without Avastin
- FOLFOXIRI

Initial therapy options for treatment of mCRC in patients not appropriate for intensive therapy are:
- Infusional 5-FU with leucovorin or Xeloda with or without Avastin
- Erbitux (KRAS wild-type patients only)
- Vectibix (KRAS wild-type patients only)

Zaltrap in combination with FOLFIRI is a recommended therapeutic regimen following progression of mCRC after an oxaliplatin containing chemotherapy regimen. Stivarga is considered a treatment option in therapy after first, second, or third progression, depending on previous lines of therapy.

CONTINUED ON NEXT PAGE
CAPECITABINE

RATIONALE (CONTINUED)

Other treatment options after first or second progression include:

- Erbitux or Vectibix with irinotecan (KRAS wild-type patients only)
- FOLFOX, FOLFIRI, CapeOX, or irinotecan with or without Avastin
- Irinotecan and oxaliplatin with or without Avastin

The Xeloda prescribing information contains one study (X-ACT) supporting its use in the adjuvant setting for patients with Stage III (Duke's C) colon cancer. A total of 1987 patients were randomized to Xeloda or 5-FU/LV. With a median follow-up of 6.9 years, Xeloda was at least equivalent to 5-FU/LV in terms of disease free survival and OS.

There were two pivotal trials of identical design that evaluated Xeloda as a first line treatment for mCRC. The first trial by Hoff randomized a total of 605 patients to treatment with either Xeloda or 5-FU/LV. The Xeloda treated patients experienced a higher overall objective tumor response rate than the 5-FU/LV patients (24.8% vs. 15.5%). The median time to disease progression (4.3 vs. 4.7 months) and median OS (12.5 vs. 13.3) were similar between treatment arms. Quality of life data was not reported. (32) The second trial led by Van Cutsem included 602 patients. The Xeloda treated patients experienced similar overall response rates (18.9% vs. 15.0%), median time to disease progression (5.2 vs. 4.7 months) and OS (13.2 vs. 12.1 months) as the 5-FU/LV group.

Later the XELOX-1 (Study NO16966) trial investigated Xeloda as a first line treatment in combination with oxaliplatin (XELOX) compared to FOLFOX-4. The trial was later amended to include Avastin resulting in four treatment arms: XELOX vs. FOLFOX-4, with either Avastin or placebo. OS was 19.8 months in the pooled XELOX/XELOX placebo/ XELOX Avastin arms vs. 19.5 months in the pooled FOLFOX4/FOLFOX4-placebo/FOLFOX4-Avastin. In the pooled XELOX/XELOX-placebo arms, median OS was 19.0 vs. 18.9 months in the pooled FOLFOX4/FOLFOX4-placebo arms.

A trial led by Duerreux evaluated XELOX vs. FOLFOX-6 for the first line treatment of mCRC. Efficacy of the two regimens was similar with median PFS of 8.8 months with XELOX and 9.3 months with FOLFOX-6, and median OS of 19.9 and 20.5 months, respectively. A quality of life analysis was performed using two scales: the Cancer Quality of Life Questionnaire-C30 (QLQ-C30) and the module ‘Chemotherapy Convenience and Satisfaction Questionnaire’ (CCSQ) of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System; which is a collection of HRQoL questionnaires related to the management of chronic illnesses, measures the health-care satisfaction of patients. Both regimens had a similar quality of life profile but XELOX was perceived as more convenient and satisfactory to patients.

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CAPECITABINE

FDA APPROVED INDICATIONS
Xeloda is approved for:

- Adjuvant Colon Cancer
  - Patients with Stage III (Duke’s C) colon cancer
- Metastatic Colorectal Cancer
  - First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred
- Metastatic Breast Cancer
  - In combination with docetaxel after failure of prior anthracycline containing therapy
  - As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen

REFERENCES


Created: 06/15
Effective: 07/22/17

Client Approval: 06/29/17
P&T Approval: 08/13
CAPSAICIN

<table>
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<td>QUTENZA</td>
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GUIDELINES FOR USE

Our guideline for approval of CAPSAICIN requires a diagnosis of neuropathic pain associated with postherpetic neuralgia (PHN).

CAPSAICIN

RATIONALE

To ensure appropriate utilization of Qutenza based on FDA indication.

FDA APPROVED INDICATION

Qutenza is indicated for the management of neuropathic pain associated with postherpetic neuralgia (PHN).

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/11
CARBIDOPA-LEVODOPA

<table>
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<td>DUOPA</td>
<td></td>
<td>37829</td>
<td>ROUTE = Percutaneous endoscopic gastrostomy with jejunal tube (PEG-J)</td>
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</tbody>
</table>

GUIDELINES FOR USE

Our guideline for **CARBIDOPA-LEVODOPA** requires a diagnosis of advanced Parkinson’s disease.

RATIONAL

Promote appropriate utilization of Duopa based on FDA approved indication.

Duopa is the first agent to provide continuous treatment via the enteral route for motor fluctuations in patients with Parkinson’s disease. It provides patients with the same active ingredients as orally-administered carbidopa and levodopa immediate release, but is delivered in a suspension that bypasses the stomach and goes directly into the small intestine via a tube placed by a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J).

FDA APPROVED INDICATIONS

Duopa is indicated for the treatment of motor fluctuations in patients with advanced Parkinson’s disease.

DOSE

Duopa is administered over a 16-hour infusion period. The daily dose is determined by individualized patient titration and composed of a morning dose, a continuous dose, and extra doses. The maximum recommended daily dose of Duopa is 2000mg of the levodopa component. At the end of the daily 16-hour infusion, patients will disconnect with the PEG-J and take their nighttime dose of oral immediate release carbidopa/levodopa tablets.

Duopa is administered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) with the CADD®-Legacy 1400 portable infusion pump. A Duopa cassette should be taken out of the refrigerator and out of the carton 20 minutes prior to use so that it can be administered at room temperature. The cassettes are for single-use only.

REFERENCES


Created: 05/15
Effective: 07/01/17
Client Approval: 05/01/17
P&T Approval: 05/15
GUIDELINES FOR USE

Our guideline for CARISOPRODOL PRODUCTS (SOMA, SOMA COMPOUND) requires that the patient has an acute musculoskeletal condition that was diagnosed in the last 6 months. In addition, the following criteria must also be met:

- No history of meprobamate use in the past 90 days
- Trial and failure of at least one of the following preferred muscle relaxants in the past 30 days: baclofen, chlorzoxazone, cyclobenzaprine IR, methocarbamol, orphenadrine citrate or tizanidine
- Patient will not use the requested carisoprodol product concurrently with opioid analgesics or benzodiazepines

RATIONALE
Promote appropriate utilization of carisoprodol products based on FDA approved indications and patient safety.

FDA APPROVED INDICATION
Soma (carisoprodol) is a centrally acting skeletal muscle relaxant indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults.

Soma Compound is a fixed-dose combination product containing a centrally-acting muscle relaxant (carisoprodol) and an analgesic with antipyretic and anti-inflammatory properties (aspirin). Soma Compound is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults. Soma and Soma Compound should only be used for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use has not been established and because acute, painful musculoskeletal conditions are generally of short duration.

DOSAGE
The recommended dose of Soma is 250 mg to 350 mg three times a day and at bedtime. The recommended maximum duration of Soma use is up to two or three weeks.

The recommended dose of Soma Compound is 1 or 2 tablets, four times daily in adults. One Soma Compound tablet contains 200 mg of carisoprodol and 325 mg of aspirin. The maximum daily dose (i.e., two tablets taken four times daily) will provide 1600 mg of carisoprodol and 2600 mg of aspirin per day. The recommended maximum duration of Soma Compound use is up to two or three weeks.

REFERENCES
GUIDELINES FOR USE

The guideline named CENEGERMIN-BKBJ (Oxervate) requires a diagnosis of neurotrophic keratitis. In addition, the following criteria must be met:

- Therapy is prescribed by or in consultation with an ophthalmologist
- The patient has a medical history supportive of causative etiology for trigeminal nerve damage (e.g., herpes zoster infection, multiple sclerosis, diabetes, ocular surgical damage)
- Physician attestation that patient has loss of corneal sensitivity, corneal epithelium changes, and/or loss of tear production
- The patient is refractory to conservative management (i.e., artificial tears, ocular lubricants, topical antibiotics, therapeutic contact lenses)

RATIONALE
For further information, please refer to the Prescribing Information and/or Drug Monograph for Oxervate.

REFERENCES

Created: 09/19
Effective: 01/01/20
Client Approval: 10/14/19
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for CERITINIB (Zykadia) requires a diagnosis of metastatic non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK)-positive tumors (as detected by an FDA approved test).

RATIONALE

Promote clinically appropriate utilization of Zykadia based on its FDA approved indication and dosage.

The recommended dose of Zykadia is 450 mg orally once daily with food until disease progression or unacceptable toxicity.

If a dose of Zykadia is missed, make up that dose unless the next dose is due within 12 hours.

If vomiting occurs during the course of treatment, do not administer an additional dose and continue with the next scheduled dose of Zykadia.

Table 1: Zykadia Dose Reduction Increments.

<table>
<thead>
<tr>
<th>Dose Reduction Schedule</th>
<th>Dose Level</th>
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<tbody>
<tr>
<td>Starting dose</td>
<td>450 mg taken orally once daily</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>300 mg taken orally once daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>150 mg taken orally once daily</td>
</tr>
</tbody>
</table>

Discontinue Zykadia for patients unable to tolerate 150 mg daily.

FDA APPROVED INDICATIONS

Zykadia is a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

REFERENCES


Created: 06/15
Effective: 06/24/19
Client Approval: 06/07/19
P&T Approval: 08/14
CERTOLIZUMAB PEGOL

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for CERTOLIZUMAB PEGOL requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or moderate to severe Crohn's disease. Additional guideline requirements apply.

For patients with moderate to severe rheumatoid arthritis, our guideline requires:
• Therapy initiated by or in consultation with a rheumatologist
• Previous trial or contraindication to at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
• Age 18 years or older

For patients with psoriatic arthritis, our guideline requires:
• Therapy initiated by or in consultation with a rheumatologist or dermatologist
• Previous trial or contraindication to at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
• Age 18 years or older

For patients with ankylosing spondylitis, our guideline requires:
• Therapy initiated by or in consultation with a rheumatologist
• Age 18 years or older

For patients with moderate to severe Crohn's disease, our guideline requires:
• Therapy initiated by or in consultation with a gastroenterologist
• Previous trial or contraindication to one or more conventional agents, such as: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalazine
• Age 18 years or older

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA

Our guideline for the renewal of CERTOLIZUMAB PEGOL requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or moderate to severe Crohn's disease. Additional guideline requirements apply.

Renewal for the diagnosis of moderate to severe rheumatoid arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy.

Renewal for the diagnosis of psoriatic arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy.

Renewal for the diagnosis of ankylosing spondylitis requires:
- Documentation of at least 50% improvement or increase of 2 units from baseline on the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index).

Renewal for the diagnosis of moderate to severe Crohn's disease (CD) requires:
- Documentation that the patient has experienced or maintained symptomatic improvement while on therapy.

RATIONALE

Ensure appropriate diagnostic, utilization and safety criteria are used for the management of prior authorization requests for Cimzia.

DOSAGE

Cimzia is administered by subcutaneous injection. The initial dose of Cimzia is 400 mg (given as two subcutaneous injections of 200 mg).

- **Crohn's Disease:** 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks.
- **Rheumatoid Arthritis:** 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.
- **Psoriatic Arthritis:** 400 mg initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.
- **Ankylosing Spondylitis:** 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

FDA APPROVED INDICATIONS

Cimzia is a tumor necrosis factor (TNF) blocker indicated for:
- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Treatment of adults with moderately to severely active rheumatoid arthritis.
- Treatment of adult patients with active psoriatic arthritis.
- Treatment of adults with active ankylosing spondylitis.
REFERENCES

Created: 03/15
Effective: 07/01/17
Client Approval: 05/31/17
P&T Approval: 06/15
CHENODIOL

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<td>CHENODAL</td>
<td>01364</td>
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This drug requires a written request for prior authorization

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline for CHENODIOL requires a diagnosis of radiolucent gallstones or cerebrotendinous xanthomatosis. The following criteria must also be met:

For the diagnosis of radiolucent gallstones:
- Previous trial of or contraindication to ursodiol
- The patient has not received previous chenodiol therapy with a total duration exceeding 24 months

RENEWAL CRITERIA

The guideline for CHENODIOL requires a diagnosis of radiolucent gallstones or cerebrotendinous xanthomatosis. The following criteria must also be met:

For the diagnosis of radiolucent gallstones:
- The patient has NOT exceeded a total of 24 months of previous chenodiol therapy
- The patient does NOT have complete or no gallstone dissolution seen on imaging (e.g., oral cholecystograms or ultrasonograms) after 12 months of therapy
- The patient has partial gallstone dissolution seen on imaging (e.g., oral cholecystograms or ultrasonograms) after 12 months of therapy

For the diagnosis of cerebrotendinous xanthomatosis:
- Physician attestation of improvement in ONE of the following:
  - Normalization of elevated serum or urine bile alcohols
  - Normalization of elevated serum cholestanol levels
  - Improvement in neurologic and psychiatric symptoms (dementia, pyramidal tract and cerebellar signs)

CONTINUED ON NEXT PAGE
CHENODIOL

RATIONALE
Ensure appropriate utilization for chenodiol.

FDA APPROVED INDICATIONS

Chenodiol is indicated for patients with radiolucent stones in well-opacifying gallbladders, in whom selective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age. The likelihood of successful dissolution is far greater if the stones are floatable or small. For patients with nonfloatable stones, dissolution is less likely and added weight should be given to the risk that more emergent surgery might result from a delay due to unsuccessful treatment. Safety of use beyond 24 months is not established. Chenodiol will not dissolve calcified (radiopaque) or radiolucent bile pigment stones.

Because of the potential hepatotoxicity of chenodiol, poor response rate in some subgroups of chenodiol-treated patients, and an increased rate of a need for cholecystectomy in other chenodiol-treated subgroups, chenodiol is not an appropriate treatment for many patients with gallstones. Chenodiol should be reserved for carefully selected patients and treatment must be accompanied by systematic monitoring for liver function alterations. Aspects of patient selection, response rates and risks versus benefits are given in the package insert.

Chenodiol is used off-label for the treatment of cerebrotendinous xanthomatosis.

DOSAGE AND ADMINISTRATION

Radiolucent gallstones:
The recommended dose range for chenodiol is 13 to 16mg/kg/day in two divided doses, morning and night. Starting with 250 mg two times a day for the first two weeks and increasing by 250 mg/day each week thereafter until the recommended or maximum tolerated dose is reached. If diarrhea occurs during dosage buildup or later in treatment, it usually can be controlled by temporary dosage adjustment until symptoms abate, after which the previous dosage usually is tolerated. Dosage less than 10 mg/kg usually is ineffective and may be associated with increased risk of cholecystectomy, so is not recommended.

CONTINUED ON NEXT PAGE
Cerebrotendinous xanthomatosis:
The recommended dose for chenodiol for adults is 250 mg three times a day and 15 mg/kg per day in three divided doses for children.

REFERENCES
- UpToDate, Inc. Cerebrotendinous xanthomatosis. UpToDate [database online]. Last updated Dec 20, 2016.

Created: 03/19
Effective: 07/01/19
Client Approval: 05/13/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for **CHOLIC ACID** requires that the patient exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption secondary to one of the following conditions:

- Bile acid synthesis disorders or
- Peroxisomal disorders (i.e., Zellweger spectrum disorders).

RENEWAL CRITERIA

Our guideline for **CHOLIC ACID** renewal requires improvement in liver function (as defined by at least one of the following criteria):

- ALT or AST values reduced to <50 U/L or baseline levels reduced by 80% or
- Total bilirubin values reduced to <1 mg/dL or
- No evidence of cholestasis on liver biopsy.

CHOLIC ACID RATIONALE

Promote appropriate utilization of Cholbam (cholic acid) based on FDA approved indication.

Cholbam (cholic acid) is the first FDA approved treatment for pediatric and adult patients with bile acid synthesis disorders due to single enzyme defects (SEDS), and for patients with peroxisomal disorders (PDs), including Zellweger spectrum disorders. Ursodeoxycholic acid treatment has been found to have limited benefits for the treatment of bile acid defects, however, oral primary bile acid replacement by chenodeoxycholic acid or cholic acid is required for these defects to down-regulate endogenous bile acid synthesis. Cholic acid is now recognized as the bile acid of choice because it is not hepatotoxic, and it is effective therapy for errors in bile acid synthesis due to SEDs. Cholic acid has previously been available as an Investigation New Drug (IND), and study trials for cholic acid have exceeded eighteen years in duration.

The combined incidence of peroxisomal disorders is in excess of 1 in 20,000 individuals. Zellweger syndrome (ZWS) is the most common peroxisomal disorder to manifest itself in early infancy. Its incidence has been estimated to be 1 in 50,000-100,000. Patients with these rare disorders lack the enzymes needed to synthesize cholic acid, a primary bile acid normally produced in the liver from cholesterol. The absence of cholic acid in these patients leads to reduced bile flow, and malabsorption of fats and fat-soluble vitamins in the diet. If untreated, patients fail to grow and can develop life-threatening liver injury.

CONTINUED ON NEXT PAGE
CHOLIC ACID

FDA APPROVED INDICATIONS
- Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).
- Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat-soluble vitamin absorption.

Limitations of use: The effectiveness of Cholbam for the management of extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs has not been established.

DOSEAGE
The dosage regimen for bile acid synthesis disorders due to SEDs and for PDs, including Zellweger Spectrum Disorders, is 10 to 15mg/kg given orally once daily or in two divided doses. Patients with newly diagnosed or a family history of familial hypertriglyceridemia may have poor absorption of Cholbam and require a 10% increase in the recommended dosage (11 to 17mg/kg orally once or twice daily).

Cholbam is available in 50mg and 250mg capsules and should be given in the lowest dose that effectively maintains liver function. Cholbam should be taken with food, and at least one hour before or 4-6 hours after a bile acid binding resin or an aluminum-based antacid. For patients unable to swallow the capsules, the capsules can be opened and the contents mixed with either infant formula or expressed breast milk (for younger children), or soft food such as mashed potatoes or apple puree (for older children and adults) in order to mask any unpleasant taste.

REFERENCES

Created: 05/15
Effective: 11/01/15
Client Approval: 09/15
P&T Approval: 05/15
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named CLADRIBINE (Mavenclad) requires a diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., relapsing-remitting MS [RRMS], active secondary progressive MS [SPMS], etc.). In addition, the following criteria must be met:

- The patient is 18 years of age or older
- The patient meets ONE of the following:
  - The patient had a previous trial of ONE agent indicated for the treatment of multiple sclerosis (MS) (Please note: The following agents are preferred and may also require prior authorization: Avonex, Aubagio, Copaxone 40, Gilenya, Glatopa, Rebif, Tecfidera)
  - Physician attestation that the patient shows signs of severe disease requiring high-efficacy disease modifying therapy (DMT) (e.g., high lesion volume and/or count, walking disability, or rapid decline)

RENEWAL CRITERIA

The guideline named CLADRIBINE (Mavenclad) requires a diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., relapsing-remitting MS [RRMS], active secondary progressive MS [SPMS], etc.) AND the patient has not received a total of two years of Mavenclad treatment. In addition, the following criteria must be met:

- Physician attestation that the patient has demonstrated a clinical benefit compared to pre-treatment baseline
- The patient does not have lymphopenia

RATIONALE

To ensure safe and appropriate use of Mavenclad per approved indication and dosing.

FDA APPROVED INDICATIONS

Mavenclad is a purine antimetabolite indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION
The recommended cumulative dosage of Mavenclad is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course) (see Table 1).

Each treatment course is divided into 2 treatment cycles:
- Administration of First Treatment Course
  - First Course/First Cycle: start any time.
  - First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle.
- Administration of Second Treatment Course
  - Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle.
  - Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle.

Table 1: Dose of Mavenclad by Patient Weight in Each Treatment Course

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Dose in mg (Number of 10mg Tablets) per Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Cycle</td>
</tr>
<tr>
<td>40* to less than 50</td>
<td>40 mg (4 tablets)</td>
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<tr>
<td>50 to less than 60</td>
<td>50 mg (5 tablets)</td>
</tr>
<tr>
<td>60 to less than 70</td>
<td>60 mg (6 tablets)</td>
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<tr>
<td>70 to less than 80</td>
<td>70 mg (7 tablets)</td>
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<tr>
<td>80 to less than 90</td>
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<td>90 to less than 100</td>
<td>90 mg (9 tablets)</td>
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<tr>
<td>100 to less than 110</td>
<td>100 mg (10 tablets)</td>
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<tr>
<td>110 and above</td>
<td>100 mg (10 tablets)</td>
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</tbody>
</table>

*The use of Mavenclad in patients weighing less than 40 kg has not been investigated.

Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days. Do not administer more than 2 tablets daily.

REFERENCES

Created: 12/19
Effective: 12/16/19
Client Approval: 12/03/19
P&T Approval: N/A
CLONIDINE/GUANFACINE

<table>
<thead>
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<th>Generic</th>
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<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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<td>CLONIDINE HCL</td>
<td>CATAPRES</td>
<td>00113</td>
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<td>CLONIDINE</td>
<td>CATAPRES-TTS</td>
<td>00113, 36550</td>
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<td>CLONIDINE HCL</td>
<td>KAPVAY</td>
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<td>INTUNIV</td>
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GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

See appendix for standard monthly quantity limits.

Our guideline named CLONIDINE/GUANFACINE does not allow the use of the requested medication at the requested dose/regimen. Please consider an alternate dose or dosing schedule.

Our guideline for CLONIDINE/GUANFACINE for patients with claims suggesting therapeutic duplication requires that the medications are being cross-tapered. Duplication of therapy will be allowed for patients who meet ALL of the following criteria:

- Diagnosis of ADD/ADHD or hypertension
- Systolic blood pressure > 100
- The prescriber has provided rationale as to why the same chemical entity (i.e., clonidine ER with clonidine IR, guanfacine IR with guanfacine ER) cannot be used throughout the day rather than duplicating therapy with two alpha2-adrenergic agonists

*Please note that the following concurrent uses will be allowed:
- Clonidine ER product with a clonidine IR product
- Guanfacine ER product with a guanfacine IR product

RENEWAL CRITERIA

The guideline for CLONIDINE/GUANFACINE renewal requires that there is history of paid claims for the requested alpha2-adrenergic agonist (i.e., clonidine or guanfacine) for 90 of the past 120 days and that the patient has been previously approved for the requested therapy.

CONTINUED ON NEXT PAGE
RATIONALE
To promote prudent prescribing of alpha₂-adrenergic agonists.

Duplicate alpha₂-adrenergic agonist therapy is characterized as claims for two different chemical entities.

The following concurrent uses will be allowed:
- Clonidine ER product with a clonidine IR product
- Guanfacine ER product with a guanfacine IR product

APPENDIX: Alpha₂-Adrenergic Agonist Quantity Limits

<table>
<thead>
<tr>
<th>GPID</th>
<th>Generic Name</th>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Route</th>
<th>Strength</th>
<th>Utilization Edit</th>
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<tr>
<td>23870</td>
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<td>CATAPRES-TTS-1</td>
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<td>23871</td>
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<td>CATAPRES-TTS-2</td>
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<tr>
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<td>CATAPRES-TTS-3</td>
<td>PTWK</td>
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<td>0.3MG/24 HR</td>
<td>2 PATCHES/WEEK</td>
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<tr>
<td>29319</td>
<td>CLONIDINE HCL</td>
<td>KAPVAY</td>
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<td>OR</td>
<td>0.1MG</td>
<td>4/DAY</td>
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<tr>
<td>27576</td>
<td>GUANFACINE HCL</td>
<td>INTUNIV</td>
<td>TB24</td>
<td>OR</td>
<td>1MG</td>
<td>1/DAY</td>
</tr>
<tr>
<td>27578</td>
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<td>TB24</td>
<td>OR</td>
<td>2MG</td>
<td>1/DAY</td>
</tr>
<tr>
<td>27579</td>
<td>GUANFACINE HCL</td>
<td>INTUNIV</td>
<td>TB24</td>
<td>OR</td>
<td>3MG</td>
<td>1/DAY</td>
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<tr>
<td>27582</td>
<td>GUANFACINE HCL</td>
<td>INTUNIV</td>
<td>TB24</td>
<td>OR</td>
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Created: 10/19
Effective: 01/01/20
Client Approval: 12/13/19
P&T Approval: N/A
### CNS STIMULANTS

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<th>GCN</th>
<th>Exception/Other</th>
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<td>AMPHETAMINE ER SUSPENSION</td>
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<td>AMPHETAMINE</td>
<td>ADZENYS XR-ODT, ADZENYS ER</td>
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<td>EVEKEO, EVEKEO ODT</td>
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<td>AMPHETAMINE/D-AMPHETAMINE</td>
<td>ADDERAL, ADDERAL XR, MYDAYIS</td>
<td>13449</td>
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<td>DEXMETHYPHENIDATE HCL</td>
<td>FOCALIN, FOCALIN XR</td>
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<td>DEXTOAMPHETAMINE SULFATE</td>
<td>DEXEDRINE, PROCENTRA, ZENZEDI</td>
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<td>LISDEXAMFETAMINE DIMESYLATE</td>
<td>VYVANSE</td>
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<td>34486</td>
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<td>METHAMPHETAMINE HCL</td>
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<td>ADHANSIA XR, APTENSIO XR, CONCERTA, JORNAY PM, METADATE CD, METADATE ER, METHYLIN, QUILLIVANT XR, RITALIN, RITALIN LA, RITALIN SR, QUILLICHEW ER, RELEXXII</td>
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<td>01682</td>
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GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline named CNS STIMULANTS does not allow the use of the requested medication under the age limit listed in the appendix below. Please consider another CNS stimulant without an age restriction.

Our guideline named CNS STIMULANTS does not allow the use of the requested medication above the quantity/dosing limit listed in the appendix below. Please consider an alternate dose or dosing schedule.

Our guideline for CNS STIMULANTS for patients with claims suggesting therapeutic duplication requires that the medications are being cross-tapered, or that historical medication is being discontinue. Concurrent use of Vyvanse with either dextroamphetamine IR or amphetamine salts IR will be allowed. Duplication of therapy will be allowed for patients who have a diagnosis of ADD/ADHD or narcolepsy in whom both of the requested stimulants are prescribed by or in consultation with a psychiatrist and who have history of at least 2 weeks of single-drug therapy at the maximum labeled dose of one medication involved in the therapeutic duplication in the past year.

Please note that the following concurrent uses will be allowed:

- Methylphenidate ER product with a methylphenidate IR product
- Amphetamine salts (Adderall) ER product with an amphetamine salts IR product
- Amphetamine ER (i.e., Dyanavel) product with an amphetamine IR (i.e., Evekeo) product
- Dexamethylphenidate ER product with a dexamethylphenidate IR product
- Dextroamphetamine ER product with a dextroamphetamine IR product
- Vyvanse with IR dextroamphetamine or IR amphetamine salts

RENEWAL CRITERIA

Our guideline for CNS STIMULANTS renewal requires that there is history of paid claims for BOTH medications identified in the therapeutic duplication for 90 of the past 120 days and that the patient has previous authorizations on file for BOTH medications identified in the therapeutic duplication.

CONTINUED ON NEXT PAGE
CNS STIMULANTS

RATIONALE
To promote prudent prescribing of CNS stimulants.

A look back period of 60 days will be utilized to identify potential therapeutic duplication.

Duplicate stimulant therapy is characterized as claims for two different chemical entities.

The following concurrent uses will be allowed:
- Methylphenidate ER product with a methylphenidate IR product
- Amphetamine salts (Adderall) ER product with an amphetamine salts IR product
- Amphetamine ER (i.e., Dyanavel) product with an amphetamine IR (i.e., Evekeo) product
- Dexmethylphenidate ER product with a dexmethylphenidate IR product
- Dextroamphetamine ER product with a dextroamphetamine IR product
- Vyvanse with IR dextroamphetamine or IR amphetamine salts

Concomitant claims for immediate-release dextroamphetamine tablets or amphetamine salts (generic Adderall IR) and Vyvanse do not require prior authorization.

APPENDIX: Stimulant Age Edits and Quantity Limits

<table>
<thead>
<tr>
<th>GPID</th>
<th>Generic Name</th>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Route</th>
<th>Strength</th>
<th>Utilization Edit</th>
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</thead>
<tbody>
<tr>
<td>39686</td>
<td>AMPHETAMINE</td>
<td>DYANAVEL XR</td>
<td>SUSP</td>
<td>OR</td>
<td>2.5 MG/ML</td>
<td>8 ML/DAY; Age 6 years and older</td>
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<tr>
<td>40647</td>
<td>AMPHETAMINE</td>
<td>ADZENYS XR-ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>3.1 MG</td>
<td>1/DAY; Age 6 years and older</td>
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<tr>
<td>40648</td>
<td>AMPHETAMINE</td>
<td>ADZENYS XR-ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>6.3 MG</td>
<td>1/DAY; Age 6 years and older</td>
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<td>AMPHETAMINE</td>
<td>ADZENYS XR-ODT</td>
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<td>9.4 MG</td>
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<td>TBDP</td>
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<td>1/DAY; Age 6 years and older</td>
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<td>40653</td>
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<td>ADZENYS XR-ODT</td>
<td>TBDP</td>
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<td>15.7 MG</td>
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<td>40654</td>
<td>AMPHETAMINE</td>
<td>ADZENYS XR-ODT</td>
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<td>43864</td>
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<td>ADZENYS ER</td>
<td>SUSP</td>
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<td>EVEKEO</td>
<td>TABS</td>
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<td>5 MG</td>
<td>2/DAY; Age 3 years and older</td>
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<td>19821</td>
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<td>JORNAY PM</td>
<td>OR</td>
<td>80 MG</td>
<td>1/DAY; Age 6 years and older</td>
</tr>
<tr>
<td>45110</td>
<td>METHYLPHENIDATE HCL</td>
<td>JORNAY PM</td>
<td>OR</td>
<td>100 MG</td>
<td>1/DAY; Age 6 years and older</td>
</tr>
</tbody>
</table>

Created: 09/16  
Effective: 01/01/20  
Client Approval: 12/09/19  
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for COBICISTAT requires that Tybost (cobicistat) be used in combination with once daily Prezista (darunavir) or Reyataz (atazanavir) for the treatment of HIV-1. A trial of Norvir (ritonavir) is also required.

COBICISTAT

RATIONALE
Ensure cost-effective use of Tybost as per FDA approved indication and dosing and to prefer the formulary alternative, Norvir (ritonavir).

FDA APPROVED INDICATIONS
Tybost is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection.

Limitations of Use:

- Tybost is not interchangeable with ritonavir to increase systemic exposure of darunavir 600 mg twice daily, fosamprenavir, saquinavir, or tipranavir due to lack of exposure data. The use of Tybost is not recommended with darunavir 600 mg twice daily, fosamprenavir, saquinavir or tipranavir.
- Complex or unknown mechanisms of drug interactions preclude extrapolation of ritonavir drug interactions to certain Tybost interactions. Tybost and ritonavir when administered with either atazanavir or darunavir may result in different drug interactions when used with concomitant medications.

DOsing
One 150mg Tybost tablet must be coadministered with Reyataz or Prezista at the same time, with food, and in combination with other HIV-1 antiretroviral agents.

Recommended dosage

<table>
<thead>
<tr>
<th>Tybost Dosage</th>
<th>Coadministered Agent Dosage</th>
<th>Patient Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg orally once daily</td>
<td>atazanavir 300 mg orally once daily</td>
<td>Treatment-naïve or experienced</td>
</tr>
<tr>
<td>darunavir 800 mg orally once daily</td>
<td>Treatment-experienced with no darunavir resistance associated substitutions</td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES

- Tybost [Prescribing Information]. Foster City, CA: Gilead Sciences Inc., September 2014

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/14
GUIDELINES FOR USE

Our guideline for COBIMETINIB (Cotellic) requires a diagnosis of unresectable or metastatic melanoma. In addition, both of the following criteria must be met:

- Positive for BRAF V600E OR V600K mutation, and
- Cobimetinib will be used in combination with vemurafenib (Zelboraf).

RATIONALE
To ensure appropriate use of Cotellic consistent with FDA approved indication.

FDA APPROVED INDICATION
Cotellic (cobimetinib) is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. Cotellic is not indicated for treatment of patients with wild-type BRAF melanoma.

DOSAGE
The recommended dose is 60 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.

AVAILABLE STRENGTHS:
- 20 mg tablet

REFERENCES

Created: 02/18
Effective: 07/01/18
Client Approval: 05/21/18
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for CORTICOTROPIN requires a diagnosis of acute exacerbation of multiple sclerosis and an attempt to treat the current exacerbation with corticosteroids, or a diagnosis of infantile spasms in patients less than 2 years of age. For all other FDA indications, consider the use of IV corticosteroids or alternate therapies, as appropriate.

FDA approved indications include: infantile spasm, acute multiple sclerosis, psoriatic arthritis, rheumatoid arthritis including juvenile rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus or systemic dermatomyositis (polymyositis), severe erythema multiforme, Stevens-Johnson syndrome, serum sickness, severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa (such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation), symptomatic sarcoidosis, or to induce a diuresis or a remission of proteinuria (in the nephrotic syndrome without uremia of the idiopathic type, or that due to lupus erythematosus).

RATIONALE

Ensure appropriate therapeutic use of this long acting corticotropin formulation.

The recommended regimen for use in infantile spasms is a daily dose of 150 units/m² (divided into twice daily intramuscular injections of 75 units/m²) then a gradual taper over a 2-week period. A suggested taper schedule is 30 units/m² every morning for 3 days, 15 units/m² every morning for 3 days, 10 units/m² every morning for 3 days, and then 10 units/m² every other morning for 6 days.

8 vials per 28 days supply based on dosage of 150 units/m²/day with an estimate of 0.7m² body surface area, estimated maximum for a child less than 40 pounds (two years old).

The American Academy of Neurology guidelines for treatment of infantile spasms state that response is usually within 2 weeks and current clinical data is insufficient to determine optimum dosage and duration.

The recommended regimen for use of Acthar in treatment of acute exacerbations of multiple sclerosis (MS) is daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks.

In a comparable efficacy study to assess IV methylprednisolone (IVMP) versus Acthar, there was no demonstrated difference between efficacy of IVMP and Acthar for the treatment of acute exacerbations of multiple sclerosis.

The manufacturer states that the H.P. Acthar Gel vial expires 28 days after initial puncture, when stored under ideal conditions (per USP standard guidelines).

CONTINUED ON NEXT PAGE
CORTICOTROPIN

FDA APPROVED INDICATIONS
Acthar Gel is indicated for the treatment of infantile spasms, for acute exacerbations of multiple sclerosis, and for numerous other diseases and disorders. (See below).

INFANTILE SPASMS: Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

MULTIPLE SCLEROSIS: Treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown H.P. Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease.

RHEUMATIC DISORDERS: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), and ankylosing spondylitis.

COLLAGEN DISEASES: During an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus or systemic dermatomyositis (polymyositis).

DERMATOLOGIC DISEASES: Severe erythema multiforme (Stevens-Johnson syndrome).

ALLERGIC STATES: Serum sickness.

OPHTHALMIC DISEASES: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.

RESPIRATORY DISEASES: Symptomatic sarcoidosis.

EDEMATOUS STATE: To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

CONTINUED ON NEXT PAGE
REFERENCES


Created: 06/15  
Effective: 09/01/17  
Client Approval: 08/14/17  
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for **CRIZOTINIB** requires a diagnosis metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK) positive, have MET amplification, or ROS1 gene fusions.

**RATIONALE**

Based on FDA approved indications and NCCN recommendations. Xalkori is indicated for the treatment of locally advanced or metastatic NSCLC that is anaplastic lymphoma kinase (ALK) positive. NCCN recommends Xalkori for ALK positive NSCLC and NSCLC with MET amplification or ROS1 gene fusions.

The recommended dose of crizotinib is 250mg twice daily with or without food. Dose reduction to 200mg twice daily, 250mg daily, or discontinuation is recommended in the presence of certain toxicities.

Xalkori (Single Arm): Advanced ALK Positive NSCLC (21)
The use of single-agent Xalkori (250mg twice daily) in the treatment of locally advanced or metastatic ALK-positive NSCLC was approved based on two single arm pivotal trials, PROFILE 1005 and Study 1001 (Study A and Study B in the prescribing information). Patients enrolled into these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or metastatic disease. The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST).

Locally Advanced or Metastatic ALK-Positive NSCLC Efficacy Results from Studies A and B* (From Xalkori Prescribing information)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study A (N=136)</th>
<th>Study B (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (CR+PR) [ % (95% CI)]</td>
<td>50% (42%, 59%)</td>
<td>61% (52%, 70%)</td>
</tr>
<tr>
<td>Number of Responders</td>
<td>68</td>
<td>71</td>
</tr>
<tr>
<td>Duration of Response [Median (range) weeks]</td>
<td>41.9 (6.1+, 42.1+)</td>
<td>48.1 (4.1+, 76.6+)</td>
</tr>
</tbody>
</table>

*Response as assessed by the Investigator.

*a patient was not evaluable for response in Study A; 3 patients were not evaluable for response in Study B.

*Preliminary estimate using Kaplan-Meier method.

+Censored values

CONTINUED ON NEXT PAGE
CRIZOTINIB

RATIONALE (CONTINUED)

PROFILE 1005 included patient reported outcomes using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Lung Cancer Module (EORTC QLQ-LC13) every 3 weeks. Statistically significant and clinically meaningful improvements from baseline were observed for patient-reported overall pain, pain in chest, cough, dyspnea, insomnia, fatigue, and global quality of life. (22)

Xalkori versus Alimta or Docetaxel: 2nd Line Advanced ALK Positive NSCLC (23)

PROFILE 1007 was an open label phase 3 trial in 347 patients with locally advanced or metastatic ALK-positive lung cancer who had received one prior platinum-based regimen. Patients were randomly assigned to receive Xalkori (250mg twice daily) or intravenous chemotherapy with either Alimta (500mg per square meter of body-surface area) or docetaxel (75mg per square meter) every 3 weeks. The majority of patients were younger than 65 years of age, had never smoked, and had adenocarcinoma of the lung; characteristics that were consistent with those of patients with ALK-positive non–small-cell lung cancer in prior studies.

The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (Alimta and docetaxel combined) (hazard ratio for progression or death with Xalkori, 0.49; P<0.001). The progression-free survival for Alimta treated patients was 4.2 months. An interim analysis of overall survival showed no significant improvement with Xalkori as compared with chemotherapy. Patients reported greater reductions in symptoms of lung cancer and greater improvement in global quality of life with Xalkori than with chemotherapy using European Organization for Research and Treatment of Cancer quality-of-life questionnaire (QLQ-C30) 20 and its corresponding module for lung cancer (QLQ-LC13).

PROFILE 1007 Progression-free Survival in the Intention-to-treat Population (A) and As-treated Population (B)

PROFILE 1014 is an ongoing phase 3 trial with results expected in November 2013. It is comparing Xalkori to Alimta with cisplatin or carboplatin as first-line treatment of patients with ALK-positive non-squamous carcinoma. (24)

CONTINUED ON NEXT PAGE
RATIONAL (CONTINUED)

Xalkori: ROS1 Positive NSCLC
In a preclinical trial ROS1 positive NSCLC cells showed evidence of sensitivity to Xalkori. (7) A single arm phase 2 trial of NSCLC patients whose cancer is ROS1-positive and ALK-negative is expected to complete in July 2016. (25)

Xalkori: MET Amplification-positive NSCLC
Xalkori demonstrated antitumor activity in a preclinical trial of MET amplification-positive lung cancer cells.

FDA APPROVED INDICATIONS
Xalkori is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

This indication is based on response rate. There are no data available demonstrating improvements in patient reported outcomes or survival with Xalkori.

REFERENCES
  http://clinicaltrials.gov/ct2/show/NCT01154140?term=crizotinib&rank=34
  http://clinicaltrials.gov/ct2/show/NCT01945021?term=crizotinib+ros1&rank=1
GUIDELINES FOR USE

Our guideline for CYSTEAMINE BITARTRATE requires a diagnosis of nephropathic cystinosis, patient age of at least 2 years old and previous trial of an immediate release formulation of cysteamine bitartrate such as Cystagon.

CYSTEAMINE BITARTRATE

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYSTEAMINE BITARTRATE</td>
<td>PROCYSBI</td>
<td></td>
<td>34656, 34657</td>
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</table>

RATIONALE

To ensure appropriate use of Procysbi consistent with FDA approved indication and to promote cost-effective treatment alternatives.

Procysbi is a new long acting formulation of the existing brand of cysteamine bitartrate, Cystagon. Both products share the same indication except that Cystagon does not have a minimum pediatric age requirement. Procysbi is given twice daily versus Cystagon which is administered four times daily. Cystagon is known to cause a “rotten egg” odor on the breath and body, and has gastrointestinal effects (i.e. nausea, and vomiting). Although the unpleasant odor is reduced with Procysbi, it is not eliminated. Cystaran, a branded ophthalmic treatment, is only indicated for corneal cystine crystal accumulation in patients with cystinosis. Orally administered cysteamine does not reach the cornea and is therefore ineffective in reducing the ocular effects of cystinosis.

Affecting an estimated 500 patients in the United States (3,000 patients globally), cystinosis is a rare metabolic disease characterized by an accumulation of cystine in different organs and tissues, leading to potentially severe and lethal organ dysfunction if left untreated. There are three distinct types of cystinosis: nephropathic (infantile) cystinosis, intermediate (adolescent) cystinosis, and ocular non-nephropathic (adult/benign) cystinosis. Nephropathic cystinosis is by far the most common form of cystinosis.

Cystine is a product of protein degradation that is normally transported through the lysosomal membrane to the cytosol. In cystinosis, a defect in the transport system causes cystine to accumulate inside the lysosomes. Since cystine is poorly soluble, crystals form as the cystine concentration increases. Although the adult form of the disease may be limited to ocular symptoms, patients with infantile cystinosis can have both renal and extrarenal symptoms as cystine deposits in the cornea and the conjunctiva can be seen on slit-lamp examination. When cysteine accumulates in the kidney, excessive amounts of sugar, proteins, and salts are excreted in the urine resulting in poor body growth, weak bones, and worsening kidney failure. Cysteamine acts as a cystine-depleting agent by entering the cell, reacting with cystine, and forming both cysteine and a cysteine-cysteamine complex which are able to leave the lysosomes.

CONTINUED ON NEXT PAGE
CYSTEAMINE BITARTRATE

FDA APPROVED INDICATIONS
For the management of nephropathic cystinosis in adults and children ages 2 years and older

DOsing
For patients’ naïve to cysteamine therapy, the initial dose is 1/6 to 1/4 of the maintenance dose of Procysbi and should be increased gradually over 4 to 6 weeks to help reduce the risk of side-effects. The maintenance dose is 1.3 grams/m²/day in two divided doses, every 12 hours. Goal of therapy is to maintain a white blood cell (WBC) cystine level < 1 nmol ½ cystine/mg protein or a plasma cysteamine concentration > 0.1 mg/L. The dose can be increased up to 1.95 grams/m²/day if the white blood cell cystine level remains higher than the target WBC cystine level and/or the target cysteamine concentration has not been achieved. Procysbi should be administered at least 2 hours after and at least 30 minutes before eating. The capsules should be swallowed whole or administered within 30 minutes if sprinkled on 4 ounces of food (applesauce or berry jelly) or mixed in 4 ounces of recommended liquids (orange juice or apple juice).

Patients switching from immediate release Cystagon to Procysbi should use a total daily dose of Procysbi equal to their previous total daily dose of immediate-release Cystagon.

REFERENCES
GUIDELINES FOR USE

Approval requires that Cystaran be used in the treatment of corneal cystine crystal accumulation in patients with cystinosis.

CYSTEAMINE HYDROCHLORIDE

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<tr>
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<td>CYSTEAMINE HCL</td>
<td>CYSTARAN</td>
<td></td>
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RATIONAL

To ensure appropriate use aligned with FDA approved indication.

Instill one drop of Cystaran in each eye, every waking hour. Discard after 1 week of use.

Cystinosis is a metabolic disease characterized by an accumulation of cystine in different organs and tissues, leading to potentially severe organ dysfunction. There are three distinct types of cystinosis: nephropathic (infantile) cystinosis, intermediate (adolescent) cystinosis, and ocular non-nephropathic (adult/benign) cystinosis. Nephropathic cystinosis, which is by far the most common, has been estimated to affect one of every 100,000 to 200,000 children.

Cystine is a product of protein degradation that is normally transported through the lysosomal membrane to the cytosol. In cystinosis, a defect in the transport system causes cystine to accumulate inside the lysosomes. Since cystine is poorly soluble, crystals form as the cystine concentration increases. Although the adult form of the disease may be limited to ocular symptoms, patients with infantile cystinosis can have both renal and extrarenal symptoms as cystine deposits in the cornea and the conjunctiva can be seen on slit-lamp examination. These deposits are responsible for photophobia, watering, and blepharospasm. Irregular and peripheral depigmentation of the retina is also an early finding. Visual impairment may occur later, in children older than 10 years. Hemorrhagic retinopathy may also be a complication of this disorder. Cysteamine acts as a cystine-depleting agent by entering the cell, reacting with cystine, and forming both cysteine and a cysteine-cysteamine complex, which are able to leave the lysosomes.

The safety and efficacy of Cystaran was evaluated in controlled clinical trials that examined in approximately 300 patients. The primary efficacy endpoint was the response rate of eyes that had a reduction of at least 1 unit in the photo-rated Corneal Cystine Crystal Score (CCCS) at some time point during the study when baseline CCCS ≥1, or a lack of an increase of more than 1 unit in CCCS throughout the study when baseline CCCS <1.

Study 1 combined the data from three smaller studies. For eyes with a lower baseline of CCCS <1, the response rate was 13% (4/30) [95% CI: (4, 32)]. For eyes with a higher baseline of CCCS ≥1, the response rate was 32% (94/291) [95% CI: (27, 38)].
CYSTEAMINE HYDROCHLORIDE

RATIONALE (CONTINUED)

Study 2 evaluated ocular cystinosis patients who had a baseline of CCCS ≥1. The response rate was 67% (10/15) [95% CI: (38, 88)].

Study 3 also evaluated ocular cystinosis patients; for eyes with a baseline of CCCS ≥1, the response rate was 33% (3/9) [95% CI: (8, 70)].

The most frequently reported ocular adverse reactions occurring in ≥10% of patients were sensitivity to light, redness, and eye pain/irritation, headache and visual field defects. There is a warning for potential association of benign intracranial hypertension (or pseudotumor cerebri) with oral cysteamine treatment. It is uncertain if this condition occurs in those who only use the ophthalmic formulation.

Cystaran is pregnancy category C.

Instill one drop of Cystaran in each eye, every waking hour. Discard after 1 week of use. Patients with contact lenses should remove lenses prior to application of solution and may reinsert lenses 15 minutes following its administration (Cystaran contains benzalkonium chloride, which may be absorbed by soft contact lenses).

Each week, one new bottle should be removed from the freezer. Patients should be advised to allow the bottle to thaw completely (approximately 24 hours) prior to use. After the bottle is completely thawed, the patient should record the discard date on the bottle label. The discard date is seven (7) days from the day the bottle is thawed. Patients should be advised to store thawed bottle at 2°C to 25°C (36°F to 77°F) for up to 1 week. The thawed bottles should not be refrozen. To minimize the risk of contamination, do not touch the dropper tip to any surface. Keep bottle tightly closed when not in use.

FDA APPROVED INDICATIONS
Cystaran is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

REFERENCES
- Cystaran [Prescribing Information]. Gaithersburg, MD: Sigma Tau Pharmaceuticals; December 2012.

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 05/13
GUIDELINES FOR USE

The guideline named DABRAFENIB (Tafinlar) requires a diagnosis of unresectable or metastatic melanoma, melanoma with the involvement of lymph node(s), metastatic non-small cell lung cancer (NSCLC), or locally advanced or metastatic anaplastic thyroid cancer (ATC) and that the following criteria are met:

For patients with unresectable or metastatic melanoma for use as a single agent:
- The patient has BRAF V600E mutation as detected by an FDA-approved test
- The medication will be used as a single agent

For patients with unresectable or metastatic melanoma for use in combination with Mekinist:
- The patient has BRAF V600E or V600K mutations as detected by an FDA-approved test
- The medication will be used in combination with Mekinist (trametinib)

For patients with melanoma with the involvement of lymph node(s):
- The patient has BRAF V600E or V600K mutations as detected by an FDA-approved test
- The medication will be used in combination with Mekinist (trametinib) as an adjuvant treatment following complete resection

For patients with metastatic non-small cell lung cancer (NSCLC):
- The patient has BRAF V600E mutation as detected by an FDA-approved test
- The medication will be used in combination with Mekinist (trametinib)

For patients with locally advanced or metastatic anaplastic thyroid cancer (ATC):
- The patient has BRAF V600E mutation as detected by an FDA-approved test
- The patient has no satisfactory locoregional treatment options
- The medication will be used in combination with Mekinist (trametinib)

DABRAFENIB RATIONALE
Ensure appropriate use of TAFINLAR based on FDA approved indications and dosing.

FDA APPROVED INDICATIONS
TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
FDA APPROVED INDICATIONS (CONTINUED)

TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with:
- Unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test
- Melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s) following complete resection
- Metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test
- Locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options

Limitation of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC.

DOSAGE AND ADMINISTRATION

Melanoma: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent. Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib.

NSCLC: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib.

ATC: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib.

The recommended dose for TAFINLAR is 150 mg orally twice daily. Take TAFINLAR at least 1 hour before or at least 2 hours after a meal.

Recommended Dose Reductions for TAFINLAR for Adverse Reactions

<table>
<thead>
<tr>
<th>Dose Reductions</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>100 mg orally twice daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>75 mg orally twice daily</td>
</tr>
<tr>
<td>Third dose reduction</td>
<td>50 mg orally twice daily</td>
</tr>
<tr>
<td>Subsequent modification if unable to tolerate 50 mg twice daily</td>
<td>Permanently discontinue TAFINLAR</td>
</tr>
</tbody>
</table>

REFERENCES


Created: 06/15
Effective: 06/18/18
Client Approval: 05/29/18
P&T Approval: N/A

HHW-HIPP0505(7/17)
Revised: 01/01/2020
Page 188
DACLIZUMAB

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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<tbody>
<tr>
<td>DACLIZUMAB</td>
<td>ZINBRYTA</td>
<td>16921</td>
<td>ROUTE = SUBCUTANEOUS</td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for DACLIZUMAB requires a diagnosis of a relapsing form of multiple sclerosis (MS) and that the patient meets the following criteria:

- Patient 18 years of age or older
- Trial of 2 preferred agents that have been FDA approved for the treatment of relapsing forms of multiple sclerosis (MS) (Please note: Other MS agents also require prior authorization [Tecfidera, Copaxone, Glatopa, Rebif, Aubagio, Gilenya, Avonex, Plegridy] and may require a prior trial of other medications first.)
- No pre-existing hepatic disease or impairment, including:
  - Active hepatitis B and C
  - Autoimmune hepatitis or other autoimmune conditions involving the liver
  - Baseline ALT and AST at least 2 times upper limit of normal (ULN)

RENEWAL CRITERIA

Our guideline for renewal of DACLIZUMAB requires that the patient meet the following criteria:

- No suspected autoimmune hepatitis
- No hepatic injury
  - Defined as elevated transaminases (>5x ULN), total bilirubin (>2x ULN), or both (ALT/AST ≥3x ULN + total bilirubin >1.5 ULN) with no other etiologies identified as a cause for the increases besides therapy with Zinbryta.

RATIONALE

Promote appropriate utilization of DACLIZUMAB based on FDA approved indication, labeled contraindications and dosing.

DOSAGE

The recommended dosage of Zinbryta is 150 milligrams injected subcutaneously once monthly.

A missed dose should be injected as soon as possible but no more than two weeks late. After two weeks, skip the missed dose and take the next dose on schedule. Administer only one dose at a time.

FDA APPROVED INDICATIONS

Zinbryta is an interleukin-2 receptor blocking antibody indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Zinbryta should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

CONTINUED ON NEXT PAGE
DACLIZUMAB

HOW SUPPLIED
A carton containing a single-dose prefilled syringe providing 1 mL of 150 mg/mL of daclizumab.

REFERENCES

Created: 08/16
Effective: 08/25/16
Client Approval: 08/17/16
P&T Approval: N/A
This drug requires a written request for prior authorization.

**GUIDELINES FOR USE**

The guideline named DACOMITINIB (Vizimpro) requires a diagnosis of metastatic non-small cell lung cancer (NSCLC). In addition, the following criteria must be met:

- The patient has epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test
- The requested medication will be used as first-line treatment

**RATIONALE**

Promote appropriate utilization of DACOMITINIB (Vizimpro) based on its FDA approved indications.

**FDA APPROVED INDICATION**

VIZIMPRO is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.

**RECOMMENDED DOSAGE**

45mg orally once daily with or without food

**HOW SUPPLIED**

Tablets: 15mg, 30mg, and 45 mg

**REFERENCES**


Created: 11/18
Effective: 11/23/18
Client Approval: 11/06/18
P&T Approval: N/A
INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Approval requires that the patient is overseen by a neurologist, has a diagnosis of multiple sclerosis, and has symptoms of walking disability.

RENEWAL CRITERIA

Continued approval requires that the patient has experienced an improvement in walking ability.

DALFAMPRIDINE

RATIONAL

Ensure appropriate utilization for dalfampridine.

FDA APPROVED INDICATIONS

Dalfampridine is approved in patients with multiple sclerosis to improve walking.

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/13
GUIDELINES FOR USE

The guideline for DAROLUTAMIDE (Nubeqa) requires a diagnosis of non-metastatic castration resistant prostate cancer (nmCRPC).

RATIONALE
Promote appropriate utilization and dosing of Nubeqa for its FDA approved indication.

FDA APPROVED INDICATIONS
Nubeqa is an androgen receptor inhibitor indicated for treatment of patients with non-metastatic castration-resistant prostate cancer.

DOSAGE AND ADMINISTRATION
600 mg of Nubeqa is administered orally twice daily.

AVAILABLE STRENGTHS
300 mg tablets

REFERENCES

Created: 10/19
Effective: 10/21/19
Client Approval: 10/07/19
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline named **DASATINIB (Sprycel)** requires a diagnosis of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic, accelerated, or myeloid or lymphoid blast phase, OR Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). In addition, the following criteria must be met:

**For the diagnosis of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, approval requires ONE of the following:**
- The patient is 18 years of age or older AND is newly diagnosed
- The patient is between 1 and 17 years of age

**For the diagnosis of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, accelerated phase, or myeloid or lymphoid blast phase, approval requires:**
- The patient is 18 years of age or older
- The patient has a resistance or intolerance to prior therapy including imatinib (Gleevec)
- The patient has had Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) mutational analysis confirming that the patient is negative for the following mutations: T315I, V299L, T315A, or F317L/V/I/C

**For the diagnosis of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), approval requires ONE of the following:**
- The patient is 18 years of age or older AND has a resistance or intolerance to prior therapy [e.g., imatinib (Gleevec) or nilotinib (Tasigna)]
- The patient is newly diagnosed, is between 1 and 17 years of age, AND is using Sprycel in combination with chemotherapy

**RATIONALE**
Ensure appropriate utilization of dasatinib based on FDA approved indication and NCCN guidelines.

**FDA APPROVED INDICATIONS**
Sprycel is a kinase inhibitor indicated for the treatment of:
- Newly diagnosed adults with Philadelphia chromosome-positive (PH+) chronic myeloid leukemia (CML) in chronic phase.
- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Philadelphia chromosome-positive chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.
- Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.
- Pediatric patients with Ph+ CML in chronic phase.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

DOsing
Chronic phase CML in adults:
• 100 mg once daily.
Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults:
• 140 mg once daily.
Chronic phase CML in pediatrics:
• Starting dose based on body weight.
• Tablet dosing is not recommended for patients weighing less than 10 kg.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Daily Dose (mg)</th>
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<tbody>
<tr>
<td>10 to less than 20</td>
<td>40 mg</td>
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<tr>
<td>20 to less than 30</td>
<td>60 mg</td>
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<tr>
<td>30 to less than 45</td>
<td>70 mg</td>
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<tr>
<td>At least 45</td>
<td>100 mg</td>
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</table>

Dose reduction to as low as 20mg daily can be considered for patients taking a strong CYP3A4 inhibitor.

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named DEFERASIROX (Exjade, Jadenu) requires a diagnosis of chronic iron overload due to blood transfusions or non-transfusion dependent thalassemia (NTDT). Treatment must be by or in consultation with a hematologist or hematologist-oncologist. The following criteria must also be met.

**Iron overload due to blood transfusions**
- At least 2 years of age and older
- Serum ferritin level consistently greater than 1000 mcg/L (at least 2 lab values in previous 3 months)

**Non-transfusion dependent thalassemia (NTDT)**
- At least 10 years of age and older
- Serum ferritin level consistently greater than 300 mcg/L (at least 2 lab values in previous 3 months)
- Liver iron concentration (LIC) at least 5 mg Fe/g dry weight or greater

RENEWAL CRITERIA

The guideline named DEFERASIROX (Exjade, Jadenu) renewal requires a diagnosis of chronic iron overload due to blood transfusions or non-transfusion dependent thalassemia (NTDT). The following criteria must also be met:

**Iron overload due to blood transfusions**
- Serum ferritin level consistently greater than 500 mcg/L (at least 2 lab values in previous 3 months)

**Non-transfusion dependent thalassemia (NTDT)**
- Serum ferritin level consistently greater than 300 mcg/L (at least 2 lab values in previous 3 months)
- Liver iron concentration (LIC) at least 3 mg Fe/g dry weight or greater. *(Liver iron concentration supersedes serum ferritin level when both measurements are available)*

CONTINUED ON NEXT PAGE
DEFERASIROX

RATIONALE
Promote appropriate utilization of DEFERASIROX based on FDA approved indication and treatment guidelines.

FDA APPROVED INDICATION
Jadenu (deferasirox, tablets or sprinkles) and Exjade (deferasirox, tablets for oral suspension) are indicated for the treatment chronic iron overload due to blood transfusions in patients 2 years of age and older. In addition, Jadenu and Exjade are indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L.

DOSAGE AND ADMINISTRATION
Exjade (deferasirox, tablets for oral suspension):
- Chronic transfusional iron overload: initial 20mg/kg orally once daily on an empty stomach, as an oral suspension. Calculate dose to the nearest whole tablet. Doses above 40mg/kg/day are not recommended.
- Non-transfusion-dependent thalassemia (NTDT): initial 10mg/kg orally once daily on an empty stomach, as an oral suspension. Calculate dose to the nearest whole tablet. Do not exceed a maximum of 20mg/kg/day.

Jadenu (deferasirox, tablets or sprinkles)
- Chronic transfusional iron overload: initial 14mg/kg orally once daily on an empty stomach or with a low-fat meal. Calculate to nearest whole tablet. Doses above 28mg/kg/day are not recommended.
- Non-transfusion-dependent thalassemia (NTDT): initial 7mg/kg orally once daily on an empty stomach or with a low-fat meal. Calculate to nearest whole tablet. Do not exceed a maximum of 14mg/kg/day.

REFERENCES
## GUIDELINES FOR USE

### INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named **DEFERIPRONE (Ferriprox)** requires a diagnosis of transfusional iron overload due to a thalassemia syndrome. Treatment must be prescribed by or in consultation with a hematologist or hematologist-oncologist. The following criteria must be also be met:

- **Trial of Exjade (deferasirox), Jadenu (deferasirox), or Desferal (deferoxamine) and the patient is experiencing one of the following:**
  - Intolerable toxicities, clinically significant adverse effects, or contraindication to current chelation therapy with Exjade, Jadenu, or Desferal.
- **Chelation therapy (i.e. Exjade [deferasirox], Jadenu [deferasirox], or Desferal [deferoxamine]) is inadequate defined by one of the following:**
  - Serum ferritin level consistently above 2500 mcg/L (at least 2 lab values in the previous 3 months).
  - The patient has evidence of cardiac iron accumulation (i.e. cardiac T2* MRI <10 milliseconds, iron induced cardiomyopathy, fall in left ventricular ejection fraction [LVEF], arrhythmia indicating inadequate chelation).

### RENEWAL CRITERIA

The guideline named **DEFERIPRONE (Ferriprox)** renewal requires a diagnosis of transfusional iron overload due to thalassemia syndromes. The following criteria must also be met:

- **Serum ferritin level consistently greater than 500 mcg/L (at least 2 lab values in the previous 3 months).**

### RATIONALE

Promote appropriate utilization of **DEFERIPRONE** based on FDA approved indication and treatment guidelines.

### FDA APPROVED INDICATIONS

**Ferriprox (deferiprone)** is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

CONTINUED ON NEXT PAGE
DEFERIPRONE

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION
Ferriprox (deferiprone): 25mg/kg to 33mg/kg orally three times per day for a total daily dose of 75mg/kg to 99mg/kg per day. Consider interrupting therapy if serum ferritin level consistently falls below 500mcg/L.

AVAILABLE STRENGTHS
Ferriprox (deferiprone) is available in 500mg film coated tablets and 100mg/mL oral solution.

REFERENCES

Created: 09/17
Effective: 01/01/18
Client Approval: 12/21/17
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named DEFEROXAMINE (Desferal) requires a diagnosis of chronic iron overload due to transfusion-dependent anemias. Treatment must be prescribed by or given in consultation with a hematologist or hematologist-oncologist. The following criteria must also be met:

- The patient is at least 3 years of age or older
- Serum ferritin level consistently greater than 1000 mcg/L (at least 2 lab values in the previous 3 months)

RENEWAL CRITERIA

The guideline named DEFEROXAMINE (Desferal) renewal requires a diagnosis of chronic iron overload due to transfusion-dependent anemias. The following criteria must also be met:

- Serum ferritin level consistently greater than 500 mcg/L (at least 2 lab values in the previous 3 months)

RATIONALE

Promote appropriate utilization of DEFEROXAMINE based on FDA approved indication and treatment guidelines.

CONTINUED ON NEXT PAGE
DEFEROXAMINE

FDA APPROVED INDICATION
Desferal (deferoxamine) is indicated for the treatment of acute iron intoxication and chronic iron overload due to transfusion-dependent anemias.

DOSAGE AND ADMINISTRATION
Desferal (deferoxamine)
- Acute iron intoxication:
  - IM (this route for patient not in shock): 1000mg following by 500mg every 4 hours for two doses. Depending on the clinical response, subsequent 500mg may be administered every 4 to 12 hours. Total amount should not exceed 6000mg in 24 hours.
  - IV (this route for patients in shock): 1000mg at a rate of 15mg/kg/hr. This may be followed by 500mg over 4 hours for a two doses. Depending on the clinical response, subsequent 500mg may be administered every 4 to 12 hours. Total amount should not exceed 6000mg in 24 hours.
- Chronic iron overload due to transfusion-dependent anemias
  - SQ: 1000 to 2000mg per day (20-40mg/kg/day) should be administered over 8 to 24 hours via a continuous infusion pump.
  - IV: in patients with intravenous access, the daily dose is 20-40mg/kg/day for children and 50-40mg/kg/day over 8 to 12 hours in adults for 5-7 days per week. Max dose in children is 40mg/kg/day and adults is 60mg/kg/day. In patients who are poorly compliant, Desferal may be administered prior to or following same day blood transfusion; however, the contribution of this mode of administration to iron balance is limited.
  - IM: 500 to 1000mg daily.

REFERENCES

Created: 08/17
Effective: 01/01/18
Client Approval: 12/21/17
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named DELAFLOXACIN (Baxdela) requires the patient to be at least 18 years of age and have an infection caused by ANY of the following pathogens: Staphylococcus aureus (including methicillin-resistant [MRSA] and methicillin susceptible [MSSA] isolates), Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae, Streptococcus anginosus Group (including Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus), Streptococcus pyogenes, and Enterococcus faecalis, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

RATIONALE
Promote appropriate utilization of Baxdela (delafloxacin) based on FDA approved indication and dosing. Inappropriate use of Baxdela could lead to an increase in resistant organisms.

FDA APPROVED INDICATIONS
BAXDELA is indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following:

Gram-positive organisms: Staphylococcus aureus (including methicillin-resistant [MRSA] and methicillin susceptible [MSSA] isolates), Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae, Streptococcus anginosus Group (including Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus), Streptococcus pyogenes, and Enterococcus faecalis.

Gram-negative organisms: Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

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FDA APPROVED INDICATIONS (CONTINUED)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of BAXDELA and other antibacterial drugs, BAXDELA should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DOSAGE AND ADMINISTRATION
Administer BAXDELA for injection 300 mg by intravenous infusion over 60 minutes, every 12 hours, or a 450-mg BAXDELA tablet orally every 12 hours for 5 to 14 days total duration.

DOSAGE FORMS
Injection: 300 mg of delafloxacin (equivalent to 433 mg delafloxacin meglumine) as a lyophilized powder in a single dose vial for reconstitution and further dilution before intravenous infusion. Oral Tablets: 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine).

REFERENCES
• Baxdela [Prescribing Information]. Lincolnshire, Illinois USA Melinta Therapeutics, Inc.; June 2017.

Created: 11/17
Effective: 01/20/18
Client Approval: 11/29/17
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE
INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for DENOSUMAB (Prolia) requires that the patient has a diagnosis of osteoporosis, the patient is receiving androgen deprivation therapy for non-metastatic prostate cancer, or the patient is receiving adjuvant aromatase inhibitor therapy for breast cancer. The following criteria must also be met:

For patients with a diagnosis of osteoporosis, approval requires ALL of the following:
- High risk for fractures defined as ONE of the following:
  - History of osteoporotic fracture(s)
  - 2 or more risk factors for fracture (e.g., history of multiple recent low trauma fractures, BMD T-score -2.5 or less, corticosteroid use, or use of GnRH analogs such as nafarelin, etc.)
  - Pre-treatment FRAX score greater than or equal to 20% for any major fracture OR greater than or equal to 3% for hip fracture
- Previous trial of or contraindication to an IV bisphosphonate (e.g. Reclast or Boniva).

For patients receiving androgen deprivation therapy with a diagnosis of non-metastatic prostate cancer, approval requires:
- Previous trial of or contraindication to an IV bisphosphonate (e.g. Reclast or pamidronate).

For patients receiving adjuvant aromatase inhibitor therapy with a diagnosis of breast cancer, approval requires:
- Previous trial of or a contraindication to an IV bisphosphonate (e.g. Reclast, pamidronate, or Boniva).

RENEWAL CRITERIA
Our guideline for renewal of DENOSUMAB (Prolia) requires that the patient has a diagnosis of osteoporosis, the patient is receiving androgen deprivation therapy for non-metastatic prostate cancer, or the patient is receiving adjuvant aromatase inhibitor therapy for breast cancer.

RATIONALE
To ensure appropriate use of PROLIA based on FDA and compendia approved indications and dosing.

PROLIA Dosing:
- Treatment of postmenopausal women with osteoporosis at high risk for fracture: Administer 60mg subcutaneously every 6 months in the upper arm, upper thigh, or abdomen.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture: Administer 60mg subcutaneously every 6 months in the upper arm, upper thigh, or abdomen.

CONTINUED ON NEXT PAGE
DENOSUMAB (PROLIA)

- Treatment to increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer: Administer 60mg subcutaneously every 6 months in the upper arm, upper thigh, or abdomen.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer: Administer 60mg subcutaneously every 6 months in the upper arm, upper thigh, or abdomen.
- Instruct patient to take calcium 1000mg daily and at least 400IU vitamin D daily.

Per American Association of Clinical Endocrinologists (AACE) medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis, alendronate, risedronate, zoledronic acid, and denosumab are first line therapy for postmenopausal women with osteoporosis. The Endocrine Society guidelines for the treatment of osteoporosis in men indicate bisphosphonates and denosumab as appropriate therapy for treatment.

National Comprehensive Cancer Network (NCCN) state the use of a bisphosphonate is generally the preferred intervention to improve bone mineral density for female patients receiving aromatase inhibitors. The NCCN also state denosumab, zolderonic acid, or alendronate are recommended for male patients receiving androgen replacement therapy when absolute fracture risk warrants drug therapy.

FDA APPROVED INDICATIONS
PROLIA is a RANK ligand (RANKL) inhibitor indicated for:
- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

REFERENCES
DENOSUMAB (XGEVA)

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<th>GCN</th>
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<td>DENOSUMAB</td>
<td>XGEVA</td>
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This drug requires a written request for prior authorization.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for DENOSUMAB (Xgeva) requires that the patient have a diagnosis of multiple myeloma, bone metastases from solid tumors, giant cell tumor of bone, or hypercalcemia of malignancy. The following criteria must also be met:

For patients with a diagnosis of multiple myeloma OR bone metastases from solid tumors, approval requires BOTH of the following:
- Xgeva is being used to prevent skeletal-related events (e.g., bone fractures or bone pain requiring radiation)
- Previous trial of or contraindication to an IV bisphosphonate (e.g. Zometa or pamidronate)

For patients with a diagnosis of giant cell tumor of bone, approval requires:
- Tumor is unresectable or surgical resection is likely to result in severe morbidity

For patients with a diagnosis of hypercalcemia of malignancy, approval requires:
- Previous trial of or contraindication to an IV bisphosphonate (e.g. Zometa or pamidronate)

RENEWAL CRITERIA

Our guideline for renewal of DENOSUMAB (Xgeva) requires that the patient have a diagnosis of multiple myeloma, bone metastases from solid tumors, giant cell tumor of the bone, or hypercalcemia of malignancy.

RATIONALE

To ensure appropriate use of denosumab based on FDA approved indication and dosing.

Xgeva Dosing:
- Multiple Myeloma and Bone Metastasis from Solid Tumors: Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen
- Giant Cell Tumor of Bone: Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.
- Hypercalcemia of Malignancy: Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.
- Administer subcutaneously in the upper arm, upper thigh, or abdomen
- Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia

CONTINUED ON NEXT PAGE
DENOSUMAB (XGEVA)

FDA APPROVED INDICATIONS
Xgeva is a RANK ligand (RANKL) inhibitor indicated for:
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

REFERENCES
GUIDELINES FOR USE

Approval requires that the patient is receiving Iprivask for the prevention of deep vein thrombosis (DVT) undergoing elective hip replacement surgery.

RATIONALE
To ensure appropriate use of desirudin for the prevention of deep vein thrombosis (DVT) in patients undergoing hip replacement surgery. The desirudin prescribing information states that the average duration of treatment is 9 to 12 days. The 2008 ACCP guidelines recommend venous thromboembolism treatment of up to 35 days.

FDA APPROVED INDICATIONS
Prophylaxis of deep vein thrombosis (DVT) in elective hip replacement surgery.

REFERENCES
The guideline named DEUTETRABENAZINE (Austedo) requires a diagnosis of chorea (involuntary movements) associated with Huntington’s disease or moderate to severe tardive dyskinesia. In addition, the following criteria must be met:

**For patients with Huntington’s chorea:**
- Therapy is prescribed by or given in consultation with a neurologist

**For patients with tardive dyskinesia:**
- Moderate to severe tardive dyskinesia has been present for at least 4 weeks
- Patient age of at least 18 years
- Therapy is prescribed by or given in consultation with a psychiatrist, neurologist, or movement disorder specialist
- Patient has history of antipsychotic medications or dopamine receptor blocking drugs used in the treatment of nausea and gastroparesis (e.g., metoclopramide, prochlorperazine, promethazine) for at least 3 months (or at least 1 month if patient is 60 years of age or older) as documented in the medical record or in prescription claims

**RATIONALE**
Promote appropriate utilization of DEUTETRABENAZINE (Austedo) based on FDA approved indication and dosing.

**FDA APPROVED INDICATION**
Austedo is indicated for the treatment of chorea associated with Huntington’s disease and for the treatment of tardive dyskinesia in adults.

**DOSAGE**
The dose of Austedo is determined individually for each patient based on reduction of chorea or tardive dyskinesia and tolerability.

**Dosing Recommendations to Initiate DEUTETRABENAZINE (Austedo) treatment**
When first prescribed to patients who are not being switched from tetrabenazine, the dosing recommendations are as follows:
- The recommended starting dose of Austedo is 6 mg administered orally once daily for patients with Huntington’s disease and 12 mg per day (6 mg twice daily) for patients with tardive dyskinesia
- The dose may be increased at weekly intervals in increments of 6 mg per day to a maximum recommended daily dosage of 48 mg
- Administer total daily dosages of 12 mg or above in two divided doses
- Administer Austedo with food. Swallow Austedo whole. Do not chew, crush, or break tablets.

CONTINUED ON NEXT PAGE
DEUTETRABENAZINE

FDA APPROVED INDICATION (CONTINUED)

Initial Dosing Recommendations for Patients Switching from Tetrabenazine to Austedo
Discontinue tetrabenazine and initiate Austedo the following day. The recommended initial dosing regimen of Austedo in patients switching from tetrabenazine to Austedo is as follows:

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<thead>
<tr>
<th>Current tetrabenazine daily dosage</th>
<th>Initial regimen of Austedo</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 mg</td>
<td>6 mg once daily</td>
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<td>25 mg</td>
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<td>24 mg twice daily</td>
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Dosage Adjustment with Strong CYP2D6 Inhibitors
In patients receiving strong CYP2D6 inhibitors (e.g., quinidine, antidepressants such as paroxetine, fluoxetine, and bupropion), the total daily dosage of Austedo should not exceed 36 mg (maximum single dose of 18 mg).

Dosage Adjustment in Poor CYP2D6 Metabolizers
In patients who are poor CYP2D6 metabolizers, the total daily dosage of Austedo should not exceed 36 mg (maximum single dose of 18 mg).

REFERENCES

Created: 04/17
Effective: 04/01/18
Client Approval: 02/18/18
P&T Approval: N/A
DEXTROMETHORPHAN WITH QUINIDINE

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GUIDELINES FOR USE

Our guideline for **DEXTROMETHORPHAN with QUINIDINE** requires a diagnosis of pseudobulbar affect (PBA).

RATIONALE

Ensure that Nuedexta is used solely for its FDA approved indication and in patients for whom it has been determined to be safe and efficacious.

FDA APPROVED INDICATION

Nuedexta is indicated for treatment of pseudobulbar affect (PBA).

REFERENCES


Created: 06/15
Effective: 07/01/17
Client Approval: 05/01/17
P&T Approval: 01/15
DIABETIC TEST STRIPS

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</table>

GUIDELINES FOR USE

Our guideline for **DIABETIC TEST STRIPS** requires that this product is only covered for patients that have tried the preferred blood glucose (diabetic) meters and test strips or are unable to use the preferred products. Test strips manufactured by Abbott or Roche are the preferred formulary agents. Approval for non-formulary test strips requires documentation of significant visual and/or cognitive impairment or the use of another manufacturer's companion insulin pump. Your physician did not indicate that you are using this product due to either of these conditions and therefore your request was not approved. Data management software is available for the formulary test strip products. Our guideline for **DIABETIC TEST STRIPS** limits testing to no more than 5 times per day unless the patient has a diagnosis of Type I diabetes mellitus or a diagnosis of Type II diabetes and is currently using an insulin pump.

RATIONALE

The intent of this guideline is to encourage the use of cost-effective formulary preferred glucose testing strips before considering coverage of non-preferred alternatives and to encourage testing frequency in accordance with treatment guidelines.

FDA APPROVED INDICATIONS

REFERENCES

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for DICHLORPHENAMIDE requires that the patient has a diagnosis of primary hypokalemic periodic paralysis, primary hyperkalemic periodic paralysis, or Paramyotonia Congenita. In addition, the following criteria must be met: patient age of at least 18 years, prescription written by or currently supervised by a neurologist, and that the patient does not have hepatic insufficiency, pulmonary obstruction, or a health condition that warrants concurrent use of high-dose aspirin. For primary hypokalemic periodic paralysis, a trial of acetazolamide AND a potassium-sparing diuretic (i.e., spironolactone, triamterene) is also required. For primary hyperkalemic periodic paralysis or Paramyotonia Congenita, a trial of acetazolamide AND a thiazide diuretic (i.e., hydrochlorothiazide) is also required. Renewal of DICHLORPHENAMIDE requires that the patient experience at least two fewer attacks per week from their baseline.

RENEWAL CRITERIA

Our guideline for DICHLORPHENAMIDE renewal requires that the patient experience at least two fewer attacks per week from their baseline.

RATIONALE

Promote appropriate utilization of DICHLORPHENAMIDE based on FDA approved indication, dosing, and contraindications. A step therapy has been implemented to promote cost-effective therapies based on previously available agents. A specialist edit has also been implemented to promote appropriate diagnosis and on-label use due to rare neuromuscular condition.

Keveyis is the first FDA approved treatment for primary hyperkalemic and primary hypokalemic periodic paralysis. The only clinical trials demonstrating a benefit for treatment in periodic paralysis involve the carbonic anhydrase inhibitor, dichlorphenamide. Dichlorphenamide was initially approved in 1958 as the branded drug Daranide for the treatment of elevated intraocular pressure but was discontinued in May 2003. In 2015, it was reintroduced as Keveyis as an orphan drug.

Affecting almost 5,000 people in the United States, periodic paralysis is a rare neuromuscular disorder related to a defect in muscle ion channels, characterized by episodes of painless but debilitating muscle weakness or paralysis (lasting minutes to an hour or two), which may be precipitated by heavy exercise, fasting, or high-carbohydrate meals. Periodic paralysis (PP) is classified as hypokalemic when episodes occur in association with low potassium blood levels or as hyperkalemic when episodes can be induced by elevated potassium. Most cases of periodic paralysis are hereditary, usually with an autosomal dominant inheritance pattern. Acquired cases of hypokalemic PP have been described in association with hyperthyroidism. When there is an established family history, episodes of periodic paralysis often require no further diagnostic evaluation. Otherwise, the diagnosis of PP is suggested by documentation of hypo/hyperkalemia during a typical attack of weakness.

CONTINUED ON NEXT PAGE
DICHLORPHENAMIDE

RATIONALE (CONTINUED)

Even when this is demonstrated, diagnosis is not as easily accomplished, as other testing is required to rule out alternative diagnoses. Genetic testing is available for most, but not all of the mutations underlying hypokalemic PP. Evidence of myotonia (seen in up to 80% with this subtype) during electromyographic (EMG) examination can help support the diagnosis of hyperkalemic PP.

Nonpharmacologic interventions that may be effective for preventing attacks include a low-carbohydrate diet and refraining from vigorous exercise. When attacks continue to be disabling, prophylactic treatment is indicated to avoid morbidity, even mortality, which can be associated with hospitalization and acute treatment. When lifestyle changes are not sufficiently effective, symptomatic potassium supplementation, diuretics, and medications such as carbonic anhydrase inhibitors are used. The mechanism whereby carbonic anhydrase inhibitors are effective in PP is not clear, but appears to be independent of carbonic anhydrase inhibition. Studies in animal models suggest that these agents trigger calcium-activated potassium channels on skeletal muscle. Acetazolamide, another carbonic anhydrase inhibitor, is also commonly reported to be effective in reducing attacks when dosed at 250mg twice daily. However, one retrospective study found that only half of patients respond to acetazolamide therapy. The subset of patients who might find acetazolamide treatment helpful are those who experience mild, fluctuating weakness between attacks. For hypokalemic PP, potassium-sparing diuretics such as spironolactone (100mg daily) or triamterene (150mg daily) can be used as a supplement or as an alternative to a carbonic anhydrase inhibitor in patients who experience worsening or intolerance. For hyperkalemic PP, thiazide diuretics (i.e. hydrochlorothiazide 25-50mg daily) have been reported as helpful in controlling attacks in some patients.

DOSE

Initiate dosing at 50 mg twice daily. The initial dose may be increased or decreased based on individual response, at weekly intervals (or sooner in case of adverse reaction). The maximum total daily dose is 200 mg.

Primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants are a heterogeneous group of conditions, for which the response to Keveyis may vary. Therefore, prescribers should evaluate the patient's response after 2 months of treatment to decide whether Keveyis should be continued.

FDA APPROVED INDICATIONS

Keveyis is an oral carbonic anhydrase inhibitor indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants.
DICHLOPHENAMIDE

REFERENCES

- Keveyis [Prescribing Information]. Hawthorne, NY: Taro Pharmaceuticals; August 2015.
- Periodic paralysis international. Available at: http://hkpp.org/patients/hyperkpp-FAQ Updated June 25, 2011.
DICLOFENAC TOPICAL

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GUIDELINES FOR USE

Approval requires a trial of or a contraindication to topical fluorouracil (Efudex, Fluoroplex, Carac).

RATIONALE
To promote clinically appropriate utilization of oral NSAIDs over Flector, Pennsaid and Voltaren.
To promote clinically appropriate utilization of Solaraze for Actinic Keratosis.

FDA APPROVED INDICATIONS
FLECTOR: Topical treatment of acute pain due to minor strains, sprains and contusions.
PENNSAID: Treatment of signs and symptoms of osteoarthritis of the knee(s).
SOLARAZE: Topical treatment of actinic keratoses.
VOLTAREN: Relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands.

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/12
DIHYDROERGOTAMINE MESYLATE

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GUIDELINES FOR USE

Our guideline for **DIHYDROERGOTAMINE MESYLATE (MIGRANAL)** requires a diagnosis of migraine headaches, excluding hemiplegic and basilar migraines. In addition, documentation of trial and failure of ALL of the following for migraine is required unless contraindicated:

- Acetaminophen
- Non-steroidal anti-inflammatory agent (NSAID) (e.g., ibuprofen, naproxen)
- **TWO** Selective serotonin agonists (e.g., sumatriptan, rizatriptan)

Chart notes indicating doses and dates of therapy are required in the absence of electronic prescription claims history.

RATIONALE

Ensure appropriate criteria are used for the management of requests for MIGRANAL according to approved indication, dosing, and national treatment guidelines.

FDA APPROVED INDICATIONS

MIGRANAL is an ergot derivative indicated for the acute treatment of migraine headaches with or without aura; not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

HOW SUPPLIED

INTRANASAL: 4 mg/mL solution

DOΣING & ADMINISTRATION

MIGRANAL is for intranasal use only. One spray should be administered in each nostril. Fifteen minutes later, an additional one spray should be administered in each nostril if needed, for a total dosage of four sprays. MIGRANAL should not be used for chronic daily administration.

REFERENCES


Created: 08/19
Effective: 01/01/20
Client Approval: 10/14/19
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires a diagnosis of relapsing-remitting multiple sclerosis and an age of at least 18 years.

RATIONALE
To ensure appropriate use aligned with FDA approved indication.

The starting dose for Tecfidera is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally.

Multiple sclerosis is an autoimmune inflammatory demyelinating disease of the central nervous system characterized by instances of disease exacerbation (relapses). Relapses cause acute neurologic dysfunction, which can last a minimum of 24 hours and peak over the course of several days or weeks. After the relapse subsides, patients may fully recover or have permanent residual impairments. In RRMS, relapses are clearly defined and the disease does not progress during the time between each relapse. Although there are other types of multiple sclerosis, RRMS is the most common.

The safety and efficacy of Tecfidera was evaluated in two randomized, multi-national, double-blind, phase III trials. The first trial, CONFIRM, randomized 1400 adults with relapsing remitting multiple sclerosis (RRMS) to one of four groups: Tecfidera 240mg twice daily, Tecfidera 240mg three times daily, Copaxone 20mg daily, and placebo. The primary endpoint for CONFIRM was annualized relapse rate (ARR) at 2 years. Secondary endpoints included the proportion of patients with relapse at two years, disability progression at two years, number of new/enlarging hyperintense lesions on T2, and number of new/enlarging hypointense lesions on T1. Tertiary endpoints included a comparison of the relative benefits and risks of Tecfidera or Copaxone versus placebo and the number of gadolinium enhancing lesions. Approximately 29% of the patients had tried injectable therapy for RRMS before participating in the trial.

The second trial, DEFINE, randomized 1200 adults with RRMS to one of three groups: Tecfidera 240mg twice daily, Tecfidera 240mg three times daily, and placebo. The primary endpoint for DEFINE was the proportion of patients with relapse at 2 years. Secondary endpoints included the ARR at 2 years, disability progression at two years, number of new/enlarging hyperintense lesions on T2 and number of gadolinium enhancing lesions. Approximately 40% of the patients had tried injectable therapy for RRMS before participating in the trial.

Tecfidera significantly reduced ARR and the proportion of patients with relapse in both studies. However only DEFINE found a significant difference in disability progression. The ability of Tecfidera to reduce the risk of relapse is 34-49%. Copaxone reduced the risk of relapse by approximately 30%. All three MRI parameters (number of new/enlarging hyperintense lesions on T2, number of new/enlarging hyperintense lesions on T1, number of gadolinium enhancing lesions).
DIMETHYL FUMARATE

RATIONAL (CONTINUED)

hypointense lesions on T1, and number of gadolinium enhancing lesions) were shown to be significant for CONFIRM. DEFINE also found significance in both of its MRI data (number of new/enlarging hyperintense lesions on T2 and number of gadolinium enhancing lesions). Post hoc analysis did not find a difference in efficacy between Tecfidera and Copaxone in any of the clinical and MRI data except that Tecfidera had significantly less hyperintense lesions on T2.

Tecfidera has a favorable safety profile compared to the other oral agents currently approved for RRMS; however, tolerability during the first month of treatment was an issue in clinical trials. The most common adverse reactions (incidence ≥10% and ≥2% more than placebo) for Tecfidera were flushing, abdominal pain, diarrhea, and nausea.

In clinical trials, approximately 40% of patients taking Tecfidera experienced flushing. Flushing symptoms were generally mild or moderate, began soon after drug initiation, and resolved over time. Taking Tecfidera with food may reduce symptoms. Three percent (3%) of patients discontinued Tecfidera for flushing.

Tecfidera caused gastrointestinal (GI) events that were observed early in the course of treatment (primarily in the first month) and usually decreased over time. The incidence of abdominal pain, diarrhea, and nausea in those taking Tecfidera was 18%, 14%, and 12%, respectively. In those taking placebo, the incidence of abdominal pain, diarrhea, and nausea was 10%, 11%, and 9%, respectively. Four percent (4%) of patients treated with Tecfidera and less than 1% of placebo patients discontinued due to GI events.

Tecfidera may decrease lymphocyte counts. During the first year, mean lymphocyte counts decreased by approximately 30% and then remained stable. Four weeks after stopping Tecfidera, mean lymphocyte counts increased but did not return to baseline. Six percent (6%) of Tecfidera patients and <1% of placebo patients experienced lymphocyte counts <0.5x10^9/L. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with Tecfidera or placebo, respectively. Before initiation of therapy, it is recommended to check a recent complete blood cell count to identify patients with pre-existing low lymphocyte counts. Tecfidera is a Pregnancy Category C.

FDA APPROVED INDICATIONS
Tecfidera is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

REFERENCES
GUIDELINES FOR USE

Approval requires a diagnosis of cystic fibrosis and requests for twice daily dosing require a trial of once daily dosing.

RATIONALE
Promote appropriate utilization of Pulmozyme based on FDA approved indication.

DOSAGE: The recommended dose for use in most cystic fibrosis patients is one 2.5mg single-use ampule inhaled once daily using a recommended nebulizer. Some patients may benefit from twice daily administration.

FDA APPROVED INDICATION
Pulmozyme is indicated in conjunction with standard therapies in the management of cystic fibrosis patients to improve pulmonary function.

REFERENCE

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 05/12
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline for DROXIDOPA (Northera) requires a diagnosis of neurogenic orthostatic hypotension (NOH) and patient age of 18 years or older. Additional guideline requirements apply:

- Patient has a documented diagnosis of Neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy
- Prescription was initiated by or in consultation with a neurologist or cardiologist
- Patient has persistent symptoms of neurogenic orthostatic hypotension, which includes dizziness, lightheadedness, and the feeling of 'blacking out'
- Prescriber performed baseline blood pressure readings while the patient is sitting and also within 3 minutes of standing from a supine (lying face up) position
- Patient has a documented decrease of at least 20 mmHg in systolic blood pressure or 10 mmHg diastolic blood pressure within 3 minutes after standing from a sitting position

RENEWAL CRITERIA

Our guideline for DROXIDOPA (Northera) renewal requires a diagnosis of neurogenic orthostatic hypotension (NOH) and that the patient meets the following criteria while on therapy with Northera:

- Patient has demonstrated improvement in severity from baseline symptoms of dizziness, lightheadedness, feeling faint, or feeling like the patient may black out
- Patient had an increase in systolic blood pressure from baseline of at least 10 mmHg upon standing from a supine (lying face up) position

RATIONALE

Promote clinically appropriate utilization of Northera (droxidopa) based on its FDA approved indication and dosing.

Northera is indicated for the treatment neurogenic orthostatic hypotension (NOH) that is associated with Parkinson's disease (PD), multiple system atrophy, and pure autonomic failure. People with NOH are severely limited in their ability to perform routine daily activities that require walking or standing. Northera is a synthetic amino acid precursor of norepinephrine, which increases blood pressure by inducing peripheral arterial and venous vasoconstriction.

Orthostatic hypotension is diagnosed when within two to five minutes of quiet standing (after a five minute period of supine rest), one or both of the following is present: a) At least a 20 mmHg fall in systolic pressure, b) At least a 10 mmHg fall in diastolic pressure.

CONTINUED ON NEXT PAGE
Northera has a boxed warning regarding the risk of increased blood pressure while lying down (supine hypertension). The most common adverse events seen in clinical trials were headache, dizziness, nausea, hypertension, and fatigue.

In the clinical trials referenced in the Northera prescribing information, a ‘responder’ to treatment had to demonstrate improvement on the OHSA Item #1 score by at least 1 point, as well as an increase in systolic blood pressure of at least 10 mm Hg post-standing, during the open-label dose titration period.

Effectiveness of Northera beyond 2 weeks of treatment has not been established. The continued effectiveness of Northera should be assessed periodically.

DOSE
The recommended starting dose of Northera is 100mg orally three times a day, upon arising in the morning, at midday, and in the late afternoon at least 3 hours prior to bedtime (to reduce the potential for supine hypertension during sleep). Northera may be administered with or without food.

Titrate to symptomatic response, in increments of 100mg three times daily every 24-48 hours up to a maximum dose of 600mg three times daily (maximum total daily dose of 1800mg).

FDA APPROVED INDICATIONS
Northera is indicated for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) caused by primary autonomic failure [Parkinson’s disease (PD), multiple system atrophy and pure autonomic failure], dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.

Northera received orphan-product designation from the FDA.

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named DUPILUMAB (Dupixent) requires a diagnosis of moderate to severe atopic dermatitis, moderate to severe asthma, or chronic rhinosinusitis with nasal polyps. In addition, the following criteria must be met:

For the diagnosis of moderate to severe atopic dermatitis, approval requires:

- The patient meets at least ONE of the following for disease severity:
  - Atopic dermatitis involving at least 10% of body surface area (BSA) OR
  - Atopic dermatitis affecting the face, head, neck, hands, feet, groin, or intertriginous areas
- The patient has at least TWO of the following:
  - Intractable pruritus
  - Cracking and oozing/bleeding of affected skin
  - Impaired activities of daily living
- Prescribed by or in consultation with a dermatologist or allergist/immunologist
- Patient is 12 years of age or older
- Documentation of inadequate response or contraindication to TWO of the following therapeutic classes within the previous 365 days: topical corticosteroids, topical calcineurin inhibitors [e.g., Elidel (pimecrolimus), Protopic (tacrolimus)], topical PDE-4 inhibitors [e.g., Eucrisa (crisaborole)], or phototherapy

For the diagnosis of moderate to severe asthma, approval requires:

- The patient has an eosinophilic phenotype asthma with a documented blood eosinophil level of at least 150 cells/mcL within the past 6 months OR oral corticosteroid-dependent asthma
- The patient is 12 years of age or older
- The patient is currently adherent on a maximally tolerated inhaled corticosteroid plus at least ONE other maintenance medication (e.g., long-acting inhaled beta2-agonist, long-acting muscarinic antagonist, a leukotriene receptor antagonist, theophylline)
- The patient has experienced at least TWO asthma exacerbations within the past 12 months (exacerbation is defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days)
- The patient has ONE of the following:
  - Asthma Control Test (ACT) score of less than 20
  - Asthma Control Questionnaire (ACQ) score of at least 1.5
  - Asthma Therapy Assessment Questionnaire (ATAQ) score of at least 1
- Dupixent will be used as add-on maintenance treatment
- The patient is not being concurrently treated with Xolair or an anti-IL5 asthma biologic (e.g., Nucala, Cinqair, Fasenra)
- Dupixent is prescribed by or given in consultation with a physician specializing in pulmonary or allergy medicine

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

For the diagnosis of chronic rhinosinusitis with nasal polyps, approval requires:
- The patient has TWO of the following symptoms for 12 weeks or longer:
  - Nasal blockage, obstruction, or congestion
  - Nasal discharge (i.e., anterior or posterior nasal drip)
  - Facial pain, pressure, or fullness
  - Reduction or loss of smell
- The patient has sinonasal inflammation documented by ONE of the following:
  - Nasal endoscopy showing edema or purulent mucus in the middle meatus or ethmoid region or nasal polyps
  - Computed tomography showing inflammation of paranasal sinuses
- Prescribed by or in consultation with an otolaryngologist
- Patient is 18 years of age or older
- Documentation of inadequate response or contraindication to BOTH of the following within the previous 365 days: intranasal corticosteroid and leukotriene inhibitor (e.g., montelukast)

RENEWAL CRITERIA

The guideline named DUPILUMAB (Dupixent) requires a diagnosis of moderate to severe atopic dermatitis, moderate to severe asthma, or chronic rhinosinusitis with nasal polyps for renewal. In addition, the following criteria must be met:

For the diagnosis of moderate to severe atopic dermatitis, approval requires:
- Documentation that the patient has experienced or maintained improvement in at least TWO of the following:
  - Intractable pruritus
  - Cracking and oozing/bleeding of affected skin
  - Impaired activities of daily living

For the diagnosis of moderate to severe asthma, approval requires:
- The patient has experienced a reduction in asthma exacerbations (defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days) from baseline
- The patient has experienced an improvement in the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Asthma Therapy Assessment Questionnaire (ATAQ) score from baseline
- The patient has decreased their total daily oral corticosteroid dose from baseline if the patient was on maintenance therapy with oral corticosteroids prior to initiation of Dupixent

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA (CONTINUED)

For the diagnosis of chronic rhinosinusitis with nasal polyps, approval requires:

- The patient has experienced an improvement in sinonasal inflammation or a reduction in number of polyps documented by **ONE** of the following:
  - Nasal endoscopy
  - Computed tomography
- The patient has experienced an improvement in **TWO** of the following symptoms:
  - Nasal blockage, obstruction, or congestion
  - Nasal discharge (i.e., anterior or posterior nasal drip)
  - Facial pain, pressure, or fullness
  - Reduction or loss of smell

RATIONALE
Ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for (Dupixent) dupilumab.

FDA APPROVED INDICATIONS
Dupixent is indicated for the treatment of:

- Patients aged 12 years and older with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids
- As an add-on maintenance treatment in patients with moderate to severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma
- As an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps

DOSING
Atopic Dermatitis
- For adults the recommended dose is an initial subcutaneous dose of 600mg (two 300mg injections in different sites), followed by 300mg subcutaneously given every other week.
- For adolescents weighing less than 60 kg, the recommended dose is an initial subcutaneous dose of 400 mg (two 200 mg injections in different sites), followed by 200 mg subcutaneously given every other week.
- For adolescents weighing 60 kg or more, the recommended dose is the same as that listed above for adults.

Asthma
- The recommended dose is an initial subcutaneous dose of 600mg (two 300mg injections in different sites), followed by 300mg subcutaneously given every other week OR an initial subcutaneous dose of 400mg (two 200mg injections in different sites), followed by 200mg subcutaneously given every other week.
- For patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which Dupixent is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week.

CONTINUED ON NEXT PAGE
DUPILUMAB

FDA APPROVED INDICATIONS (CONTINUED)

DOSING
Chronic Rhinosinusitis with Nasal Polyps
- The recommended dose for adult patients is an initial subcutaneous dose of 300 mg given every other week.

DOSAGE FORMS AND STRENGTHS
Dupixent is supplied as 200mg/1.14mL and 300mg/2mL single dose prefilled syringes.

REFERENCES
- Hamilos D, Holbrook E. Chronic rhinosinusitis: Clinical manifestations, pathophysiology, and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed June 27, 2019.
ECALLANTIDE

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This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline named ECALLANTIDE requires a diagnosis of hereditary angioedema, documented age of 12 years old or older, and administration of the medication by a healthcare professional.

RATIONALE

Ensure appropriate use of ecallantide based on FDA approved indication and dosing.

The recommended dose of ecallantide is 30mg (3mL) subcutaneously in three 10mg (1mL) injections. If symptoms do not subside, an additional 30mg dose can be given within a 24 hour period.

FDA APPROVED INDICATIONS

Kalbitor (ecallantide) is indicated for the treatment of acute attacks of hereditary angioedema in adults 12 years of age and older.

BOXED WARNING FOR ECALLANTIDE:

Anaphylaxis has occurred after administration of Kalbitor. Because of the risk of anaphylaxis, Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer Kalbitor to patients with known clinical hypersensitivity to Kalbitor.

REFERENCES


Created: 12/17
Effective: 02/02/18
Client Approval: 12/28/17
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline for Eculizumab requires a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), or generalized myasthenia gravis. The following criteria must also be met:

- Eculizumab (Soliris) is NOT being used for Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS)

For patients with generalized Myasthenia gravis (gMG), approval requires:

- The patient is 18 years of age or older
- The patient’s diagnosis is confirmed by a positive Anti-acetylcholine receptor (AchR) antibody test
- The patient has failed TWO of the following immunosuppressive therapies: corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine

For patients with paroxysmal nocturnal hemoglobinuria (PNH), approval requires:

- The patient is 18 years of age or older
- The patient has confirmed PNH as demonstrated by ALL of the following via flow cytometry:
  - At least 2 different GPI-protein deficiencies (e.g., CD55, CD59) on at least 2 cell lineages (e.g., erythrocytes, granulocytes)
  - PNH granulocyte clone size ≥10%
- The requested medication is prescribed by or in consultation with a hematologist
- The patient meets ONE of the following:
  - Transitioning from alternative complement inhibitor therapy (i.e., Ultomiris)
  - Documentation of evidence of intravascular hemolysis (e.g., lactate dehydrogenase [LDH] level ≥1.5 X ULN, hemoglobinuria) OR history of major adverse vascular event from thromboembolism

CONTINUED ON NEXT PAGE
ECULIZUMAB

RENEWAL CRITERIA
The guideline for ECULIZUMAB renewal requires a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), or generalized myasthenia gravis.

For patients with PNH, the following criterion must be met:
- Physician attestation of clinical benefit compared to baseline (e.g., reduction in number of blood transfusions, improvement/stabilization of lactate dehydrogenase (LDH) and hemoglobin levels)

For patients with aHUS, the following criterion must be met:
- Documentation (i.e., chart notes, lab results) that the patient has experienced clinical improvement (e.g., improved platelet count, serum lactate dehydrogenase levels, reduced serum creatinine, reduced need for dialysis) while receiving Soliris therapy is required

For patients with generalized myasthenia gravis, the following criterion must be met:
- Documentation (i.e., chart notes) that the patient has experienced an improvement in daily functioning (e.g., reduced muscle weakness, improved swallowing, reduction in double vision, improved grip, improved forced vital capacity) while receiving Soliris therapy is required

RATIONALE
To ensure appropriate use of Soliris based on FDA approved indication and prescribing information.

FDA APPROVED INDICATIONS
Soliris is indicated for 1) paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis, 2) atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy, and 3) for the treatment of adult patients with generalized myasthenia gravis (gMG) who are antiacetylcholine receptor (AchR) antibody positive.

Limitation of Use:
Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

CONTINUED ON NEXT PAGE
ECULIZUMAB

FDA APPROVED INDICATIONS (CONTINUED)

DOsing AND ADMINISTRATION
For patients 18 years of age and older with PNH, Soliris therapy consists of:
• 600 mg weekly for the first 4 weeks, followed by
• 900 mg for the fifth dose 1 week later, then
• 900 mg every 2 weeks thereafter.

For patients 18 years of age and older with aHUS, Soliris therapy consists of:
• 900 mg weekly for the first 4 weeks, followed by
• 1200 mg for the fifth dose 1 week later, then
• 1200 mg every 2 weeks thereafter.

For patients with generalized myasthenia gravis, Soliris therapy consists of:
• 900 mg weekly for the first 4 weeks, followed by
• 1200 mg for the fifth dose 1 week later, then
• 1200 mg every 2 weeks thereafter.

For patients less than 18 years of age, Soliris should be dosed as follows:

<table>
<thead>
<tr>
<th>Patient Body Weight</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1200 mg at week 5; then 1200 mg every 2 weeks</td>
</tr>
<tr>
<td>30 kg to less than 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20 kg to less than 30 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3; then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg to less than 20 kg</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg to less than 10 kg</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>

Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points.

CONTINUED ON NEXT PAGE
ECULIZUMAB

FDA APPROVED INDICATIONS (CONTINUED)

BOXED WARNING
Soliris contains a black box warning regarding life-threatening and fatal meningococcal infections that have occurred in patients treated with Soliris. The warning advises prescribers to comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies. Patients should be immunized with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. Patients should be monitored for early signs of meningococcal infections and evaluated immediately if infection is suspected. Soliris is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in REMS and other information are available at 1-888-SOLIRIS.

HOW SUPPLIED
Soliris (eculizumab) is supplied as 300 mg single-dose vials containing 30 mL of 10 mg/mL sterile, preservative-free Soliris solution per vial.

REFERENCES

Created: 10/15
Effective: 01/01/20
Client Approval: 10/14/19
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for **EFINACONAZOLE** requires a previous trial or contraindication to oral terbinafine or oral itraconazole and ciclopirox topical solution and one of the following: 1) a diagnosis of onychomycosis of the toenails and, 2) presence of complicating factors such as diabetes, peripheral vascular disease, a suppressed immune system, or 3) pain surrounding the nail or soft tissue.

RATIONALE

Promote clinically appropriate utilization of Jublia (efinaconazole) based on its FDA approved indication and dosing.

Jublia is an azole antifungal indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophyte*. Onychomycosis refers to nail infections caused by any fungus, including yeasts and non-dermatophyte molds. Although onychomycosis is usually a cosmetic concern to patients, it also causes physical discomfort for some, particularly with more severe or advanced disease. Patients may experience chronic pain or acute pain exacerbated by nail cutting, footwear, or pressure from bedclothes. Additionally, in patients with diabetes or other immunocompromised states, onychomycosis may increase the risk of bacterial infections such as cellulitis.

Jublia may not be as efficacious as oral antifungals (e.g. terbinafine and itraconazole) in the treatment of onychomycosis, but its safety profile is improved. The most common adverse reactions associated with Jublia are ingrown toenails, application site dermatitis, application site vesicles, and application site pain. Additionally, Jublia neither interacts with cytochrome P450 enzymes nor is associated with hepatotoxicity, as seen with oral antifungals.

DOSE

Apply one drop onto each affected toenail once daily (for the big toenail, also apply a second drop to the end of the toenail) for 48 weeks. Use the brush attached to the bottle to gently spread Jublia to the entire toenail including the cuticle, toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate.

For topical use only and not for oral, ophthalmic, or intravaginal use.

**Note:** 1 bottle of 4mL contains 200 applications.

**FDA APPROVED INDICATIONS**

Topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophyte*

CONTINUED ON NEXT PAGE
REFERENCES (CONTINUED)


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/14
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named **ELAGOLIX (Orilissa)** requires a diagnosis of moderate to severe pain associated with endometriosis. Additionally, the following criteria must be met:

- The patient is 18 years of age or older
- The requested medication is prescribed by or in consultation with an obstetrician/gynecologist
- The patient had a previous trial of or contraindication to a nonsteroidal anti-inflammatory drug (NSAID) **AND** a progestin-containing contraceptive preparation (e.g., combination hormonal contraceptive preparation, progestin-only contraceptive preparation)

Requests for Orilissa 200 mg twice daily will only be approved in patients with normal liver function or mild hepatic impairment (Child-Pugh Class A).

RENEWAL CRITERIA

The guideline named **ELAGOLIX (Orilissa)** requires a diagnosis of moderate to severe pain associated with endometriosis for renewal. The following criteria must also be met:

- Physician attestation of improvement of pain related to endometriosis while on therapy
- The patient has normal liver function or mild hepatic impairment (Child-Pugh Class A)

Requests will **not** be approved if the patient meets one of the following conditions:

- The patient has received a 6-month course of Orilissa 200 mg twice daily
- The patient has received a 6-month course of Orilissa 150 mg once daily and the patient has moderate hepatic impairment (Child-Pugh Class B)
- The patient has received a 24-month course of Orilissa 150 mg once daily and the patient has normal liver function or mild hepatic impairment (Child-Pugh Class A)

RATIONALE

Ensure appropriate utilization and safety criteria are used for the management of requests for Orilissa (elagolix).

**FDA-APPROVED INDICATION**

Orilissa (elagolix) is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis.

**CONTINUED ON NEXT PAGE**
ELAGOLIX

FDA-APPROVED INDICATION (CONTINUED)

DOsing AND ADMINISTRATION
Pregnancy should be excluded before starting Orilissa (elagolix), or Orilissa (elagolix) can be initiated within 7 days from the onset of menses. The lowest effective dose should be used, taking into account the severity of symptoms and treatment objectives. Treatment duration should be limited due to the potential for decreases in bone mineral density that may not be completely reversible.

Orilissa (elagolix) is dosed according to the following table:

<table>
<thead>
<tr>
<th>Hepatic Function</th>
<th>Dosing Regimen</th>
<th>Maximum Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal hepatic function or mild hepatic impairment (Child-Pugh Class A)</td>
<td>150 mg once daily</td>
<td>24 months</td>
</tr>
<tr>
<td></td>
<td>200 mg twice daily*</td>
<td>6 months</td>
</tr>
<tr>
<td>Moderate hepatic impairment (Child-Pugh Class B)</td>
<td>150 mg once daily</td>
<td>6 months</td>
</tr>
<tr>
<td>Severe hepatic impairment (Child-Pugh Class C)</td>
<td></td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

*Regimen to be considered for those with coexisting dyspareunia

REFERENCES
GUIDELINES FOR USE

Our guideline for **ELIGLUSTAT TARTRATE** requires a diagnosis of type 1 (non-neuronopathic) Gaucher’s disease in a patient at least 18 years of age. Twice daily dosing will be approved for patients who are extensive or immediate metabolizers of CYP2D6 inhibitors. Once daily dosing will be approved for patients who are poor metabolizers of CYP2D6. This medication is not approved for the following patients: CYP2D6 ultra-rapid metabolizers or CYP2D6 indeterminate metabolizer.

**ELIGLUSTAT TARTRATE**

**RATIONALE**

Promote appropriate utilization and dosing of Cerdelga (eliglustate tartrate) based on the FDA approved indication. Eliglustat is a CYP2D6 and CYP3A substrate. Drugs that inhibit CYP2D6 and CYP3A metabolism pathways may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias.

The recommended dosage of CERDELGA is 84 mg twice daily in CYP2D6 extensive metabolizers (EMs), and intermediate metabolizers (IMs). The recommended dosage in CYP2D6 poor metabolizers (PMs) is 84 mg once daily.

Some inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient’s metabolizer status. Co-administration of CERDELGA with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the patient’s CYP2D6 metabolizer status to reduce the risk of potentially significant adverse reactions.

Reduce the dosage of CERDELGA to 84 mg once daily for:
- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors
- CYP2D6 EMs taking strong or moderate CYP3A inhibitors

**CONTINUED ON NEXT PAGE**
RATIONAL (CONTINUED)

Table 1. Established and other potentially significant drug interactions: Alteration in Cerdelga Dosage May be Recommended Based on Predicted Interaction in Extensive Metabolizers (EM) and Intermediate Metabolizers (IM)

<table>
<thead>
<tr>
<th>CYP450 Inhibitors</th>
<th>Recommended CERDELEGA Dosage, by CYP2D6 Metabolizer Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong or Moderate CYP2D6 inhibitors concomitantly with Strong or Moderate CYP3A inhibitors</td>
<td>Contraindicated</td>
</tr>
<tr>
<td><strong>Strong CYP2D6 inhibitors</strong>&lt;br&gt; e.g., paroxetine</td>
<td>84 mg once daily</td>
</tr>
<tr>
<td><strong>Moderate CYP2D6 inhibitors</strong>&lt;br&gt; e.g., terbinafine</td>
<td>84 mg once daily</td>
</tr>
<tr>
<td><strong>Strong CYP3A inhibitors</strong>&lt;br&gt; e.g., ketoconazole</td>
<td>84 mg once daily</td>
</tr>
<tr>
<td><strong>Moderate CYP3A inhibitors</strong>&lt;br&gt; e.g., fluconazole</td>
<td>84 mg once daily</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

Table 2. Established and other potentially significant drug interactions: Alteration in Cerdelga Dosage May be Recommended Based on Predicted Interaction in Poor Metabolizers

<table>
<thead>
<tr>
<th>CYP450 Inhibitors</th>
<th>Recommended CERDELGA Dosage for PMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A inhibitors e.g., ketoconazole</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Moderate CYP3A inhibitors e.g., fluconazole</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Weak CYP3A inhibitors e.g., ranitidine</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

FDA APPROVED INDICATIONS

CERDELGA is a glucosylceramide synthase inhibitor indicated for the long term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.

Limitations of Use:
- CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect
- A specific dosage cannot be recommended for CYP2D6 indeterminate metabolizers

REFERENCES
- Cerdelga [Prescribing Information]. Waterford, Ireland: Genzyme; August 2014
GUIDELINES FOR USE

Our guideline for ELOSULFASE ALFA requires a diagnosis of Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

RATIONALE

Promote appropriate utilization of Vimizim based on FDA approved indication.

Vimizim is the first agent approved to treat Morquio A syndrome. Prior to the approval of this medication, complications of Morquio A syndrome, such as, skeletal abnormalities, heart disease, hearing and vision loss, and breathing difficulties, are often treated medically and surgically as needed.

Morquio A syndrome, an autosomal recessive lysosomal storage disease, affects approximately 800 individuals in the United States. Morquio A syndrome is classified within a group of diseases called mucopolysaccharidoses (MPS) as MPS IV. Patients with Morquio A syndrome are deficient in the N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme. The first symptoms usually occur at 2-3 years of age. This enzyme deficiency causes difficulties in skeletal development and growth, and patients will typically exhibit symptoms such as abnormal bone development (including the spine), bell-shaped chest with flared ribs at bottom, coarse facial features, widely spaced teeth, hypermobile joints, knock knees, macrocephaly, and short stature. The patient with Morquio A syndrome may have physical exam abnormalities such as kyphoscoliosis, cloudy cornea, aortic regurgitation, enlarged liver, inguinal hernia, and paralysis below the neck due to underdeveloped upper vertebrae.

The most common adverse events observed in clinical trials (occurring in 10% or greater of Vimizim patients) were nausea, vomiting, abdominal pain, chills, headache, pyrexia, and fatigue. In clinical trials 7.7% of patients had anaphylactic reactions and 18.7% had hypersensitivity reactions during or after Vimizim administration.

Vimizim contains a boxed warning regarding the risk of life-threatening anaphylactic reactions that may occur during infusion. Patients must be observed during and after Vimizim infusion by a health care provider trained to manage medical emergencies. Patients with acute febrile or respiratory conditions may be at increased risk due to potential for respiratory compromise during a hypersensitivity reaction; the healthcare provider must carefully consider the patient’s clinical condition prior to infusion and consider delaying treatment with Vimizim when appropriate.

The safety and efficacy of Vimizim have not been established in patients less than 5 years old.

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DOSAGE
The recommended dose of Vimizim is 2mg per kilogram of body weight administered once weekly as an intravenous infusion. Administer Vimizim over a minimum of 3.5 to 4.5 hours (based on infusion volume). Patients should receive pretreatment with antihistamines, with or without antipyretics, 30 to 60 minutes before administration of Vimizim. If a hypersensitivity reaction occurs during the infusion, administration may be slowed, temporarily stopped or discontinued based on the severity of the reaction. Vimizim should be infused using a low-protein binding infusion set with a low-protein binding 0.2 micrometer in-line filter.

FDA APPROVED INDICATIONS
Vimizim is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline for ELTROMBOPAG (Promacta) requires a diagnosis of chronic immune (idiopathic) thrombocytopenia purpura (ITP), thrombocytopenia due to chronic hepatitis C, or severe aplastic anemia. In addition, the following must be met:

For the requests of Promacta packets for patients greater than 12 years old:
- The patient has had a trial of Promacta tablets
- Physician attestation of medical need for powder packets

For the diagnosis of chronic immune (idiopathic) thrombocytopenia (ITP), approval requires:
- The patient is 1 year of age or older
- The patient has had a trial of or contraindications to corticosteroids or immunoglobulins, or has had an insufficient response to splenectomy

For the diagnosis of thrombocytopenia due to chronic hepatitis C, approval requires:
- The patient's thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy

For the diagnosis of severe aplastic anemia, approval requires ONE of the following:
- The patient is 2 years of age or older and Promacta will be used in combination with standard immunosuppressive therapy as first-line treatment
- The patient has had an insufficient response to immunosuppressive therapy

RENEWAL CRITERIA

The guideline for ELTROMBOPAG (Promacta) requires a diagnosis of chronic immune (idiopathic) thrombocytopenia (ITP). In addition, the following must be met for renewal:
- The patient has a clinical response, as defined by an increase in platelet count to at least 50X10^{9}/L (at least 50,000 per microliter)

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ELTROMBOPAG

RATIONALE
To ensure safe and appropriate utilization of Promacta per FDA labeling.

FDA APPROVED INDICATIONS
Promacta is a thrombopoietin receptor agonist indicated:

• For the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

• For the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Promacta should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.

• In combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.

• For the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

Limitations of use:

• Promacta is not indicated for the treatment of patients with myelodysplastic syndrome.

• Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

DOSING
Take on empty stomach (1 hour before or 2 hours after a meal).

Chronic Immune (Idiopathic) Thrombocytopenia
Initiate Promacta at 50mg once daily for most adult and pediatric patients 6 years and older, and at 25mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of Asian ancestry. Adjust to maintain platelet count greater than or equal to 50X10^9/L. Do not exceed 75mg per day.

First-line Severe Aplastic Anemia
Initiate Promacta once daily at 2.5mg/kg (in pediatric patients aged 2 to 5 years old), 75mg (pediatric patients aged 6 to 11 years old), or 150mg for patients aged 12 years and older concurrently with standard immunosuppressive therapy. Reduce initial dose in patients of Asian ancestry. Modify dosage for toxicity or elevated platelet counts.

Refractory Severe Aplastic Anemia
Initiate Promacta at 50mg once daily. Reduce initial dose in patients with hepatic impairment or patients of Asian ancestry. Adjust to maintain platelet count greater than 50X10^9/L. Do not exceed 150 mg per day.

Chronic Hepatitis C-associated Thrombocytopenia
Initiate Promacta at a dose of 25 mg once daily. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a dose of 100 mg daily.
ELTROMBOPAG

FDA APPROVED INDICATIONS (CONTINUED)

HOW SUPPLIED
Tablets: 12.5, 25, 50, 75, 100mg
Oral suspension: 12.5, 25mg

REFERENCES

Created: 06/15
Effective: 01/01/20  Client Approval: 10/14/19  P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ELUXADOLINE (Viberzi) requires a diagnosis of irritable bowel syndrome with diarrhea (IBS-D). The following criteria must also be met:

- The patient is at least 18 years old
- The medication is being prescribed by or in consultation with a gastroenterologist
- The patient has had a trial of or contraindication to ALL of the following: loperamide AND a tricyclic anti-depressant (e.g., amitriptyline, desipramine) AND dicyclomine
- The patient has had a trial of or contraindication to Xifaxan (rifaximin)

RENEWAL CRITERIA

Our guideline for ELUXADOLINE (Viberzi) renewal requires a diagnosis of irritable bowel syndrome with diarrhea (IBS-D). The following criteria must also be met:

- Patient has experienced at least 30% decrease in abdominal pain (on a 0-10 point pain scale).
- Patient has experienced at least 50% reduction in the number of days per week with a stool consistency of mushy stool (Bristol Stool scale type 6) or entirely liquid stool (Bristol Stool scale type 7).

RATIONALE

To ensure appropriate utilization of Viberzi for irritable bowel syndrome with diarrhea (IBS-D).

Per the American College of Gastroenterology, there is high quality evidence that tricyclic anti-depressants are effective in providing symptom relief in IBS-D. However, tolerance to these agents could be an issue for some patients. Rifaximin is indicated for the treatment of IBS-D.

Renewal criteria for IBS-D is based on the definition of a responder used in Study 1 and 2 of the Viberzi pivotal trials. Efficacy of Viberzi was assessed in both trials using an overall composite responder primary endpoint. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by ≥30% as compared to the baseline weekly average AND a reduction in the BSS to <5 on at least 50% of the days within a 12-week time interval. Improvement in daily worst abdominal pain in the absence of a concurrent bowel movement was also considered a response day.

FDA APPROVED INDICATIONS

Viberzi is a mu-opioid receptor agonist, indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

CONTINUED ON NEXT PAGE
ELUXADOLINE

FDA APPROVED INDICATIONS (CONTINUED)

**DOSING**
The recommended dosage in adults is 100 mg twice daily taken with food. The recommended dosage is 75 mg twice daily taken with food in patients who:
- Do not have a gallbladder
- Are unable to tolerate the 100 mg dose
- Are receiving concomitant OATP1B1 inhibitors

**REFERENCES**
ENASIDENIB

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENASIDENIB</td>
<td>IDHIFA</td>
<td>44450</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

The guideline named **ENASIDENIB (Idhifa)** requires a diagnosis of relapsed or refractory acute myeloid leukemia (AML). In addition, the following criteria must also be met:

- The patient is isocitrate dehydrogenase-2 (IDH2) mutation positive as detected by an FDA-approved diagnostic test
- The patient is 18 years of age or older

RATIONALE

Promote appropriate utilization of **ENASIDENIB** based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS

Idhifa is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

The recommended dose of Idhifa is 100mg taken orally once daily with or without food. Idhifa tablets should not be split or crushed.

REFERENCES


Created: 08/17
Effective: 02/23/18
Client Approval: 09/01/17
P&T Approval: N/A
ENCORAFENIB

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENCORAFENIB</td>
<td>BRAFTOVI</td>
<td>45039</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

The guideline named ENCORAFENIB (Braftovi) requires a diagnosis of unresectable or metastatic melanoma. In addition, the following criteria must be met:

- The patient has BRAF V600E or V600K mutation as detected by an FDA-approved test
- The medication will be used in combination with Mektovi (binimetinib)

RATIONALE

To promote appropriate utilization of BRAFTOVI based on FDA approved indication and dosing.

FDA APPROVED INDICATION

Braftovi is a kinase inhibitor indicated, in combination with Mektovi (binimetinib), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Limitations of Use: Braftovi is not indicated for treatment of patients with wild-type BRAF melanoma.

DOSAGE & ADMINISTRATION

The recommended dosage of Braftovi is 450 mg orally taken once daily in combination with Mektovi (binimetinib) until disease progression or unacceptable toxicity. Refer to the Mektovi (binimetinib) prescribing information for recommended Mektovi (binimetinib) dosing information.

Braftovi may be taken with or without food. Do not take a missed dose of Braftovi within 12 hours of the next dose of Braftovi. Do not take an additional dose if vomiting occurs after Braftovi administration but continue with the next scheduled dose.

REFERENCES


Created: 08/18
Effective: 10/22/18
Client Approval: 09/11/18
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ENDOTHELIN RECEPTOR ANTAGONISTS requires a diagnosis of pulmonary arterial hypertension (WHO Group I). Additional guideline requirements apply.

For Letairis, the following criteria must be met:
- The requested medication is prescribed by or given in consultation with a cardiologist or pulmonologist
- The patient has NYHA-WHO Functional Class II to IV symptoms
- The patient does not have idiopathic pulmonary fibrosis (IPF).

For Tracleer, the following criteria must be met:
- The requested medication is prescribed by or given in consultation with a cardiologist or pulmonologist
- The patient is 3 years of age or older
- The patient has NYHA-WHO Functional Class II to IV symptoms
- The patient does not have idiopathic pulmonary fibrosis (IPF)
- The patient is not concurrently taking cyclosporine A or glyburide

For Opsumit, the following criteria must be met:
- The requested medication is prescribed by or given in consultation with a cardiologist or pulmonologist
- The patient has NYHA-WHO Functional Class II to IV symptoms

RENEWAL CRITERIA

The guideline for ENDOTHELIN RECEPTOR ANTAGONISTS (Letairis, Tracleer, Opsumit) renewal requires a diagnosis of pulmonary arterial hypertension. The following criteria must also be met.
- The patient has shown improvement from baseline in the 6-minute walk distance test OR
- The patient has a stable 6-minute walk distance test with a stable or improved WHO functional class

CONTINUED ON NEXT PAGE
ENDOTHELIN RECEPTOR ANTAGONISTS

RATIONALE
Ensure appropriate utilization of Tracleer, Letairis and Opsumit.

FDA APPROVED INDICATIONS
LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA-WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

TRACLEER is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA-WHO Class II to IV symptoms to improve exercise capacity and decrease clinical worsening.

OPSUMIT is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to delay disease progression, including death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6 minute walk distance, worsened PAH symptoms and need for additional PAH treatment. Opsumit also reduced hospitalization for PAH.

REFERENCES
The guideline named **ENTRECTINIB (Rozlytrek)** requires a diagnosis of metastatic non-small cell lung cancer (NSCLC) or solid tumor. In addition, the following criteria must be met:

**For a diagnosis of metastatic non-small cell lung cancer (NSCLC), approval requires:**
- The patient is 18 years of age or older
- The patient has **ROS1**-positive tumors

**For a diagnosis of solid tumor, approval requires:**
- The patient is 12 years of age or older
- The tumor has a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation
- The tumor is metastatic or surgical resection is likely to result in severe morbidity
- There are no satisfactory alternative treatments, or the patient has progressed following treatment

**RATIONALE**
For further information, please refer to the Prescribing Information for Rozlytrek.

**REFERENCES**

Created: 10/19
Effective: 11/08/19
Client Approval: 10/07/19
P&T Approval: 10/19
GUIDELINES FOR USE

Our guideline for ENZALUTAMIDE requires a diagnosis of metastatic castration-resistant prostate cancer.

RATIONALE
To ensure appropriate and cost effective use of Xtandi.

FDA APPROVED INDICATIONS
Xtandi is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

DOSAGE
The recommended dosage is 160 mg (four 40 mg capsules) once daily with or without food. If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted. Concomitant use of strong CYP2C8 inhibitors such as gemfibrozil should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, reduce the Xtandi dose to 80 mg once daily.

Xtandi is an oral once daily androgen receptor inhibitor for the treatment of metastatic castration-resistant prostate cancer. It decreases proliferation and induces cell death of prostate cancer. Xtandi joins Zytiga as the second oral agent available in this setting. While both are dosed once daily, Zytiga also requires twice daily prednisone dosing.

REFERENCES
GUIDELINES FOR USE
The guideline entitled RETACRIT (epoetin alfa-epbx) requires that the patient have a diagnosis of anemia due to ONE of the following: chronic kidney disease (CKD), zidovudine therapy for HIV, the effects of concomitant myelosuppressive chemotherapy with a minimum of two additional months of planned chemotherapy or the requested medication is being used to reduce the number of allogeneic RBC transfusions in a patient undergoing an elective, noncardiac, nonvascular surgery.

RATIONALE
Promote appropriate utilization of Retacrit based on FDA approved indication and dosing.

DOSAGE
The recommended dosing for Retacrit varies depending on indication:
- CKD on dialysis:
  - Adults: 50-100 units/kg 3 times weekly IV or SC, Pediatrics: 50 units/kg 3 times weekly IV or SC
- CKD not on dialysis:
  - Adults: 50-100 units/kg 3 times weekly IV or SC
- Zidovudine-treated HIV-infected patients
  - Adults: 100 units/kg 3 times weekly IV or SC
- Cancer chemotherapy:
  - Adults: 150 units/kg SC 3 times per week until completion of a chemotherapy course, or 40,000 units SC weekly until completion of a chemotherapy course, Pediatrics: 600 units/kg IV until completion of a chemotherapy course
- Surgery:
  - 300 units/kg per day SC for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.
  - 600 units/kg SC in 4 does administered 21, 14, and 7 days before surgery and on the day of surgery.

FDA APPROVED INDICATIONS
Treatment of anemia due to:
- Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis.
- Zidovudine in patients with HIV-infections.
- The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline for **EPOPROSTENOL (Flolan, Veletri)** requires a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1). The following criteria must also be met.
- The requested medication is prescribed by or given in consultation with a cardiologist or pulmonologist
- The patient has NYHA/WHO Functional Class III-IV symptoms

RENEWAL CRITERIA

The guideline for **EPOPROSTENOL (Flolan, Veletri)** renewal requires a diagnosis of pulmonary arterial hypertension (PAH). The following criteria must also be met.
- The patient has shown improvement from baseline in the 6-minute walk distance test **OR**
- The patient has a stable 6-minute walk distance test with a stable or improved WHO functional class.

RATIONALE

Ensure appropriate use of Flolan and Veletri based on FDA approved indication.

Diagnosis of PAH involves a logical sequence of steps utilizing different diagnostic tests to assist in confirmation of PAH (chest x-ray, echocardiogram, electrocardiogram, CT angiogram, pulmonary function tests, VQ scan); however, right heart catheterization (RHC) remains the gold standard and is an essential component in the definitive diagnosis, prognosis, and evaluation of PAH. RHC is critical in distinguishing PH due to other etiologies, for example PH due to left heart disease (e.g. diastolic dysfunction) or severe lung disease, which may appear similar to PAH on an echocardiogram. In addition, RHC can be used to monitor the therapeutic and adverse effects of medical interventions, to assess the severity of hemodynamic impairment, and to test the vasoreactivity of the pulmonary circulation.

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EPOPROSTENOL IV

FDA APPROVED INDICATION
Epoprostenol is indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA/WHO Class III and Class IV patients who do not respond adequately to conventional therapy.

Veletri is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

REFERENCES

Created: 09/18
Effective: 10/01/18
Client Approval: 08/22/18
P&T Approval: 3QTR
GUIDELINES FOR USE

The guideline named **ERDAFITINIB (Balversa)** requires a diagnosis of locally advanced or metastatic urothelial carcinoma. In addition, the following criteria must be met:

- The patient is 18 years of age or older
- The patient has susceptible Fibroblast growth factor receptor (FGFR3) or (FGFR2) genetic alterations as detected by an Food and Drug Administration (FDA)-approved companion diagnostic test
- The patient meets **ONE** of the following criteria:
  - The patient has progressed during or following at least one line of prior platinum-containing chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin)
  - The patient has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin)

RATIONALE

For further information, please refer to the Prescribing Information and/or Drug Monograph for Balversa.

REFERENCES

- Balversa [Prescribing Information]. Horsham, PA: Janssen Products, LP; April 2019.

Created: 06/19
Effective: 07/15/19
Client Approval: 06/10/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named ERENUMAB-AOOE (Aimovig) requires a diagnosis of migraines. The following criteria must also be met:

- The patient is 18 years of age or older
- Documentation that the patient has had a previous trial of any THREE of the following preventative migraine treatments (chart notes required in the absence of electronic prescription claims history):
  - beta-blocker (such as propranolol or nadolol)
  - candesartan
  - cyproheptadine
  - lisinopril
  - tricyclic antidepressant (such as amitriptyline, nortriptyline, or doxepin)
  - topiramate
  - valproic acid/divalproex sodium
  - venlafaxine/desvenlafaxine
  - verapamil

For a dose of 140 mg per month, approval requires prior treatment with a dose of 70 mg per month.

RENEWAL CRITERIA

The guideline named ERENUMAB-AOOE (Aimovig) requires that at least ONE of the following criteria has been met:

- The patient has experienced a reduction in migraine or headache frequency of at least 2 days per month with Aimovig therapy
- The patient has experienced a reduction in migraine severity with therapy
- The patient has experienced a reduction in migraine duration with therapy

RATIONALE

Ensure appropriate criteria are used for the management of requests for AIMOVIG according to approved indication, dosing, and national treatment guidelines.

FDA APPROVED INDICATIONS

AIMOVIG is a calcitonin gene-related peptide (CGRP) receptor antagonist indicated for the preventive treatment of migraine in adults.

CONTINUED ON NEXT PAGE
HOW SUPPLIED
Injection: 70 mg/mL solution in a single-dose prefilled SureClick® autoinjector
Injection: 140 mg/mL in a single-dose prefilled SureClick® autoinjector
Injection: 70 mg/mL solution in a single-dose prefilled syringe
Injection: 140 mg/mL solution in a single-dose prefilled syringe

DOSING & ADMINISTRATION
AIMOVIG is for subcutaneous use only.

The recommended dosage of AIMOVIG is 70 mg injected subcutaneously once monthly. Some patients may benefit from a dosage of 140 mg injected subcutaneously once monthly, which is administered as two consecutive subcutaneous injections of 70 mg each.

REFERENCES
- Guinn, D. Hickenbottom, S. Lee MJ. Headache in pregnant and postpartum women. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed June 11, 2019

Created: 06/18
Effective: 08/01/19
Client Approval: 07/12/19
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named **ERLOTINIB (Tarceva)** requires a diagnosis of metastatic non-small cell lung cancer (NSCLC) or locally advanced, unresectable, or metastatic pancreatic cancer. In addition, the following criteria must also be met:

**For the diagnosis of metastatic non-small cell lung cancer (NSCLC)**, approval requires:
- The patient's tumor has epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test

**For the diagnosis of locally advanced, unresectable, or metastatic pancreatic cancer**, approval requires:
- The requested medication will be used in combination with gemcitabine

RATIONALE

To promote appropriate utilization of erlotinib based on FDA approved indications.

FDA approved dosage of 100 mg daily for pancreatic cancer and 150 mg daily for NSCLC, available as 25 mg, 100 mg, and 150 mg tablets. Dose reduction in 50 mg increments for specific adverse effects and drug interactions. Dose increase in 50 mg increments for drug interactions to a maximum of 450 mg daily.

FDA APPROVED INDICATIONS

Tarceva is a kinase inhibitor indicated for:
- Treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second-line or greater treatment
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

Limitations of Use:
- Tarceva is not recommended for use in combination with platinum-based chemotherapy.
- Safety and efficacy of Tarceva have not been evaluated in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution.

DOSAGE & ADMINISTRATION

The recommended daily dose of Tarceva for NSCLC is 150 mg taken on an empty stomach, i.e., at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity.

The recommended daily dose of Tarceva for pancreatic cancer is 100 mg taken once daily in combination with gemcitabine. Take Tarceva on an empty stomach, i.e., at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity.
REFERENCES


Created: 06/15
Effective: 07/01/17
Client Approval: 05/02/17
P&T Approval: 11/13
GUIDELINES FOR USE

** Please use the criteria for the specific drug requested **

INITIAL CRITERIA FOR PROCRIT (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ERYTHROPOIESIS STIMULATING AGENTS (PROCRIT) requires a specific diagnosis and specific blood test level. Additional guideline requirements apply.

- Approval for the diagnosis of anemia associated with chronic renal failure requires a hemoglobin level of less than 10g/dL.
- Approval for the diagnosis of anemia due to the effect of cancer chemotherapy requires one of the following:
  - Hemoglobin level of less than 11g/dL OR
  - The patient’s hemoglobin has decreased at least 2g/dL below their baseline level.
- Approval for the diagnosis of anemia related to zidovudine therapy requires a hemoglobin level of less than 10g/dL.
- Approval for the diagnosis of anemia due to concurrent hepatitis C treatment requires all of the following:
  - A lower dose of ribavirin (ribavirin dose reduction) AND
  - Hemoglobin level of less than 10g/dL.
- Approval for patients scheduled for surgery (elective, noncardiac, nonvascular surgery) requires a hemoglobin level of less than 13g/dL.

INITIAL CRITERIA FOR ARANESP (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ERYTHROPOIESIS STIMULATING AGENTS (ARANESP) requires a specific diagnosis, a specific blood test level, and a trial with the preferred drug, Procrit. Additional guideline requirements apply.

- Approval for the diagnosis of anemia associated with chronic renal failure requires:
  - The patient has tried Procrit AND
  - Hemoglobin level of less than 10g/dL.
- Approval for the diagnosis of anemia due to the effect of cancer chemotherapy requires:
  - The patient has tried Procrit AND
  One of the following:
  - Hemoglobin level of less than 11g/dL OR
  - The patient’s hemoglobin has decreased at least 2g/dL below their baseline level.
- Approval for the diagnosis of anemia due to concurrent hepatitis C treatment requires:
  - The patient has tried Procrit AND

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INITIAL CRITERIA FOR EPOGEN (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ERYTHROPOIESIS STIMULATING AGENTS (EPOGEN) requires a specific diagnosis, a specific blood test level, and a trial with the preferred drug, Procrit. Additional guideline requirements apply.

- Approval for the diagnosis of anemia associated with chronic renal failure requires:
  - The patient has tried Procrit AND
  - Hemoglobin level of less than 10g/dL.

- Approval for the diagnosis of anemia due to the effect of cancer chemotherapy requires:
  - The patient has tried Procrit AND
  One of the following:
  - Hemoglobin level of less than 11g/dL OR
  - The patient’s hemoglobin has decreased at least 2g/dL below their baseline level.

- Approval for the diagnosis of anemia related to zidovudine therapy requires:
  - The patient has tried Procrit AND
  - Hemoglobin level of less than 10g/dL.

- Approval for the diagnosis of anemia due to concurrent hepatitis C treatment requires all of the following:
  - The patient has tried Procrit AND
  - A lower dose of ribavirin (ribavirin dose reduction) AND
  - Hemoglobin level of less than 10g/dL.

- Approval for patients scheduled for surgery (elective, noncardiac, nonvascular surgery) requires:
  - The patient has tried Procrit AND
  - Hemoglobin level of less than 13g/dL.

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GUIDELINES FOR USE (CONTINUED)

INITIAL CRITERIA FOR MIRCERA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ERYTHROPOIESIS STIMULATING AGENTS (MIRCERA) requires a specific diagnosis, a specific blood test level, and a trial with the preferred drug. Additional guideline requirements apply. Approval for the diagnosis of anemia associated with chronic renal failure requires:

- The patient has tried Procrit AND
- Hemoglobin level of less than 10g/dL

Please discuss the information needed to get the drug approved with your physician.

RENEWAL CRITERIA FOR PROCRIT

Our guideline for ERYTHROPOIESIS STIMULATING AGENTS (PROCRIT) renewal requires a specific diagnosis and a specific blood test level. Additional guideline requirements apply.

- Approval for the diagnosis of anemia associated with chronic renal failure requires one of the following:
  - Hemoglobin level less than 10g/dL if not on dialysis OR
  - Hemoglobin level less than 11g/dL if on dialysis OR
  - Hemoglobin has reached 10g/dL (if not on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions OR
  - Hemoglobin has reached 11g/dL (if on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions.
- Approval for the diagnosis of anemia due to the effect of cancer chemotherapy requires a hemoglobin level between 10 and 12g/dL.
- Approval for the diagnosis of anemia related to zidovudine therapy requires a hemoglobin level between 10 and 12g/dL.
- Approval for the diagnosis of anemia due to concurrent hepatitis C treatment requires a hemoglobin level between 10 and 12g/dL.

RENEWAL CRITERIA FOR ARANESP

Our guideline for ERYTHROPOIESIS STIMULATING AGENTS (ARANESP) renewal requires a specific diagnosis and a specific blood test level. Additional guideline requirements apply.

- Approval for the diagnosis of anemia associated with chronic renal failure requires one of the following:
  - Hemoglobin level less than 10g/dL if not on dialysis OR
  - Hemoglobin level less than 11g/dL if on dialysis OR
  - Hemoglobin has reached 10g/dL (if not on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions OR
  - Hemoglobin has reached 11g/dL (if on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions.
- Approval for the diagnosis of anemia due to the effect of cancer chemotherapy requires a hemoglobin level between 10 and 12g/dL.

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ERYTHROPOIESIS STIMULATING AGENTS

RENEWAL GUIDELINES FOR USE (CONTINUED)

- Approval for the **diagnosis of anemia due to concurrent hepatitis C treatment** requires a hemoglobin level between 10 and 12g/dL.

RENEWAL CRITERIA FOR EPOGEN

Our guideline for **ERYTHROPOIESIS STIMULATING AGENTS (EPOGEN)** renewal requires a specific diagnosis and a specific blood test level. Additional guideline requirements apply.

- Approval for the **diagnosis of anemia associated with chronic renal failure** requires one of the following:
  - Hemoglobin level less than 10g/dL if not on dialysis **OR**
  - Hemoglobin level less than 11g/dL if on dialysis **OR**
  - Hemoglobin has reached 10g/dL (if not on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions **OR**
  - Hemoglobin has reached 11g/dL (if on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions.

- Approval for the **diagnosis of anemia due to the effect of cancer chemotherapy** requires a hemoglobin level between 10 and 12g/dL.

- Approval for the **diagnosis of anemia related to zidovudine therapy** requires a hemoglobin level between 10 and 12g/dL.

- Approval for the **diagnosis of anemia due to concurrent hepatitis C treatment** requires a hemoglobin level between 10 and 12g/dL.

RENEWAL CRITERIA FOR MIRCERA

Our guideline for **ERYTHROPOIESIS STIMULATING AGENTS (MIRCERA)** renewal requires a specific diagnosis and a specific blood test level. Additional guideline requirements apply. Approval for the diagnosis of anemia associated with chronic renal failure requires:

- Hemoglobin level of less than 10g/dL if not on dialysis **OR**
- Hemoglobin level of less than 11g/dL if on dialysis **OR**
- Hemoglobin level has reached 10g/dL (if not on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions **OR**
- Hemoglobin level has reached 11g/dL (if on dialysis) and dose reduction/interruption is required to reduce the need for blood transfusions

ERYTHROPOIESIS STIMULATING AGENTS

RATIONALE
Ensure appropriate utilization and promote use of preferred ESA treatment.

Anemia due to hepatitis C therapy is not an FDA approved indication for any ESA. AASLD does not recommend the use of ESAs, NIH/DHHS/NIDDKD state that the proper role and dose of ESAs has yet to be defined, and the AGA consider either ribavirin dose reduction or ESA use as viable options for managing treatment-related anemia. None of these guidelines provide specific

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ERYTHROPOIESIS STIMULATING AGENTS

RATIONALE (CONTINUED)

hemoglobin levels at which to initiate or maintain hemoglobin levels for this patient population, therefore the hemoglobin levels selected for this diagnosis are based off of the recommendations for zidovudine therapy.

FDA APPROVED INDICATIONS

- **CHRONIC KIDNEY DISEASE**: The prescribing information (PI) of the ESAs and an FDA safety update recommend initiation of therapy only for patients with Hgb of <10g/dL. They recommend reducing or interrupting the dose of ESA and using the lowest dose of an ESA sufficient to reduce the need for blood transfusions at Hgb of 11g/dL for patients on dialysis or Hgb of 10g/dL for patients not on dialysis.

- **ANEMIA RELATED TO CANCER CHEMOTHERAPY**: ASCO recommends initiating ESA therapy at Hgb levels at less than 10g/dL while NCCN recommends initiation at or below Hgb levels of 11g/dL. ASCO recommends maintaining Hgb levels between 10 and 12g/dL, while NCCN does not comment on a maintenance Hgb range.

- **ANEMIA RELATED TO ZIDOVUDINE THERAPY**: The clinical trials contained within the prescribing information (PI) of the ESAs recommend initiating therapy at Hgb of <10g/dL and maintaining between 10 and 12g/dL.

- **PATIENTS SCHEDULED FOR ELECTIVE, NONCARDIAC, NONVASCULAR SURGERY**: The prescribing information (PI) of the ESAs recommends therapy only for those patients with Hgb ≤13g/dL.

Aranesp

For the treatment of anemia due to:

- Chronic Kidney Disease (CKD) in patients on dialysis and patients not on dialysis
- The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Recommended starting dose:

- CKD on dialysis: 0.45mcg/kg IV/SC as a weekly injection or 0.75mcg/kg once every 2 weeks as appropriate.
- CKD not on dialysis: 0.45mcg/kg IV/SC given once at 4-week intervals as appropriate
- Cancer chemotherapy:
  - 2.25mcg/kg SC every week until completion of a chemotherapy course
  - 500 mcg every 3 weeks SC until completion of a chemotherapy course

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ERYTHROPOIESIS STIMULATING AGENTS

FDA APPROVED INDICATIONS (CONTINUED)

**Epogen & Procrit**
- Treatment of anemia due to:
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis
  - Zidovudine in HIV-infected patients
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery

Recommended starting dose:
- CKD on dialysis:
  - Adults: 50-100 units/kg 3 times weekly
  - Pediatrics: 50 units/kg 3 times weekly
- CKD not on dialysis: adult patients: 50-100 units/kg 3 times weekly
- Zidovudine-treated HIV-infected patients
  - Adults: 100 units/kg 3 times per week
- Cancer chemotherapy:
  - Adults: 150 units/kg SC 3 times per week until completion of a chemotherapy course, or 40,000 units SC weekly until completion of a chemotherapy course
  - Pediatrics: 600 units/kg IV until completion of a chemotherapy course
- Surgery:
  - 300 units/kg per day SC for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery
  - 600 units/kg SC in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery

**Mircera**
Treatment of anemia associated with chronic kidney disease (CKD in adult patients on dialysis and patients not on dialysis).

Recommended dose:
- Initial treatment: 0.6mcg/kg body weight administered once every 2 weeks.
- Conversion from another ESA: dosed once monthly or every 2 weeks based on total weekly epoetin alfa or darbepoetin alfa dose at time of conversion.

Available as 50, 75, 100, 150, 200, or 250 mcg in 0.3 mL solution of Mircera in single-use prefilled syringes.

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ERYTHROPOIESIS STIMULATING AGENTS

REFERENCES


Created: 03/15
Effective: 11/01/15
Client Approval: 09/15
P&T Approval: N/A
ETANERCEPT

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GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ETANERCEPT (Enbrel) requires a diagnosis of moderate to severe rheumatoid arthritis, moderate to severe polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, or chronic moderate to severe plaque psoriasis. The following criteria must also be met:

For patients with moderate to severe rheumatoid arthritis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older

For patients with moderate to severe polyarticular juvenile idiopathic arthritis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 2 years of age or older

For patients with psoriatic arthritis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older

For patients with ankylosing spondylitis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist
- 18 years of age or older

For patients with chronic moderate to severe plaque psoriasis, our guideline requires:
- Therapy initiated by or in consultation with a dermatologist
- Plaque psoriasis involves at least 10% body surface area (BSA) or psoriatic lesions affecting the hands, feet, or genital area
- Previous trial with at least one or more forms of preferred conventional therapies, such as PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- 4 years of age or older

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ETANERCEPT

GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

Our guideline for the renewal of ETANERCEPT (Enbrel) requires a diagnosis of moderate to severe rheumatoid arthritis, moderate to severe polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, or chronic moderate to severe plaque psoriasis. The following criteria must also be met.

Renewal for the diagnosis of moderate to severe rheumatoid arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count and swollen joint count while on therapy.

Renewal for the diagnosis of moderate to severe polyarticular juvenile idiopathic arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count and swollen joint count while on therapy.

Renewal for the diagnosis of psoriatic arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count and swollen joint count while on therapy.

Renewal for the diagnosis of ankylosing spondylitis requires:
- Documentation of at least a 50% improvement or increase of 2 units from baseline on the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) while on therapy.

Renewal for the diagnosis of chronic moderate to severe plaque psoriasis requires:
- Documentation that the patient has achieved clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50% or more while on therapy.

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ETANERCEPT

RATIONALE
Ensure that appropriate diagnostic, utilization, and safety criteria are utilized for the management of requests for etanercept.

FDA APPROVED INDICATIONS
Enbrel is a tumor necrosis factor (TNF) blocker indicated for the treatment of:
- Rheumatoid Arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO) in patients 4 years or older

DOSSING
Enbrel is administered by subcutaneous injection.
- Adult RA and PsA: 50 mg once weekly with or without methotrexate (MTX)
- AS: 50 mg once weekly
- Adult PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly
- PJIA and Pediatric PsO: 0.8 mg/kg weekly, with a maximum of 50 mg per week

DOSEAGE FORMS AND STRENGTHS
- Injection: 25 mg/0.5 mL and 50 mg/mL solution in a single-dose prefilled syringe
- Injection: 50 mg/mL solution in single-dose prefilled SureClick autoinjector
- For injection: 25 mg lyophilized powder in a multiple-dose vial for reconstitution
- Injection: 50 mg/mL solution in Enbrel Mini single-dose pre-filled cartridge for use with the AutoTouch reusable autoinjector only

REFERENCES

Created: 03/15
Effective: 03/01/19
Client Approval: 02/14/19
P&T Approval: N/A
GUIDELINES FOR USE

AFINITOR DISPERZ

The guideline named EVEROLIMUS (Afinitor Disperz) requires a diagnosis of subependymal giant cell astrocytoma (SEGA) with tuberous sclerosis complex (TSC) or TSC-associated partial-onset seizures. In addition, the following criteria must be met:

For diagnosis of subependymal giant cell astrocytoma (SEGA) in tuberous sclerosis complex (TSC), approval requires:
- The patient is 1 year of age or older
- The patient's diagnosis requires therapeutic intervention but cannot be curatively resected

For diagnosis of TSC-associated partial-onset seizures, approval requires:
- The patient is 2 year of age or older
- The medication will be used as adjunctive treatment

AFINITOR

The guideline named EVEROLIMUS (Afinitor) requires ONE of the following FDA approved indications:

- Advanced renal cell carcinoma (RCC) after failure of or contraindication to treatment with sunitinib (Sutent) or sorafenib (Nexavar), which may also require prior authorization AND the patient is 18 years of age or older
- Subependymal giant cell astrocytoma (SEGA) with tuberous sclerosis complex (TSC) that requires therapeutic intervention but cannot be curatively resected AND the patient is 1 year of age or older
- Progressive neuroendocrine tumor (NET) with unresectable, locally advanced or metastatic disease, either neuroendocrine tumor (NET) of pancreatic origin or well-differentiated, non-functional neuroendocrine tumor (NET) of gastrointestinal or lung origin. The patient must also be 18 years of age or older

(Denial text continued on the next page)
EVEROLIMUS

GUIDELINES FOR USE AFINITOR (CONTINUED)

- Renal angiomyolipoma, and tuberous sclerosis complex (TSC) that does not require immediate surgery AND the patient is 18 years of age or older
- For postmenopausal women with a diagnosis of advanced hormone receptor-positive, HER2-negative breast cancer (defined as IHC less than or equal to 3+ or FISH amplification ratio less than or equal to 2.0) in combination with Aromasin (exemestane) after failure of or contraindication to treatment with Femara (letrozole) or Arimidex (anastrozole)

RATIONALE
Ensure appropriate utilization of everolimus based on FDA approved indication and NCCN guidelines.

DOSAGE AND ADMINISTRATION
Afinitor and Afinitor Disperz are two different dosage forms. Select the recommended dosage form based on the indication. Do not combine Afinitor and Afinitor disperz to achieve the total dose. Modify the dosage for patients with hepatic impairment or for patients taking drugs that inhibit or induce pglycoprotein (P-gp) and CYP3A4.

Advanced HR+ BC, advanced NET, advanced RCC, or renal angiomyolipoma with TSC:
- AFINITOR 10 mg once daily orally until disease progression or unacceptable toxicity

SEGA with TSC:
- AFINITOR/AFINITOR DISPERZ 4.5 mg/m² once daily orally until disease progression or unacceptable toxicity
- Titrate the dose to attain trough concentrations of 5-15 ng/mL

TSC-Associated Partial-Onset Seizures
- AFINITOR DISPERZ 5 mg/m² once daily orally until disease progression or unacceptable toxicity
- Titrate the dose to attain trough concentrations of 5-15 ng/mL

FDA APPROVED INDICATIONS
AFINITOR is a kinase inhibitor indicated for the treatment of:
- Postmenopausal women with advanced hormone receptor-positive, HER2negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.
- Adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced or metastatic. The safety and effectiveness of AFINITOR in the treatment of patients with carcinoid tumors have not been established.
- Adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
- Adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in the treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

CONTINUED ON NEXT PAGE
EVEROLIMUS

FDA APPROVED INDICATIONS (CONTINUED)

AFINITOR and AFINITOR DISPERZ are kinase inhibitors indicated for the treatment of:
- Adult and pediatric patients aged 1 year and older with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected

AFINITOR DISPERZ is a kinase inhibitor indicated for:
- Adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC associated partial-onset seizures

REFERENCES

Created: 06/15
Effective: 10/01/19
Client Approval: 09/04/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline for EVOLOCUMAB (Repatha) requires that the requested medication is prescribed by, or in consultation with, a cardiologist, endocrinologist or lipidologist and that LDL cholesterol level is greater than 70 mg/dL. The following criteria must also be met:

For patients with primary hyperlipidemia (heterozygous familial hypercholesterolemia (HeFH)) or established cardiovascular disease (e.g., history of myocardial infarction or other acute coronary syndrome, coronary or other revascularization procedure, transient ischemic attack, ischemic stroke, atherosclerotic peripheral arterial disease, coronary atherosclerosis, renal atherosclerosis, aortic aneurysm secondary to atherosclerosis, carotid plaque with 50% or more stenosis), ALL of the following criteria must be met:

- The patient is 18 years of age or older, AND
- Diagnosis must be determined or substantiated by the following:
  - For heterozygous familial hypercholesterolemia (HeFH), ONE of the following criteria must be met:
    - Simon Broome diagnostic criteria for HeFH (definite)
    - Dutch Lipid Network criteria for HeFH with a score of at least 6

For patients with homozygous familial hypercholesterolemia (HoFH), ALL of the following criteria must be met:

- The patient is 13 years of age or older
- Diagnosis of HoFH must be determined by meeting ONE of the following criteria:
  - Simon Broome diagnostic criteria for HoFH (definite)
  - Dutch Lipid Network criteria for HoFH with a score of at least 8
  - A clinical diagnosis based on a history of an untreated LDL-cholesterol level greater than 500 mg/dL, in combination with either:
    - xanthoma before 10 years of age OR
    - evidence of heterozygous familial hypercholesterolemia (HeFH) in both parents

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

For statin tolerant patients, approval also requires:
- Prior to Repatha, patient must have been taking a maximal LDL-lowering drug regimen consistently for at least 6 months that includes a combination of ezetimibe and ONE of the following drugs:
  - The highest dose of a high intensity statin (e.g., atorvastatin 40-80mg daily, or rosuvastatin 20-40mg daily), OR
  - A maximally tolerated dose of any statin given that patient has had a previous trial of high-intensity statin, with prescriber's documentation regarding length of previous trials of statins and reasons why each agent could not be tolerated
- Patient intends to continue maximal statin once Repatha is started

For statin intolerant patients, approval also requires ALL of the following:
- Prior to Repatha, the patient was being treated consistently for at least 6 months with maximal lipid-lowering therapy with another lipid-lowering agent (e.g., ezetimibe, bile acid sequestrant, niacin, Juxtapid, Kynamro) or receiving regular LDL apheresis treatments
- The patient has ONE of the following:
  - The patient has an absolute contraindication to statin therapy (e.g., active decompensated liver disease, nursing female, pregnancy or plans to become pregnant, hypersensitivity reaction)
  - The patient has complete statin intolerance as defined by severe and intolerable adverse effects (e.g., creatine kinase elevation greater than or equal to 10 times the upper limit of normal, liver function test elevation greater than or equal to 3 times the upper limit of normal, rhabdomyolysis, severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group) that have occurred with trials of at least two separate statins and have improved with the discontinuation of each statin

RENEWAL CRITERIA

Our guidelines for EVOLOCUMAB (Repatha) renewal require that the patient is not concurrently using Praluent, has had at least 12 weeks of therapy, is adherent to statin and Repatha regimen during therapy (unless statin intolerant), and has an LDL reduction on therapy as noted below.
- For the diagnosis of heterozygous familial hypercholesterolemia, approval requires an LDL reduction of at least 35% from baseline after evolocumab therapy.
- For the diagnosis of homozygous familial hypercholesterolemia for those not using LDL apheresis, approval requires an LDL reduction of at least 20% from baseline after evolocumab therapy.
- For the diagnosis of homozygous familial hypercholesterolemia for those using LDL apheresis, approval requires an LDL reduction of at least 9% from baseline after evolocumab therapy.
- For the diagnosis of atherosclerotic cardiovascular disease, approval requires an LDL reduction of at least 40% after evolocumab therapy.

(Renewal denial text continued on next page)
EVOLOCUMAB

RENEWAL CRITERIA (CONTINUED)

- For statin intolerant patients, approval also requires ALL of the following:
  - The patient is adherent to both Repatha and another lipid-lowering agent (e.g., ezetimibe, bile acid sequestrant, niacin) or receiving regular LDL apheresis treatments
  - The patient has ONE of the following:
    - The patient has an absolute contraindication to statin therapy (e.g., active decompensated liver disease, nursing female, pregnancy or plans to become pregnant, hypersensitivity reaction)
    - The patient has complete statin intolerance as defined by severe and intolerable adverse effects (e.g., creatine kinase elevation greater than or equal to 10 times the upper limit of normal, liver function test elevation greater than or equal to 3 times the upper limit of normal, rhabdomyolysis, severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group) that have occurred with trials of at least two separate statins and have improved with the discontinuation of each statin

Since the safety and efficacy of Kynamro or Juxtapid in combination with PCSK9 inhibitors has not been evaluated, the Repatha guideline requires patients to have discontinued therapy with Kynamro or Juxtapid prior to renewal in order to receive additional approval after the 12-week initial approval. Patients taking Kynamro or Juxtapid are required to continue another lipid-lowering therapy (e.g., ezetimibe) and/or apheresis with Repatha.

RATIONALE
Promote appropriate utilization of Repatha based on FDA approved indication and appropriate clinical criteria.

FDA APPROVED INDICATIONS
For use as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). Repatha is also approved for use with other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Limitations of Use:
The effect of Repatha on cardiovascular morbidity and mortality has not been determined.

Efficacy
The efficacy of Repatha for patients with primary hyperlipidemia and clinical atherosclerotic cardiovascular disease (CVD) was studied in two multicenter, double-blind, randomized, controlled trials (Study 1 and Study 2).

CONTINUED ON NEXT PAGE
EVOLOCUMAB

FDA APPROVED INDICATIONS (CONTINUED)

EFFICACY

In Study 1 patients received an open-label, specific statin regimen over a 4 week lipid stabilization period, then were randomized to either Repatha 140mg subcutaneously every 2 weeks (q2wk), Repatha 420mg subcutaneously every 4 weeks (q4wk), or placebo for 12 weeks. Repatha or placebo was add-on therapy to daily statin treatment (atorvastatin 80mg, rosvavastatin 40mg, or simvastatin 40mg daily). Patient characteristics included mean age 63 years (range 32-80 years), 45% were 65 years or older, 33% female, 98% Caucasian, 5% Hispanic or Latino, 2% of African descent, and less than 1% Asian. After 4 weeks of lipid stabilization period (with statin treatment), the mean baseline LDL cholesterol was 108mg/dL. After 12 weeks of treatment the difference in percentage change in LDL-C between placebo- and Repatha-treated groups was -71%. The mean percentage change from baseline in the treatment groups are provided below in figure 1.

Study 2 was placebo-controlled. All 139 patients enrolled received background lipid-lowering therapy with atorvastatin 80mg daily, with or without ezetimibe 10mg daily; after stabilization on background therapy they were randomized to either placebo or Repatha 420mg once monthly. Patient characteristics included mean age 59 years (range 35-75 years), 25% were 65 years or older, 40% female, 80% Caucasian, 5% Asian, 3% of African descent, and <1% Hispanic or Latino. After stabilization on background statin treatment with or without ezetimibe, the mean baseline LDL cholesterol was 105mg/dL. The difference between Repatha 420mg and placebo groups in mean percentage change in LDL-C from baseline to Week 52 was -54%.

The efficacy of Repatha in patients with familial hypercholesterolemia was evaluated in Study 3 (RUTHERFORD-2) and Study 4 (TESLA Part B). Study 3 and Study 4 were multi-center, double-blind, randomized, placebo-controlled, 12-week trials. Study 3 enrolled 329 patients with HeFH on statins, with or without other lipid-lowering agents, and randomized patients to either Repatha 140mg q2wk, Repatha 420mg q4wk, or placebo. Study 4 enrolled 49 patients with HoFH (not on lipid apheresis therapy).

In Study 3 100% of patients had HeFH (diagnosis by Simon Broome criteria), and 38% of patients also had ASCVD. Patient characteristics in Study 3 included mean age 51 years (range 19-79 years), 15% were 65 years or older, 42% female, 90% Caucasian, 5% Asian, and 1% of African descent. The mean baseline LDL cholesterol was 156mg/dL; approximately 76% of patients were on high intensity statin therapy at the start of the study. The difference between Repatha 140mg and placebo groups in mean percentage change in LDL-C from baseline to Week 12 was -61%. The difference between Repatha 420mg and placebo groups in mean percentage change in LDL-C from baseline to Week 12 was -60%.
FDA APPROVED INDICATIONS (CONTINUED)

Efficacy

Figure 1: Study 1- Effect of Repatha on LDL cholesterol in patients with atherosclerotic CVD when combined with statins, mean percentage change from baseline to week 12 [From Repatha Prescribing Information]

In Study 4, all patients had a diagnosis of HoFH, confirmed by genetic testing or a clinical diagnosis based on a history of untreated LDL cholesterol above 500mg/dL with either a xanthoma before 10 years of age or evidence of HeFH in both parents. Patients were randomized to Repatha 420mg once monthly or placebo in combination with other lipid-lowering therapies (statins, ezetimibe). Patient characteristics in Study 4 included mean age 31 years, 49% female, 30% were adolescents age 13-17, 90% Caucasian, 4% Asian, and 6% other race. The mean baseline LDL cholesterol prior to start of the study drug was 349 mg/dL; all patients were on atorvastatin or rosuvastatin and 92% were on ezetimibe at the start of the study. The difference between Repatha 420mg and placebo groups in mean percentage change in LDL-C from baseline to Week 12 was -31.

CONTINUED ON NEXT PAGE
EVOLOCUMAB

FDA APPROVED INDICATIONS (CONTINUED)

EFFICACY

Table 1: Effect of Repatha on lipid parameters in patients in Study 1, Study 2, Study 3, and Study 4 (Mean percentage change from baseline to Week 12, except where noted) [From Repatha Prescribing Information]

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>LDL-C</th>
<th>Non HDL-C</th>
<th>Apo B</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1 – Patients with ASCVD on atorvastatin 80mg, rosuvastatin 40mg, or simvastatin 40mg daily (Mean percentage change from baseline to Week 12)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo q2wk (n=42)</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Repatha 140mg q2wk (n=105)</td>
<td>-64</td>
<td>-56</td>
<td>-49</td>
<td>-38</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-71 (-81,-61)</td>
<td>-58 (-67,-49)</td>
<td>-55 (-62,-47)</td>
<td>-42 (-48,-36)</td>
</tr>
<tr>
<td>Placebo q4wk (n=44)</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Repatha 420mg q4wk (n=105)</td>
<td>-58</td>
<td>-47</td>
<td>-46</td>
<td>-32</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-63 (-76,-50)</td>
<td>-52 (-63,-41)</td>
<td>-49 (-58,-39)</td>
<td>-36 (-43,-28)</td>
</tr>
<tr>
<td><strong>Study 2 - Patients with ASCVD on atorvastatin 80mg with or without ezetimibe 10mg daily (Mean percentage change from baseline to Week 52)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo q4wk (n=44)</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Repatha 420mg q4wk (n=95)</td>
<td>-52</td>
<td>-41</td>
<td>-40</td>
<td>-28</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-54 (-65,-42)</td>
<td>-44 (-56,-32)</td>
<td>-40 (-50,-30)</td>
<td>-31 (-39,-24)</td>
</tr>
<tr>
<td><strong>Study 3 (RUTHERFORD-2) – Patients with HeFH (Mean percentage change from baseline to Week 12)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo q2wk (n=54)</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>Repatha 140mg q2wk (n=110)</td>
<td>-62</td>
<td>-56</td>
<td>-49</td>
<td>-42</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-61 (-67,-55)</td>
<td>-54 (-60,-49)</td>
<td>-49 (-54,-43)</td>
<td>-40 (-45,-36)</td>
</tr>
<tr>
<td>Placebo q4wk</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
The results of two extension studies, OSLER-1 and OSLER-2, currently provide longer-term data for the efficacy and safety of Repatha. Additional information will be available when FOURIER, an outcomes trial with 27,500 patients; the estimated completion is in 2017. The OSLER studies were two open-label, randomized extension studies that enrolled 4465 patients who had completed a parent trial for Repatha (DESCARTES, MENDEL-1, MENDEL-2, LAPLACETIMI 57, LAPLACE-2, GAUSS-1, GAUSS-2, RUTHERFORD 1 & 2, YUKAWA-1, and THOMAS 1 & 2). Patients were randomized to receive Repatha 140mg q2wk or Repatha 420mg q4wk with standard therapy, or standard therapy alone. Standard therapy was based on local guidelines for treatment of LDL-C. Approximately 70% of patients in the study were on statin therapy; 26.7% (Repatha treatment group) to 27.9% (standard therapy group) were on a high intensity statin, and 12.6% (Repatha treatment group) to 15.9% (standard therapy group) were on ezetimibe. Participants were followed for a median of 11.1 months. Repatha led to a 61% reduction of LDL-C as compared to the standard therapy group. The rate of cardiovascular events at one year was significantly lower for the Repatha-treated group (0.95%) compared to the standard therapy group (2.18%) (HR 0.47, 95% CI 0.28 to 0.78, p=0.003).

SAFETY
Repatha is contraindicated for patients with a history of serious hypersensitivity reaction to Repatha. The most common adverse effects of Repatha (occurring in greater than 5% of clinical trial participants and more frequently than placebo) are nasopharyngitis, injection site reactions, influenza, back pain, and upper respiratory tract infection. Allergic reactions occurred in 5.1% of patients on Repatha versus 4.6% of patients on placebo, and included rash, eczema, erythema and urticaria. Injection site reactions occurred in 3.2% of Repatha-treated patients versus 3.0% of placebo-treated patients.

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EVOLOCUMAB

FDA APPROVED INDICATIONS (CONTINUED)

SAFETY
The development of binding antibodies occurred in 0.1% of Repatha patients, based on screening by an electrochemiluminescent bridging screening immunoassay for the detection of binding anti-drug antibodies. No patients in clinical trials tested positive for neutralizing antibodies. Detection of antibody formation may vary based on the sensitivity and specificity of the assay, as well as assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Thus, comparison of the incidence of antibodies for Repatha with the incidence of antibodies to other PCSK9 inhibitor products may be misleading.

Table 2: Repatha adverse reactions - safety data from seven pooled 12-week studies
(from Repatha prescribing information)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Repatha (n=2052)</th>
<th>Placebo (n=1224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(140mg &amp; 420mg doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most common adverse reactions (reported in greater than 1% of participants receiving Repatha)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.0%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Back pain</td>
<td>2.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.1%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.8%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.8%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cough</td>
<td>1.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Influenza</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Contusion</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Table 3: Select adverse events observed in the OSLER clinical trial

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Repatha (n=2976)</th>
<th>Standard therapy group (n=1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive Events *</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Liver Enzyme Abnormalities (ALT or AST &gt;3 times upper limit of normal at any visit after baseline)</td>
<td>1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Creatine kinase greater than 5 times upper limit of normal at any visit after baseline</td>
<td>0.6%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

*= Neurocognitive events were delirium/confusion, cognitive and attention disorders or disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

SAFETY
Analysis of both placebo-controlled and active-controlled trials as well as open-label extension studies showed that 1609 patients receiving Repatha had LDL levels less than 25mg/dL. Adverse effects of very low LDL levels were not identified in Repatha clinical trials, however, the long-term consequences of very low LDL levels are not known at this time.

Repatha has not been studied in human pregnancy and lactation studies. Based on the human data from other human monoclonal antibodies, Repatha is unlikely to cross the placenta in the first trimester; however, it may cross the placenta in increasing amounts in the second and third trimester. Primate studies reveal no effects on pregnancy, embryo-fetal organ development, or postnatal development when evolocumab was administered at doses up to 12 times the maximum human dose. There is no information regarding the presence of Repatha in human milk, the effects on the breastfed infant, or the effects on milk production. However, published data involving human IgG suggests that substantial amounts of IgG antibodies do not reach the infant's circulation.

No dose adjustment is required in patients with mild or moderate renal or hepatic impairment. No data is available regarding use during severe renal or hepatic impairment. No differences in safety and efficacy were seen between geriatric and younger adults. Repatha has been studied in a total of 14 adolescents with HoFH. Efficacy and safety of Repatha in adolescent patients with HoFH appears to be similar to that for adults with HoFH. The safety and efficacy of Repatha have not been established for patients younger than 13 years old or for pediatric patients without HoFH.

DOSAGE
For patients with primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH, the recommended dose for Repatha is 140mg every 2 weeks or 420mg once monthly given by subcutaneous injection in the abdomen, thigh or upper arm. For patients with HoFH the dose is 420mg once monthly. At this time the 420mg pen or syringe dosage form is unavailable, so patients must administer 3 injections of 140mg dose consecutively within 30 minutes.

For patients with HoFH, measure LDL cholesterol levels within 4 to 8 weeks of initiating Repatha, to assess response. Response to PCSK9 inhibitor therapy in this population is dependent on the degree of LDL receptor function (patients with two LDL-receptor negative alleles did not respond to Repatha in clinical trials).

CONTINUED ON NEXT PAGE
REFERENCES


Created: 09/15
Effective: 09/01/19
Client Approval: 08/19/19
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named FEDRATINIB (Inrebic) requires a diagnosis of intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocytemia) myelofibrosis (MF). In addition, the following must be met:

- The patient is 18 years of age or older

RATIONALE

For further information, please refer to the Prescribing Information for Inrebic.

REFERENCES

MDwise MANAGED MEDICAID
PRIOR AUTHORIZATION GUIDELINES

FENTANYL (BUCCAL, NASAL, SUBLINGUAL)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENTANYL SUBLINGUAL SPRAY</td>
<td>SUBSYS</td>
<td>06438</td>
<td>31187, 31596, 31597, 31189, 31188, 31192, 31193</td>
<td>ROUTE = SUBLINGUAL</td>
</tr>
<tr>
<td>FENTANYL CITRATE</td>
<td>ACTIQ, ABSTRAL, FENTORA, LAZANDA</td>
<td>01747</td>
<td>16178, 97280, 27648, 19193, 19194, 16179, 19204, 97281, 16181, 41539, 16182, 19206, 97283, 29146, 16183, 19191, 97284, 16184, 19192, 97285, 19206</td>
<td>ROUTE = BUCCAL, NASAL, SUBLINGUAL</td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

RENEWAL CRITERIA will apply in the following scenarios only:
- For patients active with MDwise for 90 days or longer AND previous prior authorization approval for the same medication with the same strength AND recent paid pharmacy claims for the requested medication. Chart notes and/or cash pay for opioid use is not accepted.
- For patients new to MDwise within the past 90 days AND chart notes are provided that document the patient is stable on the requested medication.

All other requests will be reviewed against the INITIAL CRITERIA.

Our guideline for FENTANYL (BUCCAL, NASAL, SUBLINGUAL) for patients with past use of opioid dependency agents (i.e., buprenorphine/naloxone SL tablets/films or buprenorphine SL tablets) requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid analgesic will be authorized.

Our guideline for FENTANYL (BUCCAL, NASAL, SUBLINGUAL) does not permit concurrent use with carisoprodol-containing products.

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for FENTANYL (BUCCAL, NASAL, SUBLINGUAL) requires ALL of the following rules to be met:

- You have a diagnosis of cancer-related pain, AND
- You are taking a long-acting opioid analgesic at the same time (such as MS Contin, OxyContin, Duragesic), AND
- You have had a trial and failure of an oral short-acting opioid analgesic (such as codeine/APAP, hydrocodone/APAP, hydromorphone, morphine sulfate IR, oxycodone/APAP, oxycodone IR) OR you have difficulty swallowing, AND
- You have had a trial and failure of generic Actiq (fentanyl citrate buccal lozenge)
- Requests for Lazanda nasal spray require failure of generic Actiq AND a fentanyl buccal or sublingual product other than Actiq (e.g., Abstral, Fentora, Subsys)

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

Our guideline for FENTANYL (BUCCAL, NASAL, SUBLINGUAL) for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
- The diagnosis contributing to the need for opioid analgesic therapy and previous therapy attempted, including dates and doses of prior therapies. For a diagnosis of moderate to severe cancer-related pain, pain related to sickle cell disease, or pain in patients receiving palliative care, no additional criteria applies
- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT (Indiana controlled substance monitoring program)
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the risk of using benzodiazepines and opioid analgesics together at the same time

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for FENTANYL (BUCCAL, NASAL, SUBLINGUAL) for patients with claims in history for antipsychotics requires that your prescriber provides information indicating that the concurrent use of fentanyl and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RENEWAL CRITERIA

Our guideline for FENTANYL (BUCCAL, NASAL, SUBLINGUAL) does not permit concurrent use with carisoprodol-containing products.

Our guideline for renewal of FENATNYL (BUCCAL, NASAL, SUBLINGUAL) for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
- The diagnosis contributing to the need for opioid analgesic therapy
- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT (Indiana controlled substance monitoring program)
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the risk of using benzodiazepines and opioid analgesics together at the same time

CONTINUED ON NEXT PAGE
FENTANYL (Buccal, Nasal, Sublingual)

RENEWAL CRITERIA (CONTINUED)

Our guideline for FENTANYL (Buccal, Nasal, Sublingual) for patients with claims in history for antipsychotics requires that your prescriber provides information indicating that the concurrent use of fentanyl and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RATIONALE
To ensure opioid analgesics are used according to FDA approved indications with patient safety in mind, and to encourage the use of more cost-effective analgesics.

From 2000-2014, almost half a million people died due to drug overdose, with 2014 being the highest year for deaths on record. In that time, the number of opioids prescribed, as well as the number of opioid overdoses, has risen exponentially. At least half of all opioid overdose deaths involve a prescription opioid. Indiana was among the states that had a statistically significant increase of overdose deaths from 2013-2014.

According to recent research, the opioid epidemic has a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed opioids at double the rate of non-Medicaid patients, and are subsequently at much higher risk of prescription opioid overdose. Improving the way that opioids are prescribed can ensure safer and more effective pain treatment, and reduce the addiction, misuse, abuse, and overdose of these drugs. These guidelines are to ensure that the use of opioids is consistent with their FDA approved indications, and to initiate action combating the current opioid epidemic.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 25mcg transdermal fentanyl/hour, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid for a week or longer.

CONTINUED ON NEXT PAGE
FENTANYL (BUCCAL, NASAL, SUBLINGUAL)

Rationale (Continued)

**Opioid Conversion Table**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butorphanol</td>
<td>7</td>
<td>8.5mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
<td>400mg</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>0.12</td>
<td>0.5mg (500mcg)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Hydromorphone HCl</td>
<td>4</td>
<td>15mg</td>
</tr>
<tr>
<td>Meperidine HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
<td>1.5</td>
<td>40mg</td>
</tr>
<tr>
<td>Oxymorphone HCl</td>
<td>3</td>
<td>20mg</td>
</tr>
<tr>
<td>Pentazocine HCl</td>
<td>0.37</td>
<td>162mg</td>
</tr>
<tr>
<td>Tapentadol HCl</td>
<td>0.4</td>
<td>150mg</td>
</tr>
<tr>
<td>Tramadol HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
</tbody>
</table>

**Methadone Conversion Table**

<table>
<thead>
<tr>
<th>Methadone daily dose (mg/day)</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0, &lt;= 20</td>
<td>4</td>
<td>20mg</td>
</tr>
<tr>
<td>&gt;20, &lt;= 40</td>
<td>8</td>
<td>7.5mg</td>
</tr>
<tr>
<td>&gt;40, &lt;= 60</td>
<td>10</td>
<td>6mg</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>5mg</td>
</tr>
</tbody>
</table>

**Opioid Usage in Chronic Pain Management**

Per systematic review in the CDC Guideline for Prescribing Opioids for Chronic Pain, long-term (>1 year) efficacy of opioids in management of chronic pain, function, or quality of life is not established. Most randomized controlled trials present effectiveness within 6 weeks or less. Conversely, significant risks of adverse events are present with chronic opioid therapy, including opioid abuse and dependence, social role withdrawal, and increased risk of CNS depression, and withdrawal emergencies.

The CDC also recommends re-evaluating and re-establishing treatment goals, including realistic expectation for pain and function, as well as discontinuation strategies when benefits do not outweigh risks. The guideline provides the following recommendations for opioid selection, dosage, duration, follow-up and discontinuation:
- Immediate-release (IR) opioids are preferred over extended-release (ER) forms.

CONTINUED ON NEXT PAGE
FENTANYL (BUCCAL, NASAL, SUBLINGUAL)

RATIONALE (CONTINUED)

- The lowest effective dosage is preferred with initial opioid use. Caution is warranted at any dose and reassessing benefits and risks is recommended for 50 morphine milligram equivalents (MME) daily or more. 90 MME daily or more should be avoided if possible.
- Within 1 to 4 weeks of therapy, clinicians should evaluate benefits and harms of using opioids to treat chronic pain. Therapy continuation should be evaluated every 3 months or sooner. If benefits do not outweigh harms to continue opioid therapy, other therapies should be optimized and opioid tapering/discontinuation should be considered and encouraged.

Assessing Risk and Addressing Harms of Opioid Use

- Prior to and throughout opioid therapy, adverse events should be evaluated periodically. Factors that increase risk for opioid overdose include history of overdose or substance use disorder, 50 MME daily or more, and concurrent benzodiazepine use.
- Prescription drug monitoring program (PDMP) data (e.g., RXINSPECT) are useful to monitor total opioid dosage. PDMP data is helpful for initial and periodic opioid usage evaluations.
- Prescribing opioids and benzodiazepines concurrently should be avoided.
- For patients with substance use disorder, evidence-based treatment (medication-assisted and behavioral therapy) is recommended.

Analysis performed by the US Department of Health and Human Services Center for Disease Control and Prevention (CDC) determined the risk of harm to individuals increases as their opioid dose increases and as their length of opioid therapy increases. For example:

- Individuals taking opioid doses > 50 morphine milligram equivalents (MMEs) per day had twice the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking opioid doses > 90 (MMEs) per day had 10 times the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking an opioid for > 3 months (even at low doses) had 15 times the risk of addiction to those taking opioids for < 3 months.

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FENTANYL (BUCCAL, NASAL, SUBLINGUAL)

APPENDIX 1: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM

INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY
PRIOR AUTHORIZATION REQUEST FORM

MDwise
Fax to: (858) 790-7100
c/o MedImpact Healthcare Systems, Inc.
Attn: Prior Authorization Department
10181 Scripps Gateway Court, San Diego, CA 92131
Phone: 1-800-788-2949

Today’s Date

Note: This form must be completed by the prescribing provider.
**All sections must be completed or the request will be denied.**

<table>
<thead>
<tr>
<th>Patient’s Medicaid #</th>
<th>Date of Birth / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Name</td>
<td>Prescriber’s Name</td>
</tr>
<tr>
<td>Prescriber’s IN License #</td>
<td>Specialty</td>
</tr>
<tr>
<td>Prescriber’s NPI #</td>
<td>Prescriber’s Signature: <strong>Required below within attestation section.</strong></td>
</tr>
<tr>
<td>Return Fax #</td>
<td>Return Phone #</td>
</tr>
</tbody>
</table>

PA is required for the following:
- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).

<table>
<thead>
<tr>
<th>Benzodiazepine Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Opioid Agent(s)** | **Prescriber Name*** | **Quantity** | **Dosage Regimen/Duration**
---|---|---|---

*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:

- Are you requesting PA for: Benzodiazepine Agent(s) □ Opioid Agent(s) □ Both □
- Is/are the other prescriber(s) aware of the request for concurrent therapy? □ Yes □ No
- Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? □ Yes □ No

**PA Requirements:**

**Patient diagnosis/diagnoses for use of benzodiazepine therapy:**

Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you plan to continue benzodiazepine therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

**Patient diagnosis/diagnoses for use of opioid therapy:**

Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, ________________________________, hereby attest to the following:

(Prescriber Name)

• The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
• I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
• If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
• I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber Signature: _________________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**

CONFIDENTIAL INFORMATION
This facsimile transmission (and attachments) may contain protected health information from the Indiana Health Coverage Programs (IHCP), which is intended only for the use of the individual or entity named in this transmission sheet. Any unintended recipient is hereby notified that the information is privileged and confidential, and any use, disclosure, or reproduction of this information is prohibited.
REFERENCES


- Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016; 65(1);1-49. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm


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REFERENCES

- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).
### Fentanyl Transdermal Patch

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Duragesic</td>
<td>24635</td>
<td>19200</td>
<td>ROUTE = TRANSDERM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37952</td>
<td>19201</td>
<td>STRENGTH =</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19202</td>
<td>37947</td>
<td>12MCG/HR</td>
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<tr>
<td></td>
<td></td>
<td>37948</td>
<td>19203</td>
<td>25MCG/HR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19201</td>
<td>37947</td>
<td>37.5MCG/HR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19202</td>
<td>37948</td>
<td>50MCG/HR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37948</td>
<td>19203</td>
<td>62.5MCG/HR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19201</td>
<td>37947</td>
<td>75MCG/HR</td>
</tr>
<tr>
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<td>37948</td>
<td>19203</td>
<td>87.5MCG/HR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19201</td>
<td>37947</td>
<td>100MCG/HR</td>
</tr>
</tbody>
</table>

### Guidelines for Use

**Renewal Criteria** will apply in the following scenarios only:
- For patients active with MDwise for 90 days or longer AND previous prior authorization approval for the same medication with the same strength AND recent paid pharmacy claims for the requested medication. Chart notes and/or cash pay for opioid use is not accepted.
- For patients new to MDwise within the past 90 days AND chart notes are provided that document the patient is stable on the requested medication.

All other requests will be reviewed against the Initial Criteria.

**Initial Criteria (Note: For renewal criteria, see below)**

Our guideline for Fentanyl Transdermal Patch for patients with past use of opioid dependency agents (such as, buprenorphine/naloxone SL tablets/films or buprenorphine SL tablets) requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid analgesic will be authorized.

Our guideline for Fentanyl Transdermal Patch does not permit concurrent use with carisoprodol-containing products.

Continued on next page.
INITIAL CRITERIA (CONTINUED)

Our guideline for FENTANYL TRANSDERMAL PATCH requires that patients meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You meet the definition of opioid tolerance [defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid].
- Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted. For patients active with MDwise less than 90 days, chart notes are required to verify previous opioid use for this criterion
- You have had a trial of at least 30 days generic MS Contin in the previous 120 days (NOTE: This requirement does not apply for FENTANYL TRANSDERMAL PATCH requests in patients who have difficulty swallowing.)
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals
- FENTANYL TRANSDERMAL PATCH requests for dosing every 48 hours require a trial of every 72 hours dosing

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

Our guideline for FENTANYL TRANSDERMAL PATCH dosed every 48 hours requires a trial of fentanyl transdermal patch dosed every 72 hours.

Our guideline named FENTANYL TRANSDERMAL PATCH for concurrent use of more than one long-acting opioid analgesic requires patients to meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You experience refractory pain (pain that continues or returns) despite concurrent therapy with one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan. Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
Fentanyl Transdermal Patch

Initial Criteria (Continued)

Our guideline for Fentanyl Transdermal Patch for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
- The diagnosis contributing to the need for opioid analgesic therapy and previous therapy attempted, including dates and doses of prior therapies (if applicable). For a diagnosis of moderate to severe cancer-related pain, pain related to sickle cell disease, or pain in patients receiving palliative care, no additional criteria applies
  - For long-acting opioid therapy requested for chronic moderate to severe pain, ALL of the following are required:
    - You meet the definition of opioid tolerance (defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose (a dose of one pain medication that is the same in pain-relieving effects to that of another pain medication) of another opioid). Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted. For patients active with MDwise less than 90 days, chart notes are required to verify previous opioid use for this criterion
    - Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals
    - You have had a trial of at least 30 days generic MS Contin in the previous 120 days
  - Your prescriber has signed an attestation as to ALL of the following:
    - Your provider will regularly review your controlled substance utilization contained within INSPECT (Indiana controlled substance monitoring program)
    - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
    - Both you and your provider accept the risk of using benzodiazepines and opioid analgesics together at the same time

Continued on Next Page
INITIAL CRITERIA (CONTINUED)

Our guideline for FENTANYL TRANSDERMAL PATCH for patients with claims in history for antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RENEWAL CRITERIA

Our guideline for FENTANYL TRANSDERMAL PATCH does not permit concurrent use with carisoprodol-containing products.

Our guideline for renewal of FENTANYL TRANSDERMAL PATCH requires patients to meet ALL of the following criteria:

- Opioid therapy has resulted in a meaningful improvement in your pain and/or function
- Your doctor has developed an updated pain management plan with clear treatment goals
- A risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (for example, INSPECT)
- Adherence to prescribed opioid regimen has been periodically assessed (for example, urine drug screen, pill counts)

In addition, requests for renewal of concurrent use of (used at the same time with) more than one long-acting opioid requires that you meet ALL of the following rules:

- You have a diagnosis of moderate to severe pain
- You experience refractory pain (pain that continues or returns) despite concurrent therapy with one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals
- Exceptions may be granted if you have moderate to severe pain from cancer, have sickle cell disease (a type of red blood cell disorder) or you are receiving opioids as part of a palliative care plan (treatment for symptoms related to an illness)

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan. Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA (CONTINUED)

Our guideline for renewal of FENTANYL TRANSDERMAL PATCH for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)

- The diagnosis contributing to the need for renewal of the requested opioid analgesic therapy

- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the of using benzodiazepines and opioid analgesics together at the same time

Our guideline for FENTANYL TRANSDERMAL PATCH for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

CONTINUED ON NEXT PAGE
RATIONAL
To ensure opioid analgesics are used according to FDA approved indications with patient safety in mind, and to encourage the use of more cost-effective analgesics.

From 2000-2014, almost half a million people died due to drug overdose, with 2014 being the highest year for deaths on record. In that time, the number of opioids prescribed, as well as the number of opioid overdoses, has risen exponentially. At least half of all opioid overdose deaths involve a prescription opioid. Indiana was among the states that had a statistically significant increase of overdose deaths from 2013-2014.

According to recent research, the opioid epidemic has a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed opioids at double the rate of non-Medicaid patients, and are subsequently at much higher risk of prescription opioid overdose.

Improving the way that opioids are prescribed can ensure safer and more effective pain treatment, and reduce the addiction, misuse, abuse, and overdose of these drugs. These guidelines are to ensure that the use of opioids is consistent with their FDA approved indications, and to initiate action combating the current opioid epidemic.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60mg oral morphine/day, 25mcg transdermal fentanyl/hour, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid for a week or longer.

Opioid Conversion Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butorphanol</td>
<td>7</td>
<td>8.5mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
<td>400mg</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>0.12</td>
<td>0.5mg (500mcg)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Hydromorphone HCl</td>
<td>4</td>
<td>15mg</td>
</tr>
<tr>
<td>Meperidine HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
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<td>40mg</td>
</tr>
<tr>
<td>Oxymorphone HCl</td>
<td>3</td>
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</tr>
<tr>
<td>Pentazocine HCl</td>
<td>0.37</td>
<td>162mg</td>
</tr>
<tr>
<td>Tapentadol HCl</td>
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<td>150mg</td>
</tr>
<tr>
<td>Tramadol HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
</tbody>
</table>

Methadone Conversion Table

<table>
<thead>
<tr>
<th>Methadone daily dose (mg/day)</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0, &lt;= 20</td>
<td>4</td>
<td>20mg</td>
</tr>
<tr>
<td>&gt;20, &lt;=40</td>
<td>8</td>
<td>7.5mg</td>
</tr>
<tr>
<td>&gt;40, &lt;=60</td>
<td>10</td>
<td>6mg</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>5mg</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
FENTANYL TRANSDERMAL PATCH

RATIONALE (CONTINUED)
Opioid Usage in Chronic Pain Management
Per systematic review in the CDC Guideline for Prescribing Opioids for Chronic Pain, long-term (> 1 year) efficacy of opioids in management of chronic pain, function, or quality of life is not established. Most randomized controlled trials present effectiveness within 6 weeks or less. Conversely, significant risks of adverse events are present with chronic opioid therapy, including opioid abuse and dependence, social role withdrawal, and increased risk of CNS depression, and withdrawal emergencies.

The CDC also recommends re-evaluating and re-establishing treatment goals, including realistic expectation for pain and function, as well as discontinuation strategies when benefits do not outweigh risks. The guideline provides the following recommendations for opioid selection, dosage, duration, follow-up and discontinuation:

- Immediate-release (IR) opioids are preferred over extended-release (ER) forms.
- The lowest effective dosage is preferred with initial opioid use. Caution is warranted at any dose and reassessing benefits and risks is recommended for 50 morphine milligram equivalents (MME) daily or more. 90 MME daily or more should be avoided if possible.
- Within 1 to 4 weeks of therapy, clinicians should evaluate benefits and harms of using opioids to treat chronic pain. Therapy continuation should be evaluated every 3 months or sooner. If benefits do not outweigh harms to continue opioid therapy, other therapies should be optimized and opioid tapering/discontinuation should be considered and encouraged.

Assessing Risk and Addressing Harms of Opioid Use

- Prior to and throughout opioid therapy, adverse events should be evaluated periodically. Factors that increase risk for opioid overdose include history of overdose or substance use disorder, 50 MME daily or more, and concurrent benzodiazepine use.
- Prescription drug monitoring program (PDMP) data (e.g., RXINSPECT) are useful to monitor total opioid dosage. PDMP data is helpful for initial and periodic opioid usage evaluations.
- Prescribing opioids and benzodiazepines concurrently should be avoided.
- For patients with substance use disorder, evidence-based treatment (medication-assisted and behavioral therapy) is recommended.

Analysis performed by the US Department of Health and Human Services Center for Disease Control and Prevention (CDC) determined the risk of harm to individuals increases as their opioid dose increases and as their length of opioid therapy increases. For example:

- Individuals taking opioid doses > 50 morphine milligram equivalents (MMEs) per day had twice the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking opioid doses > 90 (MMEs) per day had 10 times the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking an opioid for > 3 months (even at low doses) had 15 times the risk of addiction to those taking opioids for < 3 months.

CONTINUED ON NEXT PAGE
APPENDIX 1: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM

INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT

BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY

PRIOR AUTHORIZATION REQUEST FORM

Today’s Date

Note: This form must be completed by the prescribing provider.

**All sections must be completed or the request will be denied.**

<table>
<thead>
<tr>
<th>Patient’s Medicaid #</th>
<th>Date of Birth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Name</td>
<td>Prescriber’s Name</td>
<td></td>
</tr>
<tr>
<td>Prescriber’s IN License #</td>
<td>Specialty</td>
<td></td>
</tr>
<tr>
<td>Prescriber’s NPI #</td>
<td>Prescriber’s Signature: <strong>Required below within attestation section.</strong></td>
<td></td>
</tr>
<tr>
<td>Return Fax #</td>
<td>Return Phone #</td>
<td></td>
</tr>
</tbody>
</table>

PA is required for the following:
- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).

<table>
<thead>
<tr>
<th>Benzodiazepine Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Opioid Agent(s) | Prescriber Name* | Quantity | Dosage Regimen/Duration |
---|---|---|---|
| | | | |

*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:

- Are you requesting PA for: Benzodiazepine Agent(s) □ Opioid Agent(s) □ Both □
- Is/are the other prescriber(s) aware of the request for concurrent therapy? □ Yes □ No
- Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? □ Yes □ No

**PA Requirements:**

**Patient diagnosis/diagnoses for use of benzodiazepine therapy:**

Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Do you plan to continue benzodiazepine therapy for this patient?** □ Yes □ No
If no, please provide withdrawal plan:

**Patient diagnosis/diagnoses for use of opioid therapy:**

Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, ______________________________, hereby attest to the following:

(Prescriber Name)
• The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
• I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
• If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
• I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber Signature: ______________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**

CONFIDENTIAL INFORMATION
This facsimile transmission (and attachments) may contain protected health information from the Indiana Health Coverage Programs (IHCP), which is intended only for the use of the individual or entity named in this transmission sheet. Any unintended recipient is hereby notified that the information is privileged and confidential, and any use, disclosure, or reproduction of this information is prohibited.
REFERENCES

- Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016; 65(1);1-49. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

CONTINUED ON NEXT PAGE
REFERENCES (CONTINUED)

- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).
GUIDELINES FOR USE

Our guideline for **FINGOLIMOD** requires a diagnosis of relapsing-remitting, secondary-progressive, or progressive-relapsing multiple sclerosis and the absence of medical history or cardiac events that are contraindicated with the use of Gilenya (those that may increase risk of cardiac events associated with Gilenya).

**FINGOLIMOD**

**RATIONALE**

To prevent inappropriate utilization of fingolimod for clinically isolated syndrome (CIS) or in those patients for whom Gilenya is contraindicated.

Cardiovascular adverse effects, including bradycardia and heart block, have been associated with Gilenya, especially early in therapy. Bradycardia was observed in fingolimod clinical trials (4% in fingolimod group versus 1% in placebo group), although patients at high risk of bradycardia were excluded from the clinical trials. When Gilenya was approved, initial product labeling included information on first dose monitoring and instructed health care professionals to observe patients for at least 6 hours after the first dose.

CONTINUED ON NEXT PAGE
FINGOLIMOD

RATIONALE (CONTINUED)

Patients exhibiting symptomatic bradycardia should obtain continuous ECG monitoring until symptoms resolve. The manufacturer has recently updated labeling information to include a list of cardiovascular contraindications for Gilenya, including recent (within past 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure; history or presence of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has pacemaker; baseline QTC interval 500ms or above; or treatment with Class Ia or Class III anti-arrhythmic drugs.

FDA APPROVED INDICATIONS
Fingolimod is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS) in patients 10 years of age and older.

DOSEAGE AND ADMINISTRATION

- Recommended dosage for adults and pediatric patients (10 years of age and older) weighing more than 40 kg: 0.5 mg orally once-daily, with or without food.
- Recommended dosage for pediatric patients (10 years of age and above) weighing less than or equal to 40 kg: 0.25 mg orally once-daily, with or without food.
- First Dose Monitoring (including reinitiation after discontinuation > 14 days and dose increases):
  - Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of observation period required.
  - Monitor until resolution if heart rate < 45 beats per minute (bpm) in adults, < 55 bpm in patients aged 12 years and above, or < 60 bpm in pediatric patients aged 10 to below 12 years, atrioventricular (AV) block, or if lowest post-dose heart rate is at the end of the observation period.
  - Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first-dose monitoring for second dose.
  - Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes.

AVAILABLE STRENGTHS
0.25 mg hard capsules
0.5 mg hard capsules

REFERENCES

Created: 03/15
Effective: 07/06/18
Client Approval: 06/13/18
P&T Approval: N/A
**GUIDELINES FOR USE**

**INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)**

The guideline named FOSTAMATINIB (Tavalisse) requires a diagnosis of chronic immune thrombocytopenia (ITP). In addition, the following criteria must be met.

- The patient is 18 years of age or older
- The patient has had insufficient response to a previous treatment [e.g., splenectomy, corticosteroids, immunoglobulins, Promacta (eltrombopag), and Nplate (romiplostim)].

**RENEWAL CRITERIA**

The guideline for FOSTAMATINIB (Tavalisse) renewal requires a diagnosis of chronic immune thrombocytopenia (ITP). In addition, the following criteria must be met.

- The patient is 18 years of age or older
- The patient has achieved a platelet count of at least 50 x 10^9/L

**RATIONALE**

To ensure appropriate use of Tavalisse (fostamatinib) consistent with FDA approved indications.

**FDA APPROVED INDICATION**

Tavalisse is a kinase inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

**DOSAGE AND ADMINISTRATION**

Initiate Tavalisse at 100 mg orally twice daily with or without food. After 4 weeks, increase dose to 150 mg twice daily, if needed, to achieve platelet count of at least 50 x 10^9/L. Use the lowest dose of Tavalisse to achieve and maintain a platelet count at least 50 x 10^9/L as necessary to reduce the risk of bleeding. Please refer to the full prescribing information for recommendations on how to manage adverse reactions. Discontinue Tavalisse after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.

**REFERENCES**

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named FREMANEZUMAB-VFRM (Ajovy) requires a diagnosis of migraines. The following criteria must also be met:

- The patient is 18 years of age or older
- Documentation that the patient has had a previous trial of any THREE of the following preventive migraine treatments (chart notes required in the absence of electronic prescription claims history):
  - beta-blocker (such as propranolol or nadolol)
  - candesartan
  - cyproheptadine
  - lisinopril
  - tricyclic antidepressant (such as amitriptyline, nortriptyline, or doxepin)
  - topiramate
  - valproic acid/divalproex sodium
  - venlafaxine/desvenlafaxine
  - verapamil

RENEWAL CRITERIA

The guideline named FREMANEZUMAB-VFRM (Ajovy) requires that at least ONE of the following criteria has been met:

- The patient has experienced a reduction in migraine or headache frequency of at least 2 days per month with Ajovy therapy
- The patient has experienced a reduction in migraine severity with Ajovy therapy
- The patient has experienced a reduction in migraine duration with Ajovy therapy

RATIONALE

Ensure appropriate criteria are used for the management of requests for AJOVY according to approved indication, dosing, and national treatment guidelines.

FDA APPROVED INDICATIONS

AJOVY is a calcitonin gene-related peptide (CGRP) receptor antagonist indicated for the preventive treatment of migraine in adults.
FREMANEZUMAB-VFRM

FDA APPROVED INDICATIONS (CONTINUED)

HOW SUPPLIED
225 mg/1.5 mL solution in a single-dose prefilled syringe.

DOsing & ADMINISTRATION
AJOVY is for subcutaneous use only.

Two subcutaneous dosing options of AJOVY are available to administer the recommended dosage:
- 225 mg monthly
- 675 mg every 3 months (quarterly) - administered as 3 consecutive injections of 225 mg each.

REFERENCES
- Guinn, D. Hickenbottom, S. Lee MJ. Headache in pregnant and postpartum women. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed June 11, 2019

Created: 11/18
Effective: 08/01/19
Client Approval: 07/12/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named GALCANEZUMAB-GNLM (Emgality) requires a diagnosis of migraines or episodic cluster headaches. The following criteria must also be met:

For migraines, approval requires:
- The patient is 18 years of age or older
- Documentation that the patient has had a previous trial of any THREE of the following preventive migraine treatments (chart notes required in the absence of electronic prescription claims history):
  - beta-blocker (such as propranolol or nadolol)
  - candesartan
  - cyproheptadine
  - lisinopril
  - tricyclic antidepressant (such as amitriptyline, nortriptyline, or doxepin)
  - topiramate
  - valproic acid/divalproex sodium
  - venlafaxine/desvenlafaxine
  - verapamil

For episodic cluster headaches, approval requires:
- The patient is 18 years of age or older
- The patient has had a previous trial of verapamil for the current cluster period (date of cluster onset is required for the purposes of this criterion)

RENEWAL CRITERIA

The guideline named GALCANEZUMAB-GNLM (Emgality) requires a diagnosis of migraine or episodic cluster headaches. In addition, the following criteria apply.

For migraine, documentation (i.e., chart notes) is required that at least ONE of the following criteria has been met:
- The patient has experienced a reduction in migraine or headache frequency of at least 2 days per month with Emgality therapy
- The patient has experienced a reduction in migraine severity with Emgality therapy
- The patient has experienced a reduction in migraine duration with Emgality therapy

For episodic cluster headaches, documentation (i.e., chart notes) is required that the patient has experienced a reduction in cluster headache frequency of at least 2 days per week with Emgality therapy.

CONTINUED ON NEXT PAGE
GALCANEZUMAB-GNLN

RATIONALE
Ensure appropriate criteria are used for the management of requests for EMGALITY according to approved indication, dosing, and national treatment guidelines.

FDA APPROVED INDICATIONS
EMGALITY is a calcitonin gene-related peptide (CGRP) receptor antagonist indicated for the preventive treatment of migraine in adults.

HOW SUPPLIED
- Injection: 120 mg/mL solution in a single-dose prefilled pen
- Injection: 120 mg/mL solution in a single-dose prefilled syringe
- Injection: 100 mg/mL solution in a single-dose prefilled syringe

DOSING & ADMINISTRATION
EMGALITY is for subcutaneous use only.

Recommended dosage for migraines: 240 mg loading dose (administered as two consecutive injections of 120 mg each), followed by monthly doses of 120 mg.

Recommended dosage for episodic cluster headaches: 300 mg (three consecutive injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period.

REFERENCES
- Guinn, D. Hickenbottom, S. Lee MJ. Headache in pregnant and postpartum women. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed June 11, 2019

CONTINUED ON NEXT PAGE
REFERENCES (CONTINUED)

GUIDELINES FOR USE

Our guideline for GEFITINIB requires that the patient has a diagnosis of metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

GEFITINIB

RATIONALE
Promote appropriate utilization of GEFITINIB based on FDA approved indication and dosing.

About 85% to 90% of lung cancer is classified as NSCLC and of that population; an estimated 10% is due to an EGFR mutation. Iressa targets a specific subset of this EGFR mutation population. Although Iressa was withdrawn from the market in 2012 due to failure to demonstrate clinical benefit in NSCLC, it is now reapproved due to efficacy findings in a specific population whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

DOSAGE
The recommended dose of Iressa is 250 mg by mouth daily until disease progression or unacceptable toxicity.

Increase Iressa dose to 500 mg daily when taken concomitantly with a strong CYP3A4 inducer. Return to recommended dose of 250 mg daily 7 days after discontinuation of the strong inducer.

FDA APPROVED INDICATIONS
Iressa is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of Iressa have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.

REFERENCES

Created: 01/16
Effective: 03/01/16
Client Approval: 01/14/16
P&T Approval: 01/16
GUIDELINES FOR USE

The guideline named **GILTERITINIB (Xospata)** requires a diagnosis of relapsed or refractory acute myeloid leukemia (AML). In addition, the following criteria must be met.

- The patient is 18 years of age or older
- The patient has FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test

**RATIONALE**

For further information, please refer to the Prescribing Information for Xospata.

**REFERENCES**


Created: 01/18
Effective: 02/18/19
Client Approval: 01/23/18
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named GLASDEGIB (Daurismo) requires a diagnosis of newly-diagnosed acute myeloid leukemia (AML). In addition, the following criteria must be met.

- The requested medication will be used in combination with low-dose cytarabine
- The patient is 75 years of age or older, OR the patient has comorbidities that prevent use of intensive induction chemotherapy

RATIONALE

For further information, please refer to the Prescribing Information and/or Drug Monograph for Daurismo.

REFERENCES


Created: 01/18
Effective: 02/18/19
Client Approval: 01/23/18
P&T Approval: N/A
GLATIRAMER ACETATE

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLATIRAMER ACETATE</td>
<td>COPAXONE</td>
<td>12810</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

Approval requires a diagnosis of relapsing-remitting multiple sclerosis.

RATIONALE

To ensure appropriate use aligned with FDA approved indication.

Copaxone is for subcutaneous use only. The dosing schedule depends on the product strength that is selected. The recommended doses are:
- Copaxone 20 mg per mL: administer once per day
- Copaxone 40 mg per mL: administer three times per week and at least 48 hours apart

Copaxone 20 mg per mL and Copaxone 40 mg per mL are not interchangeable.

FDA APPROVED INDICATIONS

Copaxone is indicated for the treatment of patients with relapsing-forms of multiple sclerosis.

REFERENCES


Created: 06/15
Effective: 07/01/17 Client Approval: 05/01/17 P&T Approval: 02/14
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named L-GLUTAMINE (ENDARI) requires a diagnosis of sickle cell disease and patient must be at least 5 years old. In addition, the following criteria must be met:

- The medication is prescribed by or given in consultation with a hematologist

For patients 18 years of age and older, approval also requires documentation of ONE of the following:

- At least 3 sickle cell crises in the past year (A sickle cell crises is defined as a visit to an emergency room/medical facility for sickle cell disease-related pain which was treated with a parenterally administered narcotic or parenterally administered ketorolac, the occurrence of chest syndrome, priapism, or splenic sequestration)
- The patient is having sickle-cell associated symptoms (e.g., pain or anemia) which are interfering with activities of daily living
- The patient has a history of or has recurrent acute chest syndrome (ACS)

RENEWAL CRITERIA

The guideline for L-GLUTAMINE (Endari) renewal requires a diagnosis of sickle cell disease and documentation that the patient has maintained or experienced a reduction in acute complications of sickle-cell disease (SCD) (e.g., number of sickle cell crises, hospitalizations, ACS).

RATIONALE

Promote appropriate utilization of L-GLUTAMINE based on FDA approved indication and dosing.

FDA APPROVED INDICATIONS

Endari is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.

DOSSING & ADMINISTRATION

Administer Endari orally, twice per day at the dose based on body weight according to Table 1.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

**DOSING & ADMINISTRATION**

Table 1. Recommended Dosing

<table>
<thead>
<tr>
<th>Weight in kilograms</th>
<th>Weight in pounds</th>
<th>Per dose in grams</th>
<th>Per day in grams</th>
<th>Packets per dose</th>
<th>Packets per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>&lt; 66</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
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**REFERENCES**


Created: 06/18
Effective: 06/18/18
Client Approval: 06/07/18
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires a patient age of at least 2 months, a diagnosis of urea cycle disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone, and a trial of Buphenyl.

GLYCEROL PHENYL BUTYRATE

RATIONALE
To ensure appropriate use aligned with FDA approved indication.

Ravicti is supplied as a liquid for oral administration. It should be taken with food and administered directly into the mouth via oral syringe or dosing cup. Ravicti should be given in 3 equally divided dosages, each rounded up to the nearest 0.5 mL. The recommended dosages for patients switching from sodium phenylbutyrate to Ravicti and patients naïve to phenylbutyric acid are different.

Patients switching from sodium phenylbutyrate to Ravicti should receive the dosage of Ravicti that contains the same amount of phenylbutyric acid. The conversion is as follows:

Total daily dosage of Ravicti (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.8

The recommended dosage range in patients naïve to phenylbutyrate (PBA), based upon body surface area, is 4.5 to 11.2 mL/m2/day (5 to 12.4 g/m2/day). For patients with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m2/day.

The maximum total daily dosage is 17.5 mL (19 g).

Ravicti (glycerol phenylbutyrate) joins Buphenyl (sodium phenylbutyrate) as the second FDA approved treatment for UCDs. Ravicti is a nearly tasteless and odorless liquid taken three times a day. In contrast, Buphenyl is poorly tolerated by patients due to its unpleasant taste and odor and along with the need to take up to 40 tablets a day. Over half of UCD patients do not take Buphenyl and it is believed that is largely due to the difficulties in tolerating the drug.

UCDs are genetic metabolic disorders present in an estimated 1 in 10,000 births in the United States. Patients with UCDs are deficient in one of the key enzymes that comprise the urea cycle, the body’s primary vehicle for removing ammonia, a potent neurotoxin, from the bloodstream. Onset may occur at any age depending on the severity of the disorder. If left untreated, UCDs can cause dangerously heightened levels of ammonia in the bloodstream (hyperammonemia) resulting in brain damage, coma, and/or death.

CONTINUED ON NEXT PAGE
GLYCEROL PHENYLIBUTYRATE

RATIONALE (CONTINUED)

Ravicti is a triglyceride containing 3 molecules of phenylbutyrate (PBA). Phenylacetate (PAA), the major metabolite of PBA, is the active moiety of Ravicti. PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN), which is excreted by the kidneys. On a molar basis, PAGN, like urea, contains 2 moles of nitrogen and provides an alternate vehicle for waste nitrogen excretion.

The FDA approval of Ravicti was based on separate studies in adults and pediatrics.

A randomized, double-blind, active-controlled, crossover, non-inferiority study enrolled 45 subjects with UCDs who had been on sodium phenylbutyrate prior to enrollment. The trial was designed to compare Ravicti to sodium phenylbutyrate by evaluating venous ammonia levels. The primary endpoint was to establish non-inferiority in the 24-hour AUC (a measure of exposure to ammonia over 24 hours) for venous ammonia on days 14 and 28 when the drugs were expected to be at steady state. The subjects were randomized to sodium phenylbutyrate for 2 weeks followed by Ravicti for 2 weeks or Ravicti for 2 weeks followed by sodium phenylbutyrate for 2 weeks. The dose of Ravicti was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dose the patients were taking when they entered the trial. Both treatments were administered three times daily with meals. Forty-four subjects were evaluable for analysis. Ravicti was non-inferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Mean 24-hour AUCs for venous ammonia during steady-state dosing were 866 µmol/L hour and 977 µmol/L hour with Ravicti and sodium phenylbutyrate, respectively. Long term (12 month) studies in adults have demonstrated maintenance of normal ammonia serum values with Ravicti.

Two fixed-sequence, open-label, sodium phenylbutyrate to Ravicti switchover studies were conducted in pediatric patients ages 2 to 17 years. The first study was 7 days in duration and the second study was 10 days in duration. A total of 26 subjects were enrolled. The dose of Ravicti was calculated to deliver the same amount of PBA as the dose of sodium phenylbutyrate patients were taking when they entered the trial. Sodium phenylbutyrate or Ravicti was administered in divided doses with meals and the subjects adhered to a low-protein diet throughout the study. After a dosing period with each treatment, all subjects underwent 24 hours of venous ammonia measurements, as well as blood and urine PK assessments. The 24-hour AUCs for blood ammonia (AUC0-24h) in 11 pediatrics 6 to 17 years of age (Study 1) and 11 pediatrics 2 years to 5 years of age (Study 2) were similar between treatments. In children 6 to 17 years of age, the ammonia AUC0-24h was 604 µmol·h/L vs. 815 µmol·h/L on Ravicti versus sodium phenylbutyrate. In the patients between 2 years and 5 years of age, the ammonia AUC0-24h was 632 µmol·h/L vs. 720 µmol·h/L on Ravicti versus sodium phenylbutyrate. Long term (12 month) studies in pediatrics have also demonstrated maintenance of normal ammonia serum values with Ravicti.

The use of Ravicti in patients <2 months of age is contraindicated. Ravicti is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels. Warnings and precautions include nausea, vomiting, diarrhea, decreased appetite, hyperammonemia, dizziness, headache, upper abdominal pain, rash and fatigue. The most common adverse reactions (occurring in ≥10% of patients) reported during short-

CONTINUED ON NEXT PAGE
GLYCEROL PHENYL BUTYRATE

RATIONALE (CONTINUED)

term treatment with Ravicti were diarrhea, flatulence, and headache. Ravicti is pregnancy category C. A voluntary patient registry will include evaluation of pregnancy outcomes in patients with UCDs.

FDA APPROVED INDICATIONS
Ravicti is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age with urea cycle disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

Limitations of Use:
• Ravicti is not indicated for treatment of acute hyperammonemia in patients with UCDs.
• The safety and efficacy of Ravicti for the treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.
• The use of Ravicti in patients <2 months of age is contraindicated

REFERENCES

Created: 06/15
Effective: 07/22/15        Client Approval: 06/15        P&T Approval: 11/13
GUIDELINES FOR USE

The guideline named GLYCOPHYRONIUM TOPICAL (Qbrexza) requires that the patient has a diagnosis of primary axillary hyperhidrosis. In addition, the following criteria must be met:

- The patient is 9 years of age or older
- Documentation that the patient has primary axillary hyperhidrosis as evidenced by focal, visible, excessive sweating of at least six months duration with all secondary causes ruled out
- Documentation of at least TWO of the following:
  - Symptoms occur bilaterally
  - Symptoms impair daily activities
  - Patient has at least one episode per week
  - Onset occurred prior to patient turning 25 years old
  - Patient has a family history of primary axillary hyperhidrosis
  - Symptoms do not occur during sleep

GLYCOPHYRONIUM TOPICAL

RATIONALE

Ensure appropriate criteria are used for the management of requests for GLYCOPHYRONIUM TOPICAL (Qbrexza) according to approved indication, dosing, and national guidelines.

FDA APPROVED INDICATIONS

GLYCOPHYRONIUM TOPICAL (Qbrexza) is a topical anticholinergic indicated in adult and pediatric patients 9 years of age and older for the treatment of primary axillary hyperhidrosis.

HOW SUPPLIED

Single-use cloth pre-moistened with 2.4% glycopyrronium solution packaged in individual pouches.

DOSAGE & ADMINISTRATION

GLYCOPHYRONIUM TOPICAL (Qbrexza) is for topical use in the underarm area only and not for use in other body areas.

A single cloth should be used to apply Qbrexza to both underarms no more than once every 24 hours.

REFERENCES

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named GOLIMUMAB - IV (Simponi Aria - IV) requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. In addition, the following criteria must be met:

For the diagnosis of moderate to severe rheumatoid arthritis (RA), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- Concurrent use of methotrexate (unless contraindicated)
- The patient is 18 years of age or older
- Previous trial of TWO of the following preferred self-administered immunomodulators: Actemra SQ, Cimzia, Enbrel, Orencia SQ, or Xeljanz

For the diagnosis of psoriatic arthritis (PsA), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist or dermatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older
- Previous trial of at least TWO of the following preferred self-administered immunomodulators: Cimzia, Cosentyx, Enbrel, Orencia, or Otezla

For the diagnosis of ankylosing spondylitis (AS), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist
- The patient is 18 years of age or older
- Previous trial of at least TWO of the following preferred self-administered immunomodulators: Cimzia, Cosentyx, or Enbrel

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GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

The guideline named GOLIMUMAB - IV (Simponi Aria - IV) renewal requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis for renewal. In addition, the following criteria must be met:

For the diagnosis of moderate to severe rheumatoid arthritis (RA), approval requires:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy
• Concurrent use of methotrexate (unless contraindicated)

For the diagnosis of psoriatic arthritis (PsA), approval requires:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy

For the diagnosis of ankylosing spondylitis (AS), approval requires:
• Documentation that the patient has experienced or maintained an improvement of at least 50% or 2 units (scale of 1-10) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) while on therapy.

RATIONALE
Promote appropriate utilization of Simponi Aria (golimumab IV) based on FDA approved indication and dosing.

FDA APPROVED INDICATIONS
Simponi Aria is a tumor necrosis factor (TNF) blocker indicated for the treatment of adult patients with:
• Moderately to severely active Rheumatoid Arthritis (RA) in combination with methotrexate
• Active Psoriatic Arthritis (PsA)
• Active Ankylosing Spondylitis (AS)

DOSAGE AND ADMINISTRATION
Dosage in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis
The Simponi Aria dosage regimen is 2 mg per kg given as an intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.

For patients with rheumatoid arthritis (RA), Simponi Aria should be given in combination with methotrexate. For patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS), Simponi Aria may be given with or without methotrexate or other non-biologic Disease-modifying Antirheumatic Drugs (DMARDs). Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with Simponi Aria.

The efficacy and safety of switching between intravenous and subcutaneous formulations and routes of administration have not been established.

CONTINUED ON NEXT PAGE
Available Strengths
Each single-use vial contains 50 mg of Simponi Aria per 4 mL of solution. Simponi Aria must be refrigerated and protected from light.

REFERENCES

Created: 02/18
Effective: 06/01/18 Client Approval: 04/10/18 P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for GOLIMUMAB (Simponi) - SQ requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, moderate to severe ankylosing spondylitis, or moderately to severely active ulcerative colitis. Additional guideline requirements apply.

For patients with moderate to severe rheumatoid arthritis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- Concurrent use of methotrexate (unless contraindicated)
- 18 years of age or older

For patients with psoriatic arthritis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older

For patients with moderate to severe ankylosing spondylitis, our guideline requires:
- Therapy initiated by or in consultation with a rheumatologist
- 18 years of age or older

For patients with moderately to severely active ulcerative colitis, our guideline requires:
- Therapy initiated by or in consultation with a gastroenterologist
- Previous trial with one or more of the following conventional agents: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
- 18 years of age or older

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA

Our guideline for the renewal of GOLIMUMAB (Simponi) - SQ requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, moderate to severe ankylosing spondylitis, or moderately to severely active ulcerative colitis. Additional guideline requirements apply.

Renewal for patients with moderate to severe rheumatoid arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count and swollen joint count while on therapy.
- Concurrent use of methotrexate (unless contraindicated).

Renewal for patients with psoriatic arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count and swollen joint count while on therapy.

Renewal for patients with moderate to severe ankylosing spondylitis requires:
- Documentation that the patient has experienced or maintained an improvement of at least 50% or 2 units (scale of 1-10) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Renewal for patients with moderately to severely active ulcerative colitis requires:
- Documentation that the patient has experienced or maintained symptomatic improvement while on therapy.

RATIONALE

Ensure appropriate diagnostic, utilization and safety criteria are used for the management of prior authorization requests for golimumab.

DOSAGE

RA, PsA, and AS: 50 mg administered by subcutaneous injection once a month
UC: 200 mg initially administered by subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 100 mg every 4 weeks

FDA APPROVED INDICATIONS

Simponi is a tumor necrosis factor (TNF) blocker indicated for the treatment of adult patients with:
- Moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate
- Active psoriatic arthritis (PsA) alone, or in combination with methotrexate
- Active ankylosing spondylitis (AS)
- Moderate to severe Ulcerative colitis (UC) with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy
  - Inducing and maintaining clinical response
  - Improving endoscopic appearance of the mucosa during induction
  - Inducing clinical remission
  - Achieving and sustaining clinical remission in induction responders
REFERENCES

GUIDELINES FOR USE

Our guideline for approval requires a diagnosis of prostate cancer or endometriosis; the requested medication is being used as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding; or a diagnosis of hormone receptor positive breast cancer for a premenopausal or perimenopausal patient.

RATIONALE

Coverage of Zoladex (goserelin) is based on FDA approved indication and NCCN recommendations.

Zoladex 3.6mg implant is dosed every 28 days. For the treatment of endometriosis, no clinical data exists for treatment duration in excess of 6 months. For the treatment of prostate cancer, Zoladex 10.8mg implant can also be used every 12 weeks.

NCCN guidelines recommend premenopausal patients with hormone-positive disease have ovarian ablation/suppression (with goserelin or leuprolide) and be treated as a postmenopausal woman.

FDA APPROVED INDICATIONS

Zoladex is a gonadotropin releasing hormone (GnRH) agonist indicated for:

- Use in combination with flutamide for the management of locally confined carcinoma of the prostate
- Palliative treatment of advanced carcinoma of the prostate
- The management of endometriosis
- Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding
- Use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women

REFERENCES


Created: 10/15
Effective: 11/12/15
Client Approval: 10/19/15
P&T Approval: 10/15
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named GUSELKUMAB (Tremfya) requires a diagnosis of moderate to severe plaque psoriasis (PsO). In addition, the following criteria must be met:

• Therapy is prescribed by or in consultation with a dermatologist
• Plaque psoriasis involves at least 10% body surface area (BSA) OR psoriatic lesions affecting the hands, feet, or genital area
• Previous trial of one or more forms of conventional therapies, such as PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
• The patient is 18 years of age or older
• Previous trial of TWO of the following preferred formulary agents: Cimzia, Cosentyx, Enbrel, or Otezla

RENEWAL CRITERIA

The guideline named GUSELKUMAB (Tremfya) requires a diagnosis of moderate to severe plaque psoriasis (PsO) for renewal. The following criteria must also be met:

• Documentation that the patient has achieved or maintained clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50% or more

RATIONALE

Ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for guselkumab.

FDA APPROVED INDICATIONS

Tremfya is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

DOSGING & ADMINISTRATION

Tremfya is administered by subcutaneous injection. The recommended dose is 100 mg at Week 0, Week 4, and every 8 weeks thereafter.

REFERENCES

• Tremfya [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2017

Created: 08/17
Effective: 09/01/18
Client Approval: 08/06/18
P&T Approval: N/A
IBRUTINIB

GUIDELINES FOR USE

The guideline named IBRUTINIB (Imbruvica) requires a diagnosis of mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström’s macroglobulinemia (WM), marginal zone lymphoma (MZL), or chronic graft versus host disease (cGVHD). Requests for Ibrutinib 140 mg or 280 mg tablets require a trial of or contraindication to Ibrutinib 140 mg capsules. The following criteria must also be met:

- The patient is 18 years of age or older

**For patients with mantle cell lymphoma (MCL), approval requires:**
- Patient has received at least one prior therapy for mantle cell lymphoma (MCL)

**For patients with marginal zone lymphoma (MZL), approval requires:**
- Patient requires systemic therapy
- Patient has received at least one prior anti-CD20-based therapy (e.g., Rituxan)

**For patients with chronic graft versus host disease (cGVHD), approval requires:**
- Patient has received at least one prior systemic therapy (e.g., corticosteroids, immunosuppressants)

RATIONALE

To promote appropriate utilization of Imbruvica based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS

Imbruvica is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy.
- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).
- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.
- Waldenström’s macroglobulinemia (WM).
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Accelerated approval was granted for the indication of MCL based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

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IBRUTINIB

**DOSAGE AND ADMINISTRATION**

Administer IMBRUVICA orally once daily at approximately the same time each day. The dose should be taken orally with a glass of water. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets.

**MCL, MZL**

560mg taken orally once daily until disease progression or unacceptable toxicity

**CLL, SLL, WM:**

The recommended dose for CLL/SLL and WM as a single agent, in combination with rituximab for WM, or in combination with bendamustine and rituximab for CLL/SLL is 420mg taken orally once daily until disease progression or unacceptable toxicity. When administering IMBRUVICA in combination with rituximab, consider administering IMBRUVICA prior to rituximab when given on the same day

**cGVHD**

420mg taken orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, Imbruvica should be discontinued considering the medical assessment of the individual patient

**REFERENCES**


Created: 06/15
Effective: 04/15/19 Client Approval: 03/28/19 P&T Approval: N/A
ICATIBANT

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GUIDELINES FOR USE
Approval requires a diagnosis of hereditary angioedema, documented age of 18 years old or older and medication being prescribed or patient overseen by hematologist or immunologist.

ICATIBANT
RATIONAL
Ensure appropriate use of icatibant based on FDA approved indication and dosing.

The recommended dose of icatibant is 30 mg subcutaneously. Additional doses may be administered every 6 hours. No more than 3 doses in any 24 hour period for a total of 90 mg.

FDA APPROVED INDICATION
Firazyr (icatibant) is indicated for the treatment of acute attacks of hereditary angioedema in adults 18 years of age and older.

REFERENCE

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/13
Our guideline for IDELALISIB requires a diagnosis of relapsed chronic lymphocytic leukemia (CLL) with concomitant treatment with rituximab, relapsed follicular B-cell non-Hodgkin lymphoma (FL) or relapsed small lymphocytic lymphoma (SLL) and having received two prior systemic therapies.

Table 1. Chronic Lymphocytic Leukemia (CLL) Treatment Options (please refer to NCCN for most current guideline)

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RATIONAL
Promote appropriate utilization and dosing of idelalisib based on their FDA approved indication.

DOSE
The recommended maximum starting dose of Zydelig is 150 mg administered orally twice daily.

Dose modification may be required for specific toxicities related to Zydelig. If resuming Zydelig after interruption for other severe or life-threatening toxicities, reduce the dose to 100 mg twice daily.

FDA APPROVED INDICATIONS
Zydelig is a kinase inhibitor indicated for the treatment of patients with:

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

Accelerated approval was granted for FL and SLL based on overall response rate. Improvement in patient survival or disease related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/14
GUIDELINES FOR USE

Approval requires a diagnosis of pulmonary arterial hypertension with New York Heart Association (NYHA) and World Health Organization (WHO) Class III or IV symptoms.

RATIONALE
Ensure appropriate use of Ventavis.

FDA APPROVED INDICATION
VENTAVIS is indicated for treatment of pulmonary artery hypertension (WHO group 1) in patients with NYHA/WHO class III or IV symptoms to improve exercise capacity.

World Health Organization Classification of Pulmonary Hypertension Group 1:

- Idiopathic (familial)
- Congenital systemic-to-pulmonary shunts
- HIV infection
- Collagen vascular disease
- Portal Hypertension
- Drugs and toxins

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 02/11
GUIDELINES FOR USE

For Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, accelerated phase, or blast crisis, approval requires a diagnosis of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, accelerated phase, or blast crisis. Patients previously treated with therapy such as Tasigna, Sprycel, Bosulif, or Iclusig require a Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) mutational analysis confirming that the following mutations are not present: T315I, V299L, F317L/V/I/C, Y253H, E255K/V, or F359V/C/I. OR Approval requires a diagnosis of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements, aggressive systemic mastocytosis without D816V c-Kit mutation or with c-Kit mutational status unknown, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans, unresectable and/or metastatic malignant gastrointestinal stromal tumor (GIST) with a Kit (CD117) positive or PDGFRA (platelet-derived growth factor receptor-alpha) mutation, or adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

IMATINIB

RATIONALE
Ensure appropriate utilization of imatinib based on FDA approved indication and NCCN guidelines. Doses of 400mg or 600mg should be administrated once daily, while a dose of 800mg should be given as 400mg twice daily.

FDA APPROVED INDICATIONS
Gleevec is FDA approved for the following:
- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.
- Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia.
- Adult patient with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.
- Adult patient with aggressive systemic mastocytosis without D816V c-Kit mutation or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.

CONTINUED ON NEXT PAGE
IMATINIB (CONTINUED)

FDA APPROVED INDICATIONS (CONTINUED).

- Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans.
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.
- Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

REFERENCES

GUIDELINES FOR USE

The guideline named IMMUNE GLOBULIN requires that the patient has **ONE** of the following diagnoses:

- Primary Immunodeficiency Disease (PID)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Multifocal Motor Neuropathy (MMN)
- Kawasaki Syndrome
- B-cell Chronic Lymphocytic Leukemia (CLL) with hypogammaglobulinemia, Autoimmune Hemolytic Anemia (AIHA), Immune Thrombocytopenic Purpura (ITP), or pure Red Cell Blood Aplasia (PRCA)
- Guillain-Barre Syndrome (GBS)
- Myasthenia Gravis
- Autoimmune Graves' Ophthalmopathy

CONTINUED ON NEXT PAGE
IMMUNE GLOBULIN

GUIDELINE FOR USE (CONTINUED)

- Cytomegalovirus-induced Pneumonitis related to a solid organ transplant
- Prevention of bacterial infection in an HIV-infected child
- Reduction of secondary infections in pediatric HIV infections
- Dermatomyositis or polymyositis
- Autoimmune uveitis (Birdshot retinochoroidopathy)
- Lambert-Eaton myasthenic syndrome
- IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy
- Stiff-man syndrome
- Neonatal sepsis
- Rotavirus enterocolitis
- Toxic shock syndrome
- Enteroviral meningoencephalitis
- Toxic Epidermal Necrolysis or Stevens-Johnson syndrome
- Autoimmune Mucocutaneous Blistering Disease (AMBD) (such as pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, or epidermolysis bullosa acquisita)

For prophylaxis or passive immunization of hepatitis A, measles, varicella, or rubella, only Gamastan S-D will be approved.

For requests of Hizentra, approval requires:
- Only for subcutaneous use
- Diagnosis of primary immunodeficiency disease (PID) OR chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

For requests of Xembify, approval requires:
- Only for subcutaneous use
- Diagnosis of primary immunodeficiency disease (PID)
- Age 2 years or older

For requests of Cuvitru or Hyqvia, approval requires:
- Only for subcutaneous use
- Diagnosis of primary immunodeficiency disease (PID)

For requests for subcutaneous use of Gammagard, Gamunex-C, or Gammaked, approval requires:
- Diagnosis of primary immunodeficiency disease (PID)

CONTINUED ON NEXT PAGE
IMMUNE GLOBULIN

RATIONALE
Ensure appropriate therapeutic use based on FDA approved indications for subcutaneous immune globulin. Although Gammagard Liquid, Gammaked, Gamunex-C may be given intravenously, these products can only be used administered subcutaneously for the treatment of primary immunodeficiency disease (PID).

Ensure appropriate therapeutic use based on FDA approved indications and recommendations from the various professional practice guidelines that discuss the use of non-self administered immune globulin.

American Academy of Neurology (AAN) 2012 Intravenous Immunoglobulin in the treatment of neuromuscular disorders
AAN evaluated existing evidence for the efficacy of IVIG in treating neuromuscular disorder and made practice recommendations based on evidence level. They also noted that IVIG benefit is generally temporary and longer studies are needed to assess long-term efficacy.

IVIG is as effective as plasmapheresis for treating Guillain-Barre syndrome (GBS) in adults. However, a combination of plasmapheresis and IVIG is likely not superior to monotherapy with either treatment.

IVIG benefit is uncertain in children with GBS however many experts consider it reasonable treatment given its effectiveness for the same condition in adults. There is insufficient data to recommend an optimal IVIG dosing regimen.

IVIG is effective and should be offered for the long-term treatment of CIDP. Dosing, frequency, and duration of IVIG for CIDP may vary by patient. There is insufficient data to assess the comparative efficacy of other CIDP treatments such as steroids, plasmapheresis and immunosuppressants.

IVIG is probably effective for the treatment of myasthenia gravis (MG) in moderately or severely affected patients. A risk benefit analysis should be performed prior to treatment of patients with mild disease. There is insufficient evidence to compare the effectiveness of IVIG and plasmapheresis for the treatment of MG.

IVIG is probably effective and should be considered for the treatment of multifocal motor neuropathy (MMN). MMN requires ongoing treatment but optimal treatment dosing, interval, and duration have not been established.

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IMMUNE GLOBULIN

RATIONALE (CONTINUED)

IVIG is possibly effective for the treatment of nonresponsive dermatomyositis in adults and Lambert-Eaton myasthenic syndrome. There is insufficient evidence to assess the role of IVIG in treating the following conditions: neuropathy associated with IgM paraprotein, inclusion body myositis and postpolio syndrome.

American Academy of Allergy, Asthma and Immunology (AAAAI) 2017 evidence review of intravenous immunoglobulin in human disease

AAAAI reviewed evidence supporting the use of standard human immunoglobulin preparation for intravenous administration. Therapeutic uses are categorized by evidence of benefit as follows: definitely beneficial, probably beneficial, might provide benefit, and unlikely to be beneficial. AAAAI also comments that subcutaneous therapy can reduce the occurrence of systemic adverse events in selected patients and can improve quality of life for patients receiving intravenous immune globulin. Adverse events may also be reduced by matching specific products to specific patient characteristics.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Evidence category</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary immune defects with absent B cells</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Primary immune defects with hypogammaglobulinemia and impaired specific antibody production</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Reduction of secondary infections in pediatric HIV infections</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>CIDP</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>Graves ophthalmopathy</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
<td>Ib</td>
<td>B</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>Cytomegalovirus-induced pneumonitis in solid organ transplants</td>
<td>Ib</td>
<td>A</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
Probably Beneficial Uses of IVIG

<table>
<thead>
<tr>
<th>Disease</th>
<th>Evidence category</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia with reduced IgG and history of infections</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>Prevention of bacterial infection in HIV-infected children</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>Primary immune defects with normogammaglobulinemia and impaired specific antibody production</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Dermatomyositis and polymyositis</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Birdshot Retinochoroidopathy</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>Ib</td>
<td>B</td>
</tr>
<tr>
<td>IgM antimmel-associated glycoprotein paraprotein-associated peripheral neuropathy</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Ib-IIa</td>
<td>B</td>
</tr>
<tr>
<td>Stiff-person syndrome</td>
<td>Ib</td>
<td>B</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td>Rotaviral enterocolitis</td>
<td>Ib</td>
<td>A</td>
</tr>
<tr>
<td>Bacterial infections in lymphoproliferative diseases</td>
<td>Ib</td>
<td>B</td>
</tr>
<tr>
<td>Toxic shock Syndrome</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Enteroviral meningoencephalitis</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis and Stevens-Johnson syndrome</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children: Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics 2013

IVIG was commonly used prior to the advent of highly active anti-retroviral therapy (HAART) for infection prophylaxis in symptomatic HIV-infected children. However trimethoprim-sulfamethoxazole is now preferred in this setting. IVIG 400mg/kg every 2-4 weeks is only recommended for primary prevention of serious bacterial infections in HIV-infected children if hypogammaglobulinemia (IgG<400mg/dL) is present or functional antibody deficiency is demonstrated by poor specific antibody titers. IVIG can also be considered for secondary prophylaxis when antibiotic prophylaxis fails to prevent recurrent serious bacterial infections. (Mofenson).

HIV-infected children exposed to varicella and have no history of varicella or zoster; are seronegative for VZV by a sensitive, specific antibody assay; or lack evidence of age-appropriate vaccination should receive passive immunization within 96 hours of exposure. The preferred method of immunization is with human varicella immune globulin (VariZIG), a Canadian product lacking FDA approval that can be used under an IND protocol in the US. If VariZIG is unavailable IVIG 400mg/kg can be administered once as soon as possible, ideally within 96 hours after exposure. If more than 96 hours have passed since exposure, acyclovir 20mg/kg (max 800mg) per dose orally 4 times a day for 5-7 days can also be considered.
RATIONALE (CONTINUED)

European Federation of Neurological Societies (EFNS) Guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases 2008

The EFNS state that the efficacy of IVIG has been proven for the following immune-mediated neurological diseases: Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal mononeuropathy, and acute exacerbations and short-term treatment of myasthenia gravis.


Patients with B-cell chronic lymphocytic leukemia (CLL) are susceptible to infections due to both the underlying disease and immunosuppressive properties of the treatment agents. The main options for decreasing the occurrence of secondary infections for patients with recurrent infections and IgG level <500mg/dL are IVIG, anti-infective prophylaxis, and vaccinations. For patients with serum IVIG <500mg/dL with recurrent sinus-pulmonary infections requiring intravenous antibiotic or hospitalization it is recommended that IVIG levels be monitored and IVIG be administered monthly at a dose of 0.3-0.5 g/kg to maintain nadir levels around 500mg/dL.

Autoimmune cytopenias including: autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and pure red blood aplasia (PRCA) can occur in patients with CLL. AIHA and ITP can be managed with corticosteroids in most cases. IVIG is an option for steroid-refractory cases. Corticosteroids are typically less effective in PRCA than in AIHA or ITP, however they are still considered a first-line treatment along with IVIG and splenectomy.

The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia

Initial treatment of pediatric ITP consists of IVIG (0.8-1g/kg) or a short course of corticosteroids. IVIG can also be used if a more rapid increase in the platelet count is desired. For the treatment of adult ITP longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIG as first-line treatment. IVIG in combination with corticosteroids can be considered when a more rapid increase in platelet count is required. IVIG dosing is usually 1g/kg for a single dose; however additional doses can be administered if necessary. Pregnant patients with ITP can receive either corticosteroids or IVIG. IVIG should be used as initial treatment of ITP in patients with the hepatitis C virus. Initial treatment of ITP patients with HIV coinfection can include corticosteroids, IVIG, or anti-D immunoglobulin.

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Rationale (Continued)

Consensus Statement on the Use of Intravenous Immunoglobulin Therapy in the Treatment of Autoimmune Therapy in the Treatment of Autoimmune Mucocutaneous Blistering Diseases

A consensus statement on the use of IVIG for the treatment of autoimmune mucocutaneous blistering diseases (AMBDs) from a group of physicians was published in the Archives of Dermatology. The consensus group considered 5 distinct types of AMBDs: pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, and epidermolysis bullosa acquista. All are typically treated with corticosteroids or immunosuppressive agents. The use of IVIG treatment is recommended when one of the following is present: failure of conventional therapy, significant adverse effects with conventional therapy, contraindications to conventional therapy, disease progression with conventional therapy, uncontrolled rapid debilitating progressive disease, or rapid progressive epidermolysis bullosa acquista with generalized cutaneous disease. The recommended dose is 2g/kg per cycle, consisting of 3 consecutive daily doses every 3 to 4 weeks. Dosing and frequency may vary among patients depending on severity of disease and response to therapy.

FDA Approved Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>PI</th>
<th>ITP</th>
<th>CIDP</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivigam</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carimune NF</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuvitru (for SC use only)</td>
<td>SC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flebogamma DIF</td>
<td>IV (5%, 10%)</td>
<td>IV (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamastan S-D</td>
<td>IV</td>
<td></td>
<td></td>
<td>Hepatitis A, Measles, Varicella, Rubella (IM)</td>
</tr>
<tr>
<td>Gammagard Liquid</td>
<td>IV/SC</td>
<td></td>
<td></td>
<td>Multifocal motor neuropathy (IV)</td>
</tr>
<tr>
<td>Gammagard S-D</td>
<td>IV</td>
<td></td>
<td></td>
<td>B-cell CLL, Kawasaki syndrome (IV)</td>
</tr>
<tr>
<td>Gammaked</td>
<td>IV/SC</td>
<td></td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Gammaplex</td>
<td>IV (5%, 10%)</td>
<td>IV (5%, 10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamunex-C</td>
<td>IV/SC</td>
<td></td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Hizentra</td>
<td>SC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octagam</td>
<td>IV (5%)</td>
<td></td>
<td>IV (10%)</td>
<td></td>
</tr>
<tr>
<td>Panzyga</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Privigen</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xembify</td>
<td>SC</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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IMMUNE GLOBULIN

FDA APPROVED INDICATIONS (CONTINUED)

**Bivigam** is an immune globulin intravenous (human), 10% liquid, indicated for the treatment of:
- Primary humoral immunodeficiency (PI)

**Carimune NF** is a nanofiltered, immune globulin intravenous (human) indicated for:
- Maintenance treatment of patients with primary immunodeficiencies
- Immune thrombocytopenic purpura (ITP)

**Cuvitru** is an immune globulin subcutaneous (human), 20% solution indicated as replacement therapy for:
- Primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older.

**Flebogamma 5% DIF** is an immune globulin intravenous (human) indicated for treatment of:
- Primary (inherited) immunodeficiency (PI) in adults and pediatric patients 2 years of age and older

**Flebogamma 10% DIF** is an immune globulin intravenous (human) indicated for treatment of:
- Primary (inherited) immunodeficiency (PI)
- Chronic primary immune thrombocytopenia (ITP) in patients 2 years of age and older

**Gamastan S/D** is an immune globulin (human) for intramuscular administration indicated for:
- Hepatitis A
- Measles (rubeola)
- Varicella
- Rubella

**Gammagard Liquid** is an immune globulin infusion (human) indicated as replacement therapy for:
- Primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older.
  - This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
- Multifocal motor neuropathy (MMN)

**Gammagard S/D** is an immune globulin intravenous (human) indicated for:
- Treatment of primary immunodeficiency (PI) in adult and pediatric patients two years of age or older
- Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia (CLL)
- Prevention and/or control of bleeding in adult chronic idiopathic thrombocytopenic purpura (ITP) patients
- Prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients

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IMMUNE GLOBULIN

FDA APPROVED INDICATIONS (CONTINUED)

**Gammaked** is an immune globulin injection (human) 10% liquid that is indicated for the treatment of:
- Primary humoral immunodeficiency (PI) in patients 2 years of age and older
- Idiopathic thrombocytopenic purpura (ITP)
- Chronic Inflammatory demyelinating polyneuropathy (CIDP)

**Gammaglobulin 5%** is an immune globulin intravenous (human) 5% liquid that is indicated for the treatment of:
- Primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older
- Chronic immune thrombocytopenic purpura (ITP)

**Gammaglobulin 10%** is an immune globulin intravenous (human) 10% liquid that is indicated for the treatment of:
- Primary humoral immunodeficiency (PI) in adults
- Chronic immune thrombocytopenic purpura (ITP) in adults

**Gamunex-C** is an immune globulin injection (human) 10% liquid that is indicated for the treatment of:
- Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older
- Idiopathic thrombocytopenic purpura (ITP)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)

**Hizentra** is an immune globulin subcutaneous (human) (IGSC), 20% Liquid indicated for the treatment of:
- Primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP)

Limitations of Use:
Hizentra maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Maintenance therapy beyond these periods should be individualized based upon the patient's response and need for continued therapy

**Hyqvia** is an immune globulin with a recombinant human hyaluronidase indicated for the treatment of:
- Primary Immunodeficiency (PI) in adults

Limitation of Use:
Safety and efficacy of chronic use of recombinant human hyaluronidase in Hyqvia have not been established in conditions other than PI.
- Primary humoral immunodeficiency (PI)

**Octagam 10%** is an immune globulin intravenous (human), 10% liquid, indicated for treatment of:
- Chronic immune thrombocytopenic purpura (ITP) in adults

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FDA APPROVED INDICATIONS (CONTINUED)

Panzyga is an immune globulin intravenous (human) 10% liquid that is indicated for the treatment of:
- Primary humoral immunodeficiency (PI) in patients 2 years of age and older
- Chronic immune thrombocytopenia (ITP) in adults

Privigen is an immune globulin intravenous (human), 10% liquid, indicated for treatment of:
- Primary humoral immunodeficiency (PI)
- Chronic immune thrombocytopenic purpura (ITP) in patients aged 15 years and older
- Chronic inflammatory demyelinating polyneuropathy (CIDP) in adults

Xembify is an immune globulin intravenous (human), 20% liquid, indicated for the treatment of:
- Primary humoral immunodeficiency (PI) in patients 2 years of age and older

DOSAGE AND ADMINISTRATION

Bivigam
Administer intravenously for PI.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-800 mg/kg every 3-4 weeks</td>
<td>0.5 mg/kg/min for the first 10 minutes.</td>
<td>Increase every 20 minutes (if tolerated) by 0.8 mg/kg/min up to 6 mg/kg/min.</td>
</tr>
</tbody>
</table>

Carimune NF
Administer intravenously.

Primary immunodeficiency (PI):
- The recommended dose is 0.4 to 0.8 g/kg of body weight administered once every three to four weeks by intravenous infusion.
- The first infusion must be given as a 3% immunoglobulin solution. Subsequent infusions may be given at higher concentrations if tolerated by the patient.
- An initial infusion rate of 0.5 mg/kg/min is recommended. If tolerated, after 30 minutes the rate may be increased to 1 mg/kg/min for the next 30 minutes. Thereafter, the rate may be gradually increased in a stepwise manner up to a maximum of 3 mg/kg/min as tolerated.

Idiopathic thrombocytopenic purpura (ITP):
- The recommended dose is 0.4 g/kg of body weight administered on 2-5 consecutive days.
- A concentration of immunoglobulin solution of 6% is recommended.
- An initial infusion rate of 0.5 mg/kg/min is recommended. If tolerated, after 30 minutes the rate may be increased to 1 mg/kg/min for the next 30 minutes. Thereafter, the rate may be gradually increased in a stepwise manner up to a maximum of 3 mg/kg/min as tolerated.

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IMMUNE GLOBULIN

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Cuvitru

Administer subcutaneously at regular intervals from daily up to every two weeks. Cuvitru may be administered subcutaneously utilizing an infusion pump.

- **Weekly**: Start Hizentra 1 week after last IGIV or Hyqvia infusion
  
  \[ \text{Initial Weekly dose} = \frac{\text{Previous IGIV or HYQVIA dose (in grams)}}{\text{No. of weeks between IGIV or HYQVIA doses}} \times 1.30 \]

- **Biweekly**: Administer twice the calculated weekly dose.
- **Frequent dosing (2 to 7 times per week)**: Divide the calculated weekly dose by the desired number of administrations per week.
- **Adjust the dose based on clinical response and serum IgG trough levels.**

Flebogamma 5% DIF

Administer intravenously.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-600 mg/kg given every 3 to 4 weeks</td>
<td>0.5 mg/kg/min</td>
<td>5 mg/kg/min</td>
</tr>
</tbody>
</table>

Flebogamma 10% DIF

Administer intravenously.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-600 mg/kg given every 3 to 4 weeks</td>
<td>1 mg/kg/min</td>
<td>8 mg/kg/min</td>
</tr>
<tr>
<td>ITP</td>
<td>1 g/kg daily for 2 consecutive days</td>
<td>1 mg/kg/min</td>
<td>8 mg/kg/min</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
IMMUNE GLOBULIN

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION
Gamastan S/D
Administer only by the intramuscular route. Do not given subcutaneously or intravenously.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A (household and institutional contacts)</td>
<td>0.1 mL/kg</td>
</tr>
<tr>
<td>Measles</td>
<td>0.25 mL/kg to prevent in a susceptible person exposed fewer than 6 days previously</td>
</tr>
<tr>
<td></td>
<td>• 0.5 mL/kg should be given immediately to a susceptible child who is immunocompromised</td>
</tr>
<tr>
<td>Varicella</td>
<td>0.6-1.2 mL/kg</td>
</tr>
<tr>
<td>Rubella</td>
<td>0.55 mL/kg</td>
</tr>
</tbody>
</table>

Gammagard Liquid
Prior to switching from intravenous to subcutaneous treatment, obtain the patient's serum IgG trough level to guide subsequent dose adjustments. Start the initial subcutaneous dose approximately one week after the last intravenous infusion.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl</td>
<td>300-600 mg/kg given every 3 to 4 weeks</td>
<td>0.5 mL/kg/hr</td>
<td>Increase every 30 minutes (if tolerated) up to 5 mL/kg/hr</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>0.5-2.4 g/kg/month based on clinical response</td>
<td>0.5 mL/kg/hr</td>
<td>Infusion rate may be increased if tolerated up to 5.4 mL/kg/hr</td>
</tr>
</tbody>
</table>

| **Subcutaneous administration** |      |                       |                                          |
| Pl                              | Initial Dose is 1.37 × previous intravenous dose divided by # of weeks between intravenous doses. Maintenance dose is based on clinical response and target IgG trough level. | 40 kg BW and greater: 30 mL/site at 20 mL/hr/site. Under 40 kg BW: 20 mL/site at 15 mL/hr/site. | 40 kg BW and greater: 30 mL/site at 20 to 30 mL/hr/site. Under 40 kg BW: 20 mL/site at 15 to 20 mL/hr/site. |

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**IMMUNE GLOBULIN**

**FDA APPROVED INDICATIONS (CONTINUED)**

**DOSAGE AND ADMINISTRATION**

**Gammagard S/D**

Administer intravenously.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dosage</th>
<th>Duration</th>
<th>Administration (5% concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-600 mg/kg</td>
<td>Every 3-4 weeks</td>
<td>Recommended initial rate: 0.5 mL/kg/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum rate: 4 mL/kg/hr</td>
</tr>
<tr>
<td>CLL</td>
<td>400 mg/kg</td>
<td>Every 3-4 weeks</td>
<td></td>
</tr>
<tr>
<td>ITP</td>
<td>1 g/kg</td>
<td>Maximal 3 doses on alternate days</td>
<td></td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>Single 1 g/kg or 400 mg/kg for 4 consecutive days</td>
<td>Begin within 7 days of onset of fever</td>
<td></td>
</tr>
</tbody>
</table>

**Gammaked**

Administer intravenously for PI, ITP and CIDP. Gammaked may also be administered subcutaneously for the treatment of PI.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITP</td>
<td>2 g/kg</td>
<td>1 mg/kg/min</td>
<td>8 mg/kg/min</td>
</tr>
<tr>
<td>CIDP</td>
<td>Loading dose: 2 g/kg</td>
<td>2 mg/kg/min</td>
<td>8 mg/kg/min every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 1 g/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>300-600 mg/kg</td>
<td>1 mg/kg/min</td>
<td>8 mg/kg/min every 3 weeks</td>
</tr>
<tr>
<td><strong>Subcutaneous administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>1.37 x current IV dose in grams/IV dose interval in weeks</td>
<td>Adult: 20 mL/hr/site Pediatric: 10 mL/hr/site (&lt; 25 kg) 15 mL/hr/site (≥ 25 kg) Weekly</td>
<td>Adult: 20 mL/hr/site Pediatric: 10 mL/hr/site (&lt; 25 kg) 20 mL/hr/site (≥ 25 kg) Weekly</td>
</tr>
</tbody>
</table>

**CONTINUED ON NEXT PAGE**
IMMUNE GLOBULIN

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Gammaplex 5%
Administer intravenously.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-800 mg/kg given every 3 to 4 weeks</td>
<td>0.5 mg/kg/min for 15 minutes</td>
<td>Increase gradually every 15 minutes to 4 mg/kg/min</td>
</tr>
<tr>
<td>ITP</td>
<td>1 g/kg for 2 consecutive days</td>
<td>0.5 mg/kg/min for 15 minutes</td>
<td>Increase gradually every 15 minutes to 4 mg/kg/min</td>
</tr>
</tbody>
</table>

Gammaplex 10%
Administer intravenously.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-800 mg/kg given every 3 to 4 weeks</td>
<td>0.5 mg/kg/min for 15 minutes</td>
<td>Increase gradually every 15 minutes to 8 mg/kg/min</td>
</tr>
<tr>
<td>ITP</td>
<td>1 g/kg for 2 consecutive days</td>
<td>0.5 mg/kg/min for 15 minutes</td>
<td>Increase gradually every 15 minutes to 8 mg/kg/min</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Gamunex-C
Administer intravenously for PI, ITP and CIDP. Gamunex-C may also be administered subcutaneously for the treatment of PI.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITP</td>
<td>2 g/kg</td>
<td>1 mg/kg/min</td>
<td>8 mg/kg/min</td>
</tr>
<tr>
<td>CIDP</td>
<td>Loading dose: 2 g/kg</td>
<td>2 mg/kg/min</td>
<td>8 mg/kg/min every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 1 g/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>300-600 mg/kg</td>
<td>1 mg/kg/min</td>
<td>8 mg/kg/min every 3 weeks</td>
</tr>
<tr>
<td>Subcutaneous administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>1.37 x current IV dose in grams/IV dose interval in weeks</td>
<td>Adult: 20 mL/hr/site</td>
<td>Adult: 20 mL/hr/site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pediatric: 10 mL/hr/site (&lt; 25 kg)</td>
<td>Pediatric: 10 mL/hr/site (&lt; 25 kg) 20 mL/hr/site (≥ 25 kg) weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mL/hr/site (≥ 25 kg)</td>
<td></td>
</tr>
</tbody>
</table>

Hizentra
For subcutaneous infusion only. Do not inject into a blood vessel. Administer weekly or biweekly (every two weeks).

Primary immunodeficiency (PI):
- Before switching to Hizentra, obtain the patient's serum IgG trough level to guide subsequent dose adjustments.
- **Weekly**: Start Hizentra 1 week after last IGIV or IGSC infusion

\[
\text{Initial HIZENTRA dose} = \frac{\text{Previous IGIV dose (in grams)}}{\text{Number of weeks between IGIV doses}} \times 1.37
\]

- **Biweekly**: Start Hizentra 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly IGSC infusion. Administer twice the calculated weekly dose.
- **Frequent dosing (2 to 7 times per week)**: Start Hizentra 1 week after last IGIV/IGSC infusion. Divide the calculated weekly dose by the desired number of administrations per week.
- Adjust the dose based on clinical response and serum IgG trough levels.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):
- Initiate therapy with Hizentra 1 week after the last IGIV infusion.
- The recommended subcutaneous dose is 0.2 g/kg (1 mL/kg) body weight per week, administered in 1 or 2 sessions over 1 or 2 consecutive days.
- If symptoms worsen, consider re-initiating treatment with an IGIV approved for the treatment of CIDP, while discontinuing Hizentra.

Monitor the patient's clinical response and adjust the duration of therapy based on patient response.

Hyqvia
For subcutaneous use only.

- For patients previously on another IgG treatment, give the first dose approximately one week after the last infusion of their previous treatment.
- Increase the dose and frequency from a 1-week dose to a 3- or 4-week dose:

<table>
<thead>
<tr>
<th>Week</th>
<th>Infusion Number</th>
<th>Dose Interval</th>
<th>Example for 30 grams per 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1st infusion</td>
<td>1-week-dose</td>
<td>7.5 grams</td>
</tr>
<tr>
<td>2</td>
<td>2nd infusion</td>
<td>2-week-dose</td>
<td>15 grams</td>
</tr>
<tr>
<td>3</td>
<td>3rd infusion</td>
<td>3-week-dose</td>
<td>22.5 grams</td>
</tr>
<tr>
<td>4</td>
<td>4th infusion (if required)</td>
<td>4-week-dose</td>
<td>30 grams</td>
</tr>
<tr>
<td>5</td>
<td>No infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>No infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>No infusion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- For patients switching from IGIV, given Hyqvia at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up.
- For patients naïve to IGSC treatment or switching from IGSC, give Hyqvia at a dose of 300-600 mg/kg at 3- to 4-week intervals, after initial ramp-up.

Octagam 5%
For intravenous use only.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-600 mg/kg every 3-4 weeks</td>
<td>0.5 mg/kg/min</td>
<td>3.33 mg/kg/min</td>
</tr>
</tbody>
</table>

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IMMUNE GLOBULIN

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Octagam 10%
For intravenous use only.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic ITP</td>
<td>1 g/kg daily for 2 consecutive days</td>
<td>1 mg/kg/min</td>
<td>Up to 12 mg/kg/min</td>
</tr>
</tbody>
</table>

Panzyga
For intravenous use only.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-600 mg/kg every 3-4 weeks</td>
<td>1 mg/kg/min</td>
<td>Increase to 8 to 14 mg/kg/min</td>
</tr>
<tr>
<td>Chronic ITP</td>
<td>1 g/kg daily for 2 consecutive days</td>
<td>1 mg/kg/min</td>
<td>Increase to 8 mg/kg/min</td>
</tr>
</tbody>
</table>

Privigen
For intravenous use only.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>200-800 mg/kg every 3-4 weeks</td>
<td>0.5 mg/kg/min</td>
<td>Increase to 8 mg/kg/min</td>
</tr>
<tr>
<td>Chronic ITP</td>
<td>1 g/kg daily for 2 consecutive days</td>
<td>0.5 mg/kg/min</td>
<td>Increase to 4 mg/kg/min</td>
</tr>
<tr>
<td>CIDP</td>
<td>Loading dose: 2 g/kg in divided doses over 2 to 5 consecutive days</td>
<td>0.5 mg/kg/min</td>
<td>Increase to 4 mg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 1 g/kg administered in 1 to 2 infusions on consecutive days, every 3 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
IMMUNE GLOBULIN

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Xembify

For subcutaneous infusion only.

Before switching to Xembify, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments.

- Switching from immune globulin intravenous (human), 10% (IVIG) to XEMBIFY:
  - calculate the dose by using a dose adjustment factor (1.37)
    - Weekly: Begin XEMBIFY one week after last IVIG infusion. Establish initial weekly dose by converting the monthly (or every 3 weeks) IVIG dose into an equivalent weekly dose and increasing it using a dose adjustment factor (1.37)
    - Frequent dosing (2-7 times per week): Divide the calculated weekly dose by the desired number of times per week.

- Switching from immune globulin subcutaneous (human) treatment (IGSC):
  - Weekly dose (grams) should be the same as the weekly dose of prior IGSC treatment (grams).

REFERENCES

- Octagam 5% [Prescribing Information]. Octapharma USA Inc.: Hoboken, NJ. April 2015.
- Octagam 10% [Prescribing Information]. Octapharma USA Inc.: Hoboken, NJ. August 2015.
- Panzyga [Prescribing Information]. Octapharma USA Inc.: Hoboken, NJ. August 2018.

CONTINUED ON NEXT PAGE
REFERENCES (CONTINUED)

- Micromedx. Drugdex. [Online] [Cited: July 18, 2012.]

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Client Approval: 11/06/19
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named CUTAQUIG requires a diagnosis of primary humoral immunodeficiency (i.e., primary immunodeficiency disease [PID]). In addition, the following criterion must be met:

- The patient is 18 years of age or older

RATIONALE
To ensure the appropriate usage of Cutaquig according to diagnosis.

INDICATION
Cutaquig is a 16.5% immune globulin solution for subcutaneous infusion (IGSC) indicated for replacement therapy for primary humoral immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

REFERENCES
The guideline named INFLIXIMAB (Remicade, Renflexis or Inflectra) requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, severe plaque psoriasis, moderate to severe Crohn's disease, or moderate to severe ulcerative colitis. In addition, the following criteria must also be met:

For patients with moderate to severe rheumatoid arthritis (RA), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial of or has a contraindication to at least ONE of the following DMARDs (disease-modifying antirheumatic drugs) such as: methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- Patient is currently using or has a contraindication to methotrexate
- Previous trial of TWO of the following preferred self-administered immunomodulators: Actemra SQ, Cimzia, Enbrel, Orencia SQ, Simponi, or Xeljanz
- For Remicade or Inflectra, patient had a previous trial of Renflexis

For patients with psoriatic arthritis (PsA), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist or dermatologist
- Patient had a previous trial of or has a contraindication to at least one of the following DMARDs (disease-modifying antirheumatic drugs) such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older
- Previous trial of at least TWO of the following preferred self-administered immunomodulators: Cimzia, Cosentyx, Enbrel, Orencia, Otezla, or Simponi
- For Remicade or Inflectra, patient had a previous trial of Renflexis

For patients with ankylosing spondylitis (AS), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist
- The patient is 18 years of age or older
- Previous trial of at least TWO of the following preferred self-administered immunomodulators: Cimzia, Cosentyx, Enbrel, or Simponi
- For Remicade or Inflectra, patient had a previous trial of Renflexis.

(Initial denial text continued on next page)
MDwise MANAGED MEDICAID
PRIOR AUTHORIZATION GUIDELINES

INFLIXIMAB

INITIAL CRITERIA (CONTINUED)

For patients with severe plaque psoriasis (PsO), approval requires:
• Therapy is prescribed by or given in consultation with a dermatologist
• Presence of plaque psoriasis involving at least 10% body surface area (BSA) or psoriatic lesions affecting the hands, feet, or genital area
• Patient had a previous trial of or has a contraindication to at least one or more forms of systemic therapies, such as PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
  • Previous trial of at least TWO of the following preferred self-administered immunomodulators: Cosentyx, Enbrel, or Otezla
  • For Remicade or Inflectra, patient had a previous trial of Renflexis

For patients with moderate to severe Crohn’s disease (CD), approval requires:
• Therapy is prescribed by or given in consultation with a gastroenterologist
• Patient had a previous trial of or has a contraindication to one or more of the following conventional therapies, such as corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
• The patient is 6 years of age or older
• If age greater than or equal to 18 years, patient had a previous trial of the preferred TNF (tumor necrosis factor) inhibitor: Cimzia
• For Remicade or Inflectra, patient had a previous trial of Renflexis

For patients with moderate to severe ulcerative colitis (UC), approval requires:
• Therapy is prescribed by or given in consultation with a gastroenterologist
• Patient had a previous trial of or has a contraindication to one or more of the following conventional therapies, such as corticosteroids (i.e., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
• The patient is 6 years of age or older
• If age greater than or equal to 18 years:
  o Patient had a previous trial of the preferred self-administered TNF (tumor necrosis factor) inhibitor: Simponi SC
  o For Remicade or Inflectra, patient had a previous trial of Renflexis

RENEWAL CRITERIA

The guideline for renewal of INFLIXIMAB (Remicade, Renflexis or Inflectra) requires a diagnosis of moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, severe plaque psoriasis, moderate to severe Crohn’s disease, or moderate to severe ulcerative colitis. In addition, the following criteria must also be met:

Renewal for the diagnosis of moderate to severe rheumatoid arthritis, approval requires:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy
• Patient is currently using or has a contraindication to methotrexate

(Renewal denial text continued on next page)
RENEWAL CRITERIA (CONTINUED)

Renewal for the diagnosis of psoriatic arthritis, approval requires:
• Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy

Renewal for the diagnosis of ankylosing spondylitis, approval requires:
• Documentation that the patient has experienced or maintained an improvement of at least 50% or 2 units (scale of 1-10) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score while on therapy

Renewal for the diagnosis of severe plaque psoriasis, approval requires:
• Documentation that the patient has achieved or maintained clear or minimal disease or that the patient has experienced a PASI-50 (Psoriasis Area and Severity Index) score while on therapy

Renewal for patients with moderate to severe Crohn’s disease requires:
• Documentation that the patient has experienced or maintained symptomatic improvement while on therapy

Renewal for patients with moderately to severely active ulcerative colitis requires:
• Documentation that the patient has experienced or maintained symptomatic improvement while on therapy

RATIONALE
To ensure the appropriate usage of infliximab according to diagnosis.

DOSING
Crohn’s Disease: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.

Ulcerative Colitis: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks.

Rheumatoid Arthritis: In conjunction with methotrexate, 3 mg/kg at 0, 2, and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.

DOSING
Ankylosing Spondylitis: 5 mg/kg at 0, 2, and 6 weeks, then every 6 weeks.

Psoriatic Arthritis: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks.

Plaque Psoriasis: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks.

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INFLIXIMAB

FDA APPROVED INDICATIONS

Infliximab (Remicade, Renflexis or Inflectra) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. It is also indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

Infliximab (Remicade, Renflexis or Inflectra) is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Remicade is indicated for this use in both adults and children, while Inflectra and Renflexis are only indicated for this use in adults.

Infliximab (Remicade, Renflexis or Inflectra), in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

Infliximab (Remicade, Renflexis or Inflectra) is indicated for reducing signs and symptoms and inhibiting the progression of structural damage, and improving physical function in patients with active ankylosing spondylitis.

Infliximab (Remicade, Renflexis or Inflectra) is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

Infliximab (Remicade, Renflexis or Inflectra) is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. It should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

BLACK BOX WARNING FOR INFLIXIMAB

Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens. Infliximab should be discontinued if a patient develops a serious infection or sepsis during treatment. Perform test for latent TB; if positive, start treatment for TB prior to starting infliximab. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers. Post marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers. All cases reported in patients with Crohn's disease and ulcerative colitis, the majority of whom were adolescent or young adult males. This rare, aggressive T-cell lymphoma is fatal. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with infliximab at or prior to diagnosis.

CONTINUED ON NEXT PAGE
REFERENCES


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Effective: 06/01/18
Client Approval: 04/10/18
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guidelines for **INHALED INSULIN (Afrezza)** requires a diagnosis of type 1 or type 2 diabetes, a patient age of at least 18, and a baseline spirometry to measure FEV1. Afrezza will not be approved for patients with one of the following conditions: chronic lung disease, active lung cancer, currently in diabetic ketoacidosis, or for patients currently smoking or who have quit smoking within the past 6 months. Additional guideline requirements apply.

**For Type 1 diabetes**, approval requires **ALL** of the following:
- Concurrent use of long-acting insulin
- Trial of the preferred rapid acting insulin (e.g., Ademlog)

**For Type 2 diabetes**, approval requires **ALL** of the following:
- Concurrent use of a formulary non-insulin diabetic medication (e.g., metformin, Tanzeum, Trulicity, Tradjenta, Januvia, Actos, Invokana, or a sulfonylurea)
- Trial of preferred rapid acting insulin (e.g., Ademlog)
- Prescriber has documentation that the patient is physically unable to or unwilling to administer insulin.

RENEWAL CRITERIA

Renewal requires documentation of follow-up spirometry after 6 months of treatment and annually thereafter. The patient has not had a follow-up spirometry. Renewal will not be provided for patients with a FEV1 that has declined 20% or more from baseline.

Our guidelines for **INHALED INSULIN (Afrezza)** renewal requires a diagnosis of type 1 or type 2 diabetes, and documentation of follow up spirometry to measure FEV1 after 6 months of treatment and annually thereafter. Approval will not be granted for patients with a FEV1 that has declined 20% or more from baseline. Additional guideline requirements apply.

- **For Type 1 diabetes**, approval requires concurrent use of a long acting insulin.
- **For Type 2 diabetes**, approval requires concurrent use of a non-insulin diabetic medication.

RATIONALE

To ensure appropriate use of Afrezza according to FDA approved indication. Afrezza should not be used as first line therapy. Apply quantity limits for maximum daily insulin requirements (total daily insulin requirements 1.5 units/per kg with rapid insulin requirements of 70% of total daily insulin requirements in a 100 kg patient).

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS
Afrezza is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Patients with type 1 diabetes, must use Afrezza with a long-acting insulin. Afrezza is not recommended for the treatment of diabetic ketoacidosis or in patients who smoke.

DOSAGE AND ADMINISTRATION
Afrezza should be administered at the beginning of the meal and is administered using a single inhalation per cartridge. Dosing should be individualized. Dose adjustments may be needed when switching from another insulin to Afrezza.

Afrezza is available in 3 strengths (4 units of insulin in the blue cartridge, 8 units of insulin in the green cartridge, and 12 units of insulin in the yellow cartridge). Three cartridges are contained in a single cavity of a blister strip. Each card contains 5 blister strips separated by perforations for a total of 15 cartridges. Two inhalers are included in each unit. Each inhaler may be used up to 15 days from the date of the first use.

Starting Mealtime Dose:
- **Insulin Naïve Individuals**: Start on 4 units of Afrezza at each meal.
- **Individuals Using Subcutaneous Mealtime (Prandial) Insulin**: Determine the appropriate Afrezza dose for each meal by converting from the injected dose using Table 4.
- **Individuals Using Subcutaneous Pre-mixed Insulin**: Estimate the mealtime injected dose by dividing half of the total daily injected pre-mixed insulin dose equally among the three meals of the day. Convert each estimated injected mealtime dose to an appropriate Afrezza dose using Table 4. Administer half of the total daily injected pre-mixed dose as an injected basal insulin dose.

### Table 1. Mealtime Afrezza Dose Conversion

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>Afrezza Dose</th>
<th>Number of cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 unit (blue cartridge)</td>
</tr>
<tr>
<td>Up to 4 units</td>
<td>4 units</td>
<td>1</td>
</tr>
<tr>
<td>5 - 8 units</td>
<td>8 units</td>
<td>0</td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>1</td>
</tr>
<tr>
<td>(if not using 4 and 8 unit cartridge)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td>0</td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td>0</td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td>0</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
INHALED INSULIN

DOSAGE AND ADMINISTRATION (CONTINUED)

Mealtime Dose Adjustment
Similar to other mealtime insulin products, doses of Afrezza should be adjusted based on the individual’s metabolic needs, blood glucose monitoring results and glycemic control goal. In addition, dosages may need to be adjusted, changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness.

In patients on high doses of Afrezza, the use of subcutaneous mealtime insulin should be considered if blood glucose control is not achieved.

REFERENCES

Created: 10/15
Effective: 11/01/18
Client Approval: 09/24/18
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for **INOSITOL** requires that both the patient and the prescriber are participating in the Genomind genetic testing pilot study and that the prescriber has stated that genetic testing results demonstrate the need for Inositol therapy.

RATIONALE

The intent of this prior authorization is to allow members participating in the Genomind genetic testing pilot study to receive Inositol based upon genetic test results.

Created: 05/16
Effective: 06/01/16
Client Approval: 05/18/16
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named INOTERSEN (Tegsedi) requires a diagnosis of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR). In addition, the following criteria must be met:

- The patient is 18 years of age or older
- The requested medication is prescribed by or given in consultation with a neurologist, cardiologist, hATTR specialist, or medical geneticist
- The patient has Stage 1 or 2 polyneuropathy
- The patient has documented diagnosis of hereditary TTR amyloidosis (hATTR) as confirmed by ONE of the following:
  - Biopsy of tissue/organ to confirm amyloid presence AND chemical typing to confirm presence of TTR protein
  - DNA genetic sequencing to confirm hATTR mutation

RENEWAL CRITERIA

The guideline named INOTERSEN (Tegsedi) requires a diagnosis of hereditary TTR amyloidosis (hATTR) and physician attestation that the patient has not progressed to stage 3 polyneuropathy as evidenced by functional decline (e.g., wheelchair-bound, bedridden).

RATIONALE

Promote appropriate utilization of INOTERSEN based on clinical trial patient inclusion and FDA approved indication and dosing.

FDA APPROVED INDICATIONS

TEGSEDI is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

NOTE: Tegsedi is available only through a restricted distribution program called the TEGSEDI REMS Program. Prescribers must be certified within the program by enrolling and completing training. Patients must enroll in the program and comply with ongoing monitoring requirements (platelet count and kidney function every 1 to 2 weeks or more frequently). Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Tegsedi.

DOSING AND ADMINISTRATION

The recommended dosage is 284 mg administered by subcutaneous injection once weekly. Laboratory tests must be measured prior to treatment, continue to be monitored after treatment initiation, and for 8 weeks following discontinuation of treatment, as directed.

CONTINUED ON NEXT PAGE
INOTERSEN

REFERENCES


Created: 12/18
Effective: 01/21/19
Client Approval: 12/20/18
P&T Approval: N/A
INTERFERON AGENTS

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEGINTERFERON ALFA-2A</td>
<td>PEGASYS</td>
<td></td>
<td>24035</td>
<td></td>
</tr>
<tr>
<td>PEGASYS PROCLICK</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>INTERFERON ALFA-2B,RECOMB</td>
<td>INTRON A</td>
<td>04528</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These requests require These requests will be reviewed by a pharmacist.

GUIDELINES FOR USE

The guideline for INTERFERON AGENTS excludes treatment for hepatitis C. Coverage will be provided for INTRON A for the following diagnoses: hairy cell leukemia; condylomata acuminata; AIDS-related Kaposi’s sarcoma; chronic hepatitis B; malignant melanoma; and follicular lymphoma. Coverage will be provided for Pegasys for patients aged 18 years and older with chronic hepatitis B infection currently supervised by a gastroenterologist, infectious disease specialist or a physician specializing in the treatment of hepatitis (e.g. hepatologist).

FDA APPROVED INDICATIONS

INTRON A (Interferon alfa-2b) is indicated for treatment of hairy cell leukemia, condylomata acuminata, AIDS-related Kaposi’s sarcoma, hepatitis C (in combination), malignant melanoma, follicular lymphoma and chronic hepatitis B.

PEGASYS (peg-interferon alfa-2a) alone or in combination with COPEGUS (ribavirin) is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon or peginterferon alfa.

PEGASYS is also indicated for treatment of adults with chronic hepatitis C virus infection in patients with HIV/HCV co-infection.

PEGASYS is also indicated for treatment of adults with HBeAg positive and negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and inflammation.

REFERENCES


Created: 06/15
Effective: 06/17/17
Client Approval: 05/16/17
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for INTERFERON GAMMA-1B requires a diagnosis of chronic granulomatous disease (CGD), severe, malignant osteopetrosis (SMO), or mycosis fungoides/Sezary Syndrome (MF/SS). Additional guideline requirements apply.

For patients with chronic granulomatous disease (CGD), our guideline requires that the patient is:
- Receiving concurrent therapy with a prophylactic antibacterial agent (e.g. TMP/SMX)
- Receiving concurrent therapy with a prophylactic antifungal agent (e.g. itraconazole)

For patients with severe, malignant osteopetrosis (SMO), our guideline requires that the patient is:
- Receiving concurrent therapy with calcitriol

For patients with mycosis fungoides/Sezary syndrome (MF/SS), our guideline requires:
- Patient has been non-responsive to skin-directed therapy (e.g. ultraviolet therapy, topical corticosteroids, topical retinoids, topical imiquimod)
- The requested medication is prescribed by or in consultation with an oncologist or immunologist

RATIONALE
To ensure appropriate use of Actimmune based on FDA approved indications as well as clinical guidelines.

The National Comprehensive Cancer Network Practice Guidelines in Oncology recommend IFN-gamma as a Category A systemic treatment for mycosis fungoides/Sezary syndrome.

FDA APPROVED INDICATIONS
Actimmune is a recombinant form of interferon gamma indicated for:
- Reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease (CGD)
- Delaying time to disease progression in patients with severe, malignant osteopetrosis (SMO)

DOSAGE AND ADMINISTRATION
The recommended dose of Actimmune is 50 mcg/m² for patients whose body surface area is greater than 0.5 m² and 1.5 mcg/kg/dose for patients whose body surface area is equal to or less than 0.5 m² three times weekly. Higher doses (i.e., greater than 50 mcg/m²) are not recommended.

REFERENCES
INTERFERONS FOR MULTIPLE SCLEROSIS

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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</thead>
<tbody>
<tr>
<td>INTERFERON BETA-1A</td>
<td>AVONEX</td>
<td>11253</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>AVONEX PEN</td>
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<td></td>
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</tr>
<tr>
<td>INTERFERON BETA-1A/ALBUMIN</td>
<td>AVONEX ADMINISTRATION PACK,</td>
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<td>23230, 15914,</td>
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<td>REBIF,</td>
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<td>15918, 24286,</td>
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<td></td>
<td>REBIF REBIDOSE</td>
<td></td>
<td>34166, 34167,</td>
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<td></td>
<td>34168</td>
<td></td>
</tr>
<tr>
<td>INTERFERON BETA-1B</td>
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<td>08537</td>
<td></td>
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<tr>
<td></td>
<td>EXTAVIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEGINTERFERON BETA-1A</td>
<td>PLEGRIDY</td>
<td>41331</td>
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</tr>
</tbody>
</table>

GUIDELINES FOR USE

Our guideline for INTERFERONS FOR MULTIPLE SCLEROSIS requires a diagnosis of relapsing-remitting multiple sclerosis (RRMS). Additional guideline requirements apply. For Betaseron, Extavia, and Plegridy, our guideline requires: a trial of two of the following: Avonex, Rebif, Copaxone, Tecfidera, Gilenya, or Aubagio.

RATIONALE

Ensure appropriate utilization criteria are met for the management of requests for interferons used in the treatment of multiple sclerosis.

FDA APPROVED INDICATIONS

For the treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations.

REFERENCES

- Extavia [Prescribing Information]. East Hanover, NJ: EMD Novartis; March 2012.

Created: 03/15
Effective: 11/01/15 Client Approval: 11/11/15 P&T Approval: 06/15
GUIDELINES FOR USE

The guideline named ISTRADEFYLLINE (Nourianz) requires a diagnosis of Parkinson's disease (PD). In addition, the following criteria must be met:

- The patient is 18 years of age or older
- The patient is experiencing "off" episodes
- Nourianz will be used as adjunctive treatment to levodopa/carbidopa in patients experiencing "off" episodes

RATIONALE

To ensure safe and appropriate use of istradefylline per approved indication and dosing.

FDA APPROVED INDICATIONS

Istradefylline is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes.

DOSAGE AND ADMINISTRATION

The recommended dosage of istradefylline is 20 mg orally once daily. The dosage may be increased to a maximum of 40 mg once daily if needed.

REFERENCES

ITRACONAZOLE - TOLSURA

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITRACONAZOLE</td>
<td>TOLSURA</td>
<td></td>
<td>45848</td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

Our guideline for ITRACONAZOLE (Tolsura) requires that the patient is 18 years of age or older. In addition, the patient must have ONE of the following diagnoses:

- Blastomycosis, pulmonary and extrapulmonary
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis
- Aspergillosis, pulmonary and extrapulmonary, AND the patient is intolerant or refractory to amphotericin B therapy

RATIONALE

For further information, please refer to the Prescribing Information and/or Drug Monograph for Tolsura.

REFERENCES

Tolsura [Prescribing Information]. Greenville, NC: Mayne Pharma; December 2018.

Created: 01/19
Effective: 03/18/19
Client Approval: 02/15/19
P&T Approval: N/A
IVABRADINE

<table>
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<tr>
<th>Generic</th>
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<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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</thead>
<tbody>
<tr>
<td>IVABRADINE</td>
<td>CORLANOR</td>
<td>33396</td>
<td>26238, 26239, 46204</td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for IVABRADINE requires a diagnosis of heart failure. In addition, the following criteria must also be met.

**For adult patients with heart failure:**
- Prescribed by or in consultation with a cardiologist
- Patient is 18 years of age or older
- NYHA Class II - IV Heart failure
- Left ventricular ejection fraction of 35% or less
- Patient is in sinus rhythm (e.g., patient does not have atrial fibrillation, sick sinus syndrome, sinoatrial block, or 2nd or 3rd degree AV block unless a functioning demand pacemaker is present)
- Resting heart rate $\geq 70$ beats per minute
- Patient does not have a demand pacemaker that is set to a rate of 60 beats per minute or greater
- Patient is currently being treated with or has an intolerance to one of the following beta-blockers: metoprolol succinate, bisoprolol, or carvedilol

**For pediatric patients with heart failure due to dilated cardiomyopathy:**
- Prescribed by or in consultation with a cardiologist
- Patient is 6 months to 18 years of age
- Patient is in sinus rhythm (e.g., patient does not have atrial fibrillation, sick sinus syndrome, sinoatrial block)
- Patient has an elevated resting heart rate

In addition, requests for Corlanor solution in patients greater than 12 years of age require BOTH of the following:
- The patient has had a trial of Corlanor tablets
- Physician attestation of medical need for Corlanor solution

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE (CONTINUED)
RENEWAL CRITERIA

Our guideline for **IVABRADINE** renewal requires a diagnosis of heart failure. In addition, the following criteria must also be met:

- Patient is in sinus rhythm (for example, patient does not have atrial fibrillation, sick sinus syndrome, sinoatrial block, or 2nd or 3rd degree AV block unless a functioning demand pacemaker is present)

  In addition, requests for Corlanor solution in patients greater than 12 years of age require **BOTH** of the following:

- The patient has had a trial of Corlanor tablets
- Physician attestation of medical need for Corlanor solution

RATIONALE

Promote appropriate utilization of **IVABRADINE** based on FDA approved indication.

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated:

- To reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
- For the treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients ages 6 months and older, who are in sinus rhythm with an elevated heart rate.

DOISING

Adults

The recommended starting dose of Corlanor is 5 mg twice daily with meals. Assess patient after two weeks and adjust dose to achieve a resting heart rate between 50 and 60 beats per minute (bpm). Thereafter, adjust dose as needed based on resting heart rate and tolerability. The maximum dose is 7.5 mg twice daily. In adult patients unable to swallow tablets, Corlanor oral solution can be used

<table>
<thead>
<tr>
<th>Heart Rate in beats per minute (bpm)</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 bpm</td>
<td>Increase dose by 2.5 mg (given twice daily), up to a maximum dose of 7.5 mg twice daily</td>
</tr>
<tr>
<td>50 – 60 bpm</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>&lt; 50 bpm or signs and symptoms of bradycardia</td>
<td>Decrease dose by 2.5 mg (given twice daily) If current dose is 2.5 mg twice daily, discontinue therapy</td>
</tr>
</tbody>
</table>

In patients with a history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, initiate therapy at 2.5 mg twice daily before increasing the dose based on heart rate.

CONTINUED ON NEXT PAGE
IVABRADINE

Pediatric Patients:
The recommended starting dose of Corlanor oral solution in pediatric patients 6 months of age and older and weighing less than 40 kg is 0.05 mg/kg twice daily with food. Assess patient at two-week intervals and adjust dose by 0.05 mg/kg to target a heart rate (HR) reduction of at least 20%, based on tolerability.

The maximum dose is 0.2 mg/kg twice daily for patients 6 months to less than 1 year old, and 0.3 mg/kg twice daily for patients 1 years old and older, up to a total of 7.5 mg twice daily.

The recommended starting dose of Corlanor tablets in pediatric patients weighing more than 40 kg is 2.5 mg twice daily with food. Assess patient at two-week intervals and adjust dose by 2.5 mg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 7.5 mg twice daily.

If bradycardia develops, reduce the dose to the previous titration step. In patients who develop bradycardia at the recommended initial dosage, consider reducing the dosage to 0.02 mg/kg twice daily.

REFERENCES
GUIDELINES FOR USE

The guideline named **IVOSIDENIB (Tibsovo)** requires a diagnosis of relapsed or refractory acute myeloid leukemia (AML). In addition, the following criteria must be met:

- The patient has a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved diagnostic test
- The patient is 18 years of age or older

RATIONALE

Promote appropriate utilization of **IVOSIDENIB** based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS

Tibsovo is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

The recommended dose of Tibsovo is 500 mg orally once daily with or without food until disease progression or unacceptable toxicity. Patients taking Tibsovo should avoid a high-fat meal with dose.

REFERENCES


Created: 08/18
Effective: 10/22/18
Client Approval: 09/11/18
P&T Approval: N/A
**GUIDELINES FOR USE**

Our guideline for **IXAZOMIB** (Ninlaro) requires a diagnosis of multiple myeloma and that it be used in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy such as bortezomib, carfilzomib, thalidomide, lenalidomide, melphalan or stem cell transplantation.

**RATIONALE**

Promote appropriate utilization of ixazomib (Ninlaro) based on FDA approved indication.

Ninlaro, in combination with lenalidomide and dexamethasone offers the first all-oral treatment option for patients with relapsed and/or refractory multiple myeloma (RRMM). According to the National Cancer Institute (NCI), MM is the third most common blood cancer (after lymphoma and leukemia) in the United States. NCI estimates there will be 26,850 new cases of multiple myeloma and 11,240 related deaths in the US this year.

Standard treatment options for MM include proteasome inhibitors (Velcade [bortezomib], Kyprolis [carfilzomib]), immunomodulators (IMiDs) (Revlimid [lenalidomide], Thalomid [thalidomide], Pomalyst [pomalidomide]), alkylating agents (Alkeran [melphalan], Cytoxan [cyclophosphamide]), anthracyclines (Doxil [liposomal doxorubicin]), and corticosteroids (dexamethasone). Regimens may contain two or three drug combinations, with selected patients undergoing hematopoietic cell transplantation (HCT).

The most recent NCCN guidelines do not yet address the use of Ninlaro for the treatment of RRMM. While ongoing studies are evaluating Ninlaro for newly diagnosed MM, current labeling for Ninlaro requires at least one prior line of therapy, as the FDA approval was based only on patients with RRMM. Although Ninlaro has the convenience of an all-oral regimen, it should be reserved for patients who have progressed on currently recommended regimens.

The efficacy of Ninlaro was evaluated in a phase 3, randomized, double-blind, placebo-controlled, multicenter trial (Tourmaline-MM1) in 722 patients with RRMM. Patients had to receive at least one prior line of therapy (60-62% received one, 38-40% received two or three), but patients who were refractory to lenalidomide or PIs (e.g., Velcade) were excluded from the study. The most common types of prior therapy included melphalan-containing (80-81%), bortezomib-containing (69%), thalidomide-containing (44-47%), and stem cell transplantation (55-59%). Other prior therapies included lenalidomide-containing and carfilzomib containing regimens.

**FDA APPROVED INDICATION**

Indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

CONTINUED ON NEXT PAGE
IXAZOMIB

DOSAGE

The recommended starting dose of Ninlaro (ixazomib) is 4mg taken orally on Days 1, 8, and 15 of a 28-day cycle. Treatment should be continued until disease progression or unacceptable toxicity.

The dose may be reduced due to adverse reactions as shown in the table below.

<table>
<thead>
<tr>
<th>Recommended starting dose</th>
<th>First reduction to</th>
<th>Second reduction to</th>
<th>Discontinue</th>
</tr>
</thead>
<tbody>
<tr>
<td>4mg</td>
<td>3mg</td>
<td>2.3mg</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

REFERENCES

Ninlaro [Prescribing Information]. Takeda Pharmaceutical Company Limited. Cambridge, MA 02139

Created: 01/16
Effective: 02/04/16
Client Approval: 01/15/16
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for IXEKIZUMAB (Taltz) requires a diagnosis of moderate to severe plaque psoriasis (PsO), active psoriatic arthritis (PsA), or ankylosing spondylitis (AS). In addition, the following criteria must be met:

For the diagnosis of moderate to severe plaque psoriasis (PsO), approval requires that:

- The patient is 18 years of age or older
- Therapy is prescribed by or in consultation with a dermatologist
- The patient has psoriatic lesions involving greater than or equal to 10% of body surface area (BSA) OR psoriatic lesions affecting the hands, feet, face, or genital area
- The patient has had a previous trial of at least one preferred therapy such as PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- The patient has had a previous trial of or has a contraindication to TWO of the following preferred immunomodulators: Cimzia, Cosentyx, Enbrel, or Otezla

For the diagnosis of active psoriatic arthritis (PsA), approval requires that:

- The patient is 18 years of age or older
- Therapy is prescribed by or given in consultation with a rheumatologist or dermatologist
- The patient has had a previous trial of or has a contraindication to at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient has had a previous trial of or has a contraindication to TWO of the preferred formulary immunomodulators: Cimzia, Cosentyx, Enbrel, Otezla, Simponi, Xeljanz, Xeljanz XR, OR Orencia SC

For patients with ankylosing spondylitis, our guideline requires all of the following:

- Therapy initiated by or in consultation with a rheumatologist
- The patient is 18 years of age or older
- Previous trial with TWO of the following preferred agents: Cimzia, Cosentyx, Enbrel, or Simponi

CONTINUED ON NEXT PAGE
IXEKIZUMAB

GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

Our guideline for IXEKIZUMAB (Taltz) renewal requires a diagnosis of moderate to severe plaque psoriasis, active psoriatic arthritis, or ankylosing spondylitis. In addition, the following criteria must be met:

Renewal for the diagnosis of moderate to severe plaque psoriasis requires:

- Documentation that the patient has achieved clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50% or more

Renewal for the diagnosis of active psoriatic arthritis requires:

- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy

Renewal for the diagnosis of ankylosing spondylitis requires:

- Documentation that the patient has experienced or maintained an improvement of at least 50% or 2 units (scale of 1-10) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) while on therapy

CONTINUED ON NEXT PAGE
RATIONAL
Ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for ixekizumab.

FDA APPROVED INDICATIONS
Taltz is indicated for the treatment of adults with:
• moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
• active psoriatic arthritis.
• active ankylosing spondylitis.

DOSSING
Plaque Psoriasis
• Administer by subcutaneous injection.
• Recommended dose is 160 mg (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.

Psoriatic Arthritis
• Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks.
• For psoriatic arthritis patients with coexistent moderate-to-severe plaque psoriasis, use the dosing regimen for plaque psoriasis.
• TALTZ may be administered alone or in combination with a conventional DMARD (e.g., methotrexate).

Ankylosing Spondylitis
• Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks.

DOSSAGE FORMS AND STRENGTHS
Taltz prefilled autoinjector:
• NDC 00002-1445-11: Carton of one 80 mg/mL single-dose prefilled autoinjector
• NDC 00002-1445-27: Carton of two 80 mg/mL single-dose prefilled autoinjector
• NDC 00002-1445-09: Carton of three 80 mg/mL single-dose prefilled autoinjector

Taltz prefilled syringe:
• NDC 00002-7724-11: Carton of one 80 mg/mL single-dose prefilled syringe

REFERENCES
• Taltz [Prescribing Information]. Eli Lilly and Company: Indianapolis, IN: August 2019.

Created: 05/16
Effective: 11/01/19
Client Approval: 10/17/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named LANADELUMAB (Takhzyro) requires a diagnosis of hereditary angioedema (HAE). Additionally, the following criteria must be met:

- Diagnosis of HAE is confirmed via complement testing
- The medication is being used for prophylaxis to prevent HAE attacks
- The patient is 12 years of age or older
- The medication is prescribed by or in consultation with an allergist/immunologist or hematologist

RENEWAL CRITERIA

The guideline named LANADELUMAB (Takhzyro) requires a diagnosis of hereditary angioedema (HAE) for renewal. The following criteria must also be met.

- Physician attestation of improvement (i.e., reductions in attack frequency or attack severity) compared to baseline in HAE attacks with routine prophylaxis

RATIONALE

Ensure appropriate utilization of LANADELUMAB (Takhzyro) based on FDA-approved indication and clinical trial design.

FDA APPROVED INDICATION

Takhzyro is a plasma kallikrein inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.

DOISING & ADMINISTRATION

The recommended starting dosage of Takhzyro is 300 mg given subcutaneously every 2 weeks. A dosing interval of 300 mg every 4 weeks is also effective and may be considered if the patient is well-controlled (e.g., attack-free) for more than 6 months.

Takhzyro should be administered subcutaneously into the abdomen, thigh, or upper arm and is provided as a ready-to-use solution in a single-dose vial that does not require additional reconstitution or dilution for administration. Takhzyro is intended for self-administration or administration by a caregiver, following training by a healthcare professional. In clinical studies, the majority of patients self-administered Takhzyro over 10 to 60 seconds.

REFERENCES


Created: 11/18
Effective: 11/23/18
Client Approval: 11/06/18
P&T Approval: N/A
LANREOTIDE ACETATE

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<td>SOMATULINE DEPOT</td>
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This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Approval for Somatuline Depot requires a diagnosis of acromegaly with the failure to be treated with one of the following or the inability to be treated with any of the following: surgical resection, pituitary irradiation, or bromocriptine mesylate at maximally tolerated doses; a diagnosis of unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs); or a diagnosis of carcinoid syndrome.

LANREOTIDE ACETATE

RATIONALE

To ensure appropriate use of Somatuline Depot based on FDA approved indications and dosing.

FDA APPROVED INDICATIONS

SOMATULINE DEPOT mimics natural somatostatin and is indicated for:

- The long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- The treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
- The treatment of adults with carcinoid syndrome: when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

DOSING

Acromegaly: 90 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels. After 3 months, the dosage may be adjusted as follows:

- GH greater than 1 ng/mL to less than or equal to 2.5 ng/mL, IGF-1 normal, and clinical symptoms controlled: maintain SOMATULINE DEPOT dosage at 90 mg every 4 weeks.
- GH greater than 2.5 ng/mL, IGF-1 elevated, and/or clinical symptoms uncontrolled: increase SOMATULINE DEPOT dosage to 120 mg every 4 weeks.
- GH less than or equal to 1 ng/mL, IGF-1 normal, and clinical symptoms controlled: reduce SOMATULINE DEPOT dosage to 60 mg every 4 weeks.
- Thereafter, the dosage should be adjusted according to the response

GEP-NETs: 120 mg every 4 weeks.

Carcinoid Syndrome: 120 mg every 4 weeks. If patients are already being treated with SOMATULINE DEPOT for GEP-NET, do not administer an additional dose for carcinoid syndrome.

CONTINUED ON NEXT PAGE
LANREOTIDE

DOSAGE FORMS AND STRENGTHS
Somatuline Depot is supplied as 60mg/0.2mL, 90mg/0.3mL, and 120mg/0.5mL single dose prefilled syringes.

REFERENCES

Created: 02/18
Effective: 06/01/18
Client Approval: 04/10/18
P&T Approval: N/A
LAPATINIB

<table>
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<td>TYKERB</td>
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</table>

GUIDELINES FOR USE

Approval criteria require concurrent treatment with Xeloda (capecitabine), Herceptin (trastuzumab), or Femara (letrozole) for patients with a diagnosis of HER2-positive breast cancer with estrogen/progesterone receptor-positive breast cancer; or a diagnosis of HER2-positive breast cancer in a patient with a previous trial of Herceptin (trastuzumab).

RATIONALE

To ensure that lapatinib is used in the appropriate patient population with HER2 positive breast cancer. Lapatinib in combination with capecitabine or trastuzumab is recommended for trastuzumab-exposed HER2 positive breast cancer. Lapatinib is recommended in combination with other chemotherapy for HER2 positive breast cancer that is either estrogen or progesterone receptor-positive or negative.

FDA APPROVED INDICATIONS

Tykerb is indicated in combination with:

- Capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
- Letrozole, for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that over expresses the HER2 receptor for whom hormonal therapy is indicated.

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/13
GUIDELINES FOR USE
The guideline named LAROTRECTINIB (Vitrakvi) requires a diagnosis of a solid tumor. In addition, the following criteria must be met:

- The tumor has a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation
- The tumor is metastatic or surgical resection is likely to result in severe morbidity
- There are no satisfactory alternative treatments or the patient progressed following treatment

Requests for Vitrakvi oral solution also require that ONE of the following is met:

- The request is for a pediatric patient
- Physician attestation that the patient is unable to take Vitrakvi capsules due to difficulty swallowing or dysphagia
- Physician attestation that the patient has other medical need for the oral solution

RATIONALE
Promote appropriate utilization and dosing of Vitrakvi for its FDA approved indication.

FDA APPROVED INDICATIONS
Vitrakvi is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that:

- Have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation
- Are metastatic or where surgical resection is likely to result in severe morbidity
- Have no satisfactory alternative treatments or that have progressed following treatment

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSED AND ADMINISTRATION
- Recommended dosage in adult and pediatric patients with body surface area of at least 1.0m²: 100 mg orally twice daily
- Recommended dosage in pediatric patients with body surface area of less than 1.0m²: 100 mg/m² orally twice daily

AVAILABLE STRENGTHS
Capsules: 25mg, 100mg  Oral Solution: 20 mg/mL

REFERENCES
Vitrakvi [Prescribing Information]. Stamford, CT: Loxo Oncology, Inc: November 2018.

Created: 01/18  Effective: 01/01/20  Client Approval: 10/14/19  P&T Approval: N/A
GUIDELINES FOR USE

The guideline named LEFAMULIN (Xenleta) requires a diagnosis of community-acquired bacterial pneumonia (CABP). In addition, the following criteria must be met:

- The patient is 18 years of age or older
- Infection is caused by any of the following susceptible microorganisms: *Streptococcus pneumoniae*, *Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae*
- The patient meets **ONE** of the following criteria:
  - Therapy is prescribed by or given in consultation with an Infectious Disease (ID) specialist
  - Antimicrobial susceptibility test is available, and the infection site culture results indicate pathogenic organism(s) with 1) resistance to at least **TWO** standard of care agents for CABP (e.g., azithromycin, doxycycline, levofloxacin, moxifloxacin, amoxicillin, ceftriaxone), **AND** 2) the culture is susceptible to Xenleta
  - Antimicrobial susceptibility test is unavailable, and the patient has had a trial of or contraindication to at least **TWO** standard of care agents for CABP (e.g., azithromycin, doxycycline, levofloxacin, moxifloxacin, amoxicillin, ceftriaxone, linezolid)

RATIONALE
To ensure safe and appropriate use of lefamulin per approved indication and dosing.

FDA APPROVED INDICATIONS
Lefamulin is a pleuromutilin antibacterial indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms. To reduce the development of drug resistant bacteria and maintain the effectiveness of Xenleta and other antibacterial drugs, Xenleta should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DOSAGE AND ADMINISTRATION
For treatment of adults with CABP, the recommended dosage of XENLETA is as follows:

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg every 12 hours by intravenous infusion over 60 minutes*</td>
<td>5 to 7 days</td>
</tr>
<tr>
<td>600 mg orally every 12 hours.</td>
<td>5 days</td>
</tr>
</tbody>
</table>

*With the option to switch to XENLETA Tablets 600 mg every 12 hours to complete treatment course.

REFERENCES

Created: 11/19
Effective: 11/29/19
Client Approval: 11/06/19
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Our guideline for LENALIDOMIDE (Revlimid) requires one of the following diagnoses: multiple myeloma (MM), anemia due to a myelodysplastic syndrome (MDS), mantle cell lymphoma (MCL), follicular lymphoma (FL), or marginal zone lymphoma (MZL). The patient also must be 18 years of age or older. In addition, the following criteria must be met:

For patients with myelodysplastic syndrome (MDS), approval requires:
• The patient’s MDS is associated with a deletion 5q abnormality

For patients with mantle cell lymphoma (MCL), approval requires:
• The patient has relapsed or progressed after at least two prior therapies, one of which included Velcade (bortezomib).

For patients with follicular lymphoma (FL), approval requires:
• The patient has previously been treated for follicular lymphoma (FL)
• The requested drug is being taken in combination with a rituximab product

For patients with marginal zone lymphoma (MZL), approval requires:
• The patient has previously been treated for marginal zone lymphoma (MZL)
• The requested drug is being taken in combination with a rituximab product

RATIONALE
To ensure appropriate use aligned with FDA approved indications.

FDA APPROVED INDICATIONS
Revlimid is a thalidomide analogue indicated for the treatment of patients with:
• Multiple myeloma (MM), in combination with dexamethasone.
• Multiple Myeloma (MM) as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT).
• Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities.
• Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
• Previously treated follicular lymphoma (FL), in combination with a rituximab product.
• Previously treated marginal zone lymphoma (MZL), in combination with a rituximab product

Limitations of Use:
REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

CONTINUED ON NEXT PAGE
DOSAGE AND ADMINISTRATION

- Multiple Myeloma (MM) combination therapy: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles.
- Multiple Myeloma (MM) maintenance therapy following auto-HSCT: 10 mg once daily continuously on Days 1-28 of repeated 28-day cycles.
- Myelodysplastic Syndrome (MDS): 10 mg once daily.
- Mantle Cell Lymphoma (MCL): 25 mg once daily orally on Days 1-21 of repeated 28-day cycles.
- Follicular Lymphoma (FL) or Marginal Zone Lymphoma (MZL): 20 mg once daily orally on Days 1-21 of repeated 28-day cycles for up to 12 cycles.

REFERENCES


Created: 06/15
Effective: 11/01/19
Client Approval: 10/17/19
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named LENVATINIB (Lenvima) requires a diagnosis of differentiated thyroid cancer, advanced renal cell cancer, or unresectable hepatocellular carcinoma. In addition, the following criteria must be met.

For the diagnosis of differentiated thyroid cancer, approval requires:
- Thyroid cancer is progressive and is locally recurrent or metastatic
- Patient has tried or has contraindication to radioactive iodine therapy

For the diagnosis of advanced renal cell cancer, approval requires:
- Lenvima will be used in combination with everolimus
- Patient has previously tried one anti-angiogenic therapy

RATIONALE
Promote appropriate utilization of Lenvima based on FDA approved indication and dosing.

FDA APPROVED INDICATIONS
LENVIMA is a kinase inhibitor that is indicated for:
- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC)
- In combination with everolimus, for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

DOSAGE AND ADMINISTRATION

Recommended dose for DTC:
- The recommended daily dosage of Lenvima is 24mg (two 10mg capsules and one 4mg capsule) orally taken once daily with or without food. Continue Lenvima until disease progression or until unacceptable toxicity occurs.
- In patients with severe renal impairment (CrCl less than 30ml/min) or severe hepatic impairment, the recommended dose is 14mg orally once daily.

Recommended dose for RCC
- The recommended daily dosage of Lenvima is 18mg (one 10mg capsules and two 4mg capsule) in combination with 5 mg everolimus orally taken once daily with or without food. Continue Lenvima plus everolimus until disease progression or until unacceptable toxicity occurs.

CONTINUED ON NEXT PAGE
LENVATINIB

- In patients with severe renal impairment (CrCl less than 30ml/min) or severe hepatic impairment, the recommended dose is 10mg orally once daily

**Recommended dose for HCC:**
- The recommended dosage of Lenvima is based on actual body weight:
  - 12 mg for patients greater than or equal to 60 kg or
  - 8 mg for patients less than 60 kg.
- Take Lenvima orally once daily with or without food until disease progression or until unacceptable toxicity.

Adverse drug reactions may require dose modifications of Lenvima.

### Dose Modifications For:
- Persistent and Intolerable Grade 2 or 3 ADRs OR
- Grade 4 Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Modification</th>
<th>Adjusted Dose</th>
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<tbody>
<tr>
<td>1st occurrence</td>
<td>Interrupt until resolved to Grade 0-1 or baseline</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Interrupt until resolved to Grade 0-1 or baseline</td>
<td>14 mg daily</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Interrupt until resolved to Grade 0-1 or baseline</td>
<td>10 mg daily</td>
</tr>
</tbody>
</table>

**HOW SUPPLIED**
Lenvima capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card as follows:
- NDC 62856-724-30: 24 mg, carton with 6 cards NDC 62856-724-05 (ten 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-720-30: 20 mg, carton with 6 cards NDC 62856-720-05 (ten 10 mg capsules per card).
- NDC 62856-718-30: 18 mg, carton with 6 cards NDC 62856-718-05 (five 10 mg capsules and ten 4 mg capsules per card).
- NDC 62856-714-30: 14 mg, carton with 6 cards NDC 62856-714-05 (five 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-710-30: 10 mg, carton with 6 cards NDC 62856-710-05 (five 10 mg capsules per card).
- NDC 62856-708-30: 8 mg, carton with 6 cards NDC 62856-708-05 (ten 4 mg capsules per card).

**REFERENCES**
GUIDELINES FOR USE

The guideline named LETERMOVIR PO (Prevymis) requires the patient to be undergoing an allogeneic hematopoietic stem cell transplant (HSCT). In addition, the following criteria must also be met.

- The patient is at least 18 years of age or older.
- The patient is CMV-seropositive [R+]
- Prevymis will be used for prophylaxis of cytomegalovirus (CMV) infection and disease.
- Prevymis will be initiated between Day 0 and Day 28 post-transplantation (before or after engraftment)
- Patient is not receiving the medication beyond 100 days post-transplantation

RATIONALE
Promote appropriate utilization of LETERMOVIR based on FDA approved indication and dosing.

FDA APPROVED INDICATION
Prevymis is indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

CONTINUED ON NEXT PAGE
LETTERMOVIR

DOSAGE AND ADMINISTRATION
The recommended dosage of Prevymis is 480 mg administered orally or intravenously once daily. Prevymis is recommended to be initiated between Day 0 and Day 28 post-transplantation (before or after engraftment), and continue through Day 100 post-transplantation. Dosage of Prevymis should be decreased to 240mg once daily when co-administered with cyclosporine.

- If cyclosporine is initiated after starting Prevymis, the next dose of Prevymis should be decreased to 240mg once daily.
- If cyclosporine is discontinued after starting Prevymis, the next dose of Prevymis should be increased to 480mg once daily.
- If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of Prevymis is needed.

Prevymis injection, which contains hydroxypropyl betadex, should be used only in patients unable to take oral therapy. Patients should be switched to oral Prevymis as soon as they are able to take oral medications. Prevymis tablet and injection may be used interchangeably at the discretion of the physician, and no dosage adjustment is necessary when switching formulations.

AVAILABLE STRENGTHS
Tablet: 240mg, 480mg tablets; Injection: 240mg/12 mL (20mg/mL), 480mg/24mL (20mg/mL) single dose vials

REFERENCES

Created: 12/17
Effective: 02/02/18
Client Approval: 12/28/17
P&T Approval: N/A
GUIDELINES FOR USE

Our Guideline for approval requires a diagnosis of prostatic carcinoma; or a diagnosis of hormone receptor positive breast cancer for a premenopausal or perimenopausal patient.

RATIONALE

Coverage of Eligard (leuprolide) is based on FDA approved indication and NCCN recommendations.

Eligard is administered subcutaneously as follows: 7.5mg every month, 22.5mg every 3 months, 30mg every 4 months, 45mg every 6 months.

NCCN guidelines recommend premenopausal patients with hormone-positive disease have ovarian ablation/suppression (with goserelin or leuprolide) and be treated as a postmenopausal woman.

FDA APPROVED INDICATION

Eligard is a gonadotropin releasing hormone (GnRH) agonist indicated for the palliative treatment of advanced prostate cancer.

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/13
LEUPROLIDE ACETATE (LUPRON DEPOT, LUPRON DEPOT-PED)

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GUIDELINES FOR USE

Our guideline for approval requires a diagnosis of prostate cancer, endometriosis (≥18 years old), uterine leiomyomata (≥18 years old), or central precocious puberty (≥2 years old) confirmed by the following tests: measurement of blood concentrations of luteinizing hormone, sex steroids, and assessment of bone age versus chronological age.

LEUPROLIDE ACETATE (LUPRON DEPOT, LUPRON DEPOT-PED)

RATIONALE

Leuprolide is a gonadotropin releasing hormone agonist (GnRH-a), inhibiting gonadotropin secretion at continuous, therapeutic doses. With chronic administration, suppression of ovarian and testicular steroidogenesis occurs, and is reversible once leuprolide is discontinued.

Leuprolide given concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. A 1-month trial period of iron alone may be considered since some patients may respond to iron therapy. Leuprolide may be added if the response is considered inadequate.

Leuprolide is also effective in the treatment of endometriosis, including pain relief and reductions of endometriotic lesions.

FDA APPROVED INDICATIONS

LUPRON DEPOT 7.5 mg or -month, 22.5 mg for 3-month, 30 mg for 4-month, and 45 mg for 6-month administration are prescribed for the palliative treatment of advanced prostate cancer.

LUPRON DEPOT 3.75mg and 11.25mg are approved for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Leuprolide depot with norethindrone acetate is also indicated for initial management of endometriosis and for the management of recurrence of symptoms.

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LEUPROLIDE ACETATE (LUPRON DEPOT, LUPRON DEPOT-PED)

FDA APPROVED INDICATIONS (CONTINUED)

LUPRON DEPOT 3.75mg and 11.25mg are approved concomitantly with iron therapy for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. Experience with leuprolide depot in females has been limited to women 18 years and older and treated for 6 months or less.

LUPRON DEPOT-PED is approved for the treatment of children with central precocious puberty (CPP). CPP is the early onset of secondary sexual characteristics (generally earlier than 8 years of age in girls and 9 years of age in boys) associated with pubertal pituitary gonadotropin activation.

Prior to initiation of treatment, a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of luteinizing hormone (LH), sex steroids, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intracranial tumor), pelvic/testicular/adrenal ultrasound (to rule out steroid-secreting tumors), human chorionic gonadotropin levels (to rule out a chorionic gonadotropin-secreting tumor), and adrenal steroid measurements to exclude congenital adrenal hyperplasia.

REFERENCES

Created: 10/15
Effective: 10/20/17               Client Approval: 10/06/17               P&T Approval: 10/15
GUIDELINES FOR USE

The guideline named LEVODOPA (Inbria) requires a diagnosis of Parkinson’s disease. In addition, the following criteria must be met.

- Inbria is being used for intermittent treatment of off episodes associated with Parkinson’s disease
- The patient is currently being treated with carbidopa/levodopa

RATIONALE

For further information, please refer to the Prescribing Information and/or Drug Monograph for Inbria.

REFERENCES


Created: 03/19
Effective: 05/20/19
Client Approval: 04/04/19
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for **LINEZOLID** requires either initiation or consultation with an Infectious Disease specialist; inpatient discharge with prior therapy with Zyvox or vancomycin; vancomycin-resistant gram-positive infection; or a trial or contraindication to vancomycin or Sivextro.

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RATIONALE

Ensure that Zyvox is reserved as a second-line agent for vancomycin-resistant infections or for Sivextro (where appropriate) and vancomycin allergies. Inappropriate use of Zyvox could lead to an increase in resistant organisms.

FDA APPROVED INDICATIONS

Zyvox is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Zyvox is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

- Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates) or *Streptococcus pneumoniae*
- Community-acquired pneumonia caused by *Streptococcus pneumoniae*, including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible isolates only)
- Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, or *Streptococcus agalactiae*
- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*
- Vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

**DOsing**
The recommended dosage for Zyvox formulations for the treatment of infections is described in the table below.

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Dosage and Frequency</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatrics (Birth to 11 years of age)</strong></td>
<td><strong>Adults and Adolescents (12 years and older)</strong></td>
<td></td>
</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td>10mg/ kg every 8 hours</td>
<td>600mg every 12 hours</td>
</tr>
<tr>
<td>Community-acquired pneumonia, including concurrent bacteremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated skin and skin structure infections</td>
<td>10mg/ kg every 8 hours</td>
<td>600mg every 12 hours</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus faecium</em> infections, including concurrent bacteremia</td>
<td>10mg/ kg every 8 hours</td>
<td>600mg every 12 hours</td>
</tr>
<tr>
<td>Uncomplicated skin and skin structure infections</td>
<td>• Less than 5 years of age: 10 mg/kg every 8 hours</td>
<td>• Adolescents: 600mg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>• 5 to 11 years of age: 10 mg/kg every 12 hours</td>
<td>• Adults: 400mg every 12 hours</td>
</tr>
</tbody>
</table>

**How Supplied**
- 100mg/ 5mL oral suspension in 240mL glass bottles
- 600mg tablets

**References**

Created: 06/15
Effective: 11/23/18
Client Approval: 11/09/18
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA

The guideline named LOMITAPIDE (Juxtapid) requires a diagnosis of homozygous familial hypercholesterolemia (HoFH). The following criteria must also be met:

- The diagnosis of homozygous familial hypercholesterolemia (HoFH) is determined by meeting ONE of the following criteria:
  - Simon Broome diagnostic criteria (definite)
  - Dutch Lipid Network criteria with a score of at least 8
  - A clinical diagnosis based on a history of an untreated LDL-cholesterol level greater than 500 mg/dL, in combination with either (1) xanthoma before 10 years of age OR (2) evidence of heterozygous familial hypercholesterolemia (HeFH) in both parents

- The agent is prescribed by or given in consultation with a cardiologist, endocrinologist, or lipidologist
- The patient has a LDL-cholesterol level greater than or equal to 70 mg/dL while on maximally tolerated drug treatment
- The patient has had a previous trial of Repatha (evolocumab) unless the patient lacks functional LDL receptors

**For statin tolerant patients, approval also requires the following:**

- The patient meets ONE of the following criteria:
  - The patient has been taking a high-intensity statin (i.e., atorvastatin 40-80 mg daily, rosuvastatin 20-40 mg daily) for a duration of at least 8 weeks, OR
  - The patient has been taking a maximally tolerated dose of any statin for a duration of at least 8 weeks given that the patient cannot tolerate a high-intensity statin (i.e., atorvastatin 40-80 mg daily, rosuvastatin 20-40 mg daily)

- The patient will continue statin treatment in combination with Juxtapid

**For statin intolerant patients, approval also requires ONE of the following:**

- The patient has an absolute contraindication to statin therapy (e.g., active decompensated liver disease, nursing female, pregnancy or plans to become pregnant, hypersensitivity reaction)
- The patient has complete statin intolerance as defined by severe and intolerable adverse effects (e.g., creatine kinase elevation greater than or equal to 10 times the upper limit of normal, liver function test elevation greater than or equal to 3 times the upper limit of normal, rhabdomyolysis, severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group) that have occurred with trials of at least two separate statins and have improved with the discontinuation of each statin

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

The guideline named LOMITAPIDE (Juxtapid) renewal requires that the patient has had at least 26 weeks of therapy, with a LDL reduction of at least 30% from baseline after lomitapide therapy for 26 weeks. Patient must also be adherent to Juxtapid (lomitapide) and statin therapy (or Juxtapid and other lipid-lowering agent, if the patient is statin intolerant).

RATIONALE

To ensure appropriate use of Juxtapid based on FDA approved indication and current recommendations of experts and national treatment guidelines.

FDA APPROVED INDICATIONS

Juxtapid is indicated as an adjunct to a low-fat diet and other lipid lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apoB), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Limitations of Use:

- The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH.
- The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

DOSAGE AND ADMINISTRATION

Initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily.

Take once daily, whole, with water and without food, at least 2 hours after evening meal.

REFERENCES


Created: 06/15
Effective: 10/01/19
Client Approval: 09/04/19
P&T Approval: N/A
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LONG-ACTING OPIOID ANALGESICS

GUIDELINES FOR USE

RENEWAL CRITERIA will apply in the following scenarios only:

- For patients active with MDwise for 90 days or longer AND previous prior authorization approval for the same medication with the same strength AND recent paid pharmacy claims for the requested medication. Chart notes and/or cash pay for opioid use is not accepted.
- For patients new to MDwise within the past 90 days AND chart notes are provided that document the patient is stable on the requested medication.

All other requests will be reviewed against the INITIAL CRITERIA.

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline for LONG-ACTING OPIOID ANALGESICS for patients with past use of opioid dependency agents (such as, buprenorphine/naloxone SL tablets/films or buprenorphine SL tablets) requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid analgesic will be authorized.

Our guideline for LONG-ACTING OPIOID ANALGESICS does not permit concurrent use with carisoprodol-containing products.

Our guideline named LONG-ACTING OPIOID ANALGESIC (OPANA ER) requires you to meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You meet the definition of opioid tolerance [defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid].
- Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted. For patients active with MDwise less than 90 days, chart notes are required to verify previous opioid use for this criterion
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals
- You have had a trial of at least 30 days generic MS Contin in the previous 120 days and TWO non-preferred long-acting opioid analgesics other than methadone (such as Duragesic, Nucynta, OxyContin or Zohydro)

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for LONG-ACTING OPIOID ANALGESICS requires patient to meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You meet the definition of opioid tolerance [defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid].
- Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted. For patients active with MDwise less than 90 days, chart notes are required to verify previous opioid use for this criterion
- You have had a trial of at least 30 days generic MS Contin in the previous 120 days
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

Our guideline named LONG-ACTING OPIOID ANALGESICS for concurrent use of more than one long-acting opioid requires patients to meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You have a pain that is not responding to treatment despite concurrent (used at the same time) therapy with one short-acting opioid and one long-acting opioid, as documented in claim history or chart notes
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan.

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for **LONG-ACTING OPIOID ANALGESICS** for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting **ALL** of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)

- The diagnosis contributing to the need for opioid analgesic therapy and previous therapy attempted, including dates and doses of prior therapies (if applicable). For a diagnosis of moderate to severe cancer-related pain, pain related to sickle cell disease, or pain in patients receiving palliative care, no additional criteria applies.
  - For long-acting opioid therapy requested for chronic moderate to severe pain, **ALL** of the following are required:
    - You meet the definition of opioid tolerance (defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose (a dose of one pain medication that is the same in pain-relieving effects to that of another pain medication) of another opioid). Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history.Chart notes and/or cash pay for opioid use is not accepted.
    - For any long-acting opioid other than MS Contin, the patient has had a trial of at least 30 days generic MS Contin in the previous 120 days
  - Your prescriber has signed an attestation as to **ALL** of the following:
    - Your provider will regularly review your controlled substance utilization contained within INSPECT (Indiana controlled substance monitoring program)
    - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
    - Both you and your provider accept the risk of using benzodiazepines and opioid analgesics together at the same time

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INITIAL CRITERIA (CONTINUED)

Our guideline for LONG-ACTING OPIOID ANALGESICS for patients with claims in history for antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RENEWAL CRITERIA

Our guideline for LONG-ACTING OPIOID ANALGESICS not permit concurrent use with carisoprodol-containing products.

Our renewal guideline for LONG-ACTING OPIOID ANALGESICS requires patients to meet ALL of the following criteria:

- Opioid therapy has resulted in a meaningful improvement in your pain and/or function
- Your doctor has developed an updated pain management plan with clear treatment goals
- A risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (for example, INSPECT)
- Adherence to prescribed opioid regimen has been periodically assessed (for example, urine drug screen, pill counts)

In addition, requests for renewal of concurrent use of (used at the same time with) more than one short-acting opioid or more than one long-acting opioid requires that you meet ALL of the following rules:

- You have a diagnosis of moderate to severe pain
- You experience refractory pain (pain that continues or returns) despite concurrent therapy with one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions may be granted if you have moderate to severe pain from cancer, have sickle cell disease (a type of red blood cell disorder) or you are receiving opioids as part of a palliative care plan (treatment for symptoms related to an illness).

Please note that additional rules apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

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RENEWAL CRITERIA (CONTINUED)

Our renewal guideline for LONG-ACTING OPIOID ANALGESICS for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)

- The diagnosis contributing to the need for renewal of the requested opioid analgesic therapy and that you meet the following:
  - Opioid therapy has resulted in a meaningful improvement in your pain and/or function
  - Your doctor has developed an updated pain management plan with clear treatment goals
  - A risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (e.g., INSPECT)
  - Adherence to prescribed opioid regimen has been periodically assessed (e.g., urine drug screen, pill counts)

- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the risks of using benzodiazepines and opioid analgesics together at the same time

Our guideline for LONG-ACTING OPIOID ANALGESICS) for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult with your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

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RATIONAL
To ensure opioid analgesics are used according to FDA approved indications with patient safety in mind, and to encourage the use of more cost-effective analgesics.

From 2000-2014, almost half a million people died due to drug overdose, with 2014 being the highest year for deaths on record. In that time, the number of opioids prescribed, as well as the number of opioid overdoses, has risen exponentially. At least half of all opioid overdose deaths involve a prescription opioid. Indiana was among the states that had a statistically significant increase of overdose deaths from 2013-2014.

According to recent research, the opioid epidemic has a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed opioids at double the rate of non-Medicaid patients, and are subsequently at much higher risk of prescription opioid overdose. Improving the way that opioids are prescribed can ensure safer and more effective pain treatment, and reduce the addiction, misuse, abuse, and overdose of these drugs. These guidelines are to ensure that the use of opioids is consistent with their FDA approved indications, and to initiate action combating the current opioid epidemic.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 25mcg transdermal fentanyl/hour, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid for a week or longer.

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Opioid Conversion Table

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Opioid Usage in Chronic Pain Management
Per systematic review in the CDC Guideline for Prescribing Opioids for Chronic Pain, long-term (> 1 year) efficacy of opioids in management of chronic pain, function, or quality of life is not established. Most randomized controlled trials present effectiveness within 6 weeks or less. Conversely, significant risks of adverse events are present with chronic opioid therapy, including opioid abuse and dependence, social role withdrawal, and increased risk of CNS depression, and withdrawal emergencies.
RATIONAL (CONTINUED)
The CDC also recommends re-evaluating and re-establishing treatment goals, including realistic expectation for pain and function, as well as discontinuation strategies when benefits do not outweigh risks. The guideline provides the following recommendations for opioid selection, dosage, duration, follow-up and discontinuation:

- Immediate-release (IR) opioids are preferred over extended-release (ER) forms.
- The lowest effective dosage is preferred with initial opioid use. Caution is warranted at any dose and reassessing benefits and risks is recommended for 50 morphine milligram equivalents (MME) daily or more. 90 MME daily or more should be avoided if possible.
- Within 1 to 4 weeks of therapy, clinicians should evaluate benefits and harms of using opioids to treat chronic pain. Therapy continuation should be evaluated every 3 months or sooner. If benefits do not outweigh harms to continue opioid therapy, other therapies should be optimized and opioid tapering/discontinuation should be considered and encouraged.

Assessing Risk and Addressing Harms of Opioid Use
- Prior to and throughout opioid therapy, adverse events should be evaluated periodically. Factors that increase risk for opioid overdose include history of overdose or substance use disorder, 50 MME daily or more, and concurrent benzodiazepine use.
- Prescription drug monitoring program (PDMP) data (e.g., RXINSPECT) are useful to monitor total opioid dosage. PDMP data is helpful for initial and periodic opioid usage evaluations.
- Prescribing opioids and benzodiazepines concurrently should be avoided.
- For patients with substance use disorder, evidence-based treatment (medication-assisted and behavioral therapy) is recommended.

Analysis performed by the US Department of Health and Human Services Center for Disease Control and Prevention (CDC) determined the risk of harm to individuals increases as their opioid dose increases and as their length of opioid therapy increases. For example:

- Individuals taking opioid doses > 50 morphine milligram equivalents (MMEs) per day had twice the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking opioid doses > 90 (MMEs) per day had 10 times the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking an opioid for > 3 months (even at low doses) had 15 times the risk of addiction to those taking opioids for < 3 months.

CONTINUED ON NEXT PAGE
### APPENDIX 1: Long-Acting Opioid Analgesic Quantity Limits

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CONTINUED ON NEXT PAGE
APPENDIX 2: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM

INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY
PRIOR AUTHORIZATION REQUEST FORM

Today’s Date

Note: This form must be completed by the prescribing provider.

**All sections must be completed or the request will be denied.**

<table>
<thead>
<tr>
<th>Patient’s Medicaid #</th>
<th>Date of Birth / /</th>
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<tbody>
<tr>
<td>Patient’s Name</td>
<td>Prescriber’s Name</td>
</tr>
<tr>
<td>Prescriber’s IN License #</td>
<td>Specialty</td>
</tr>
<tr>
<td>Prescriber’s NPI #</td>
<td>Prescriber’s Signature: <strong>Required below within attestation section.</strong></td>
</tr>
</tbody>
</table>

**PA is required for the following:**
- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).

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<th>Benzodiazepine Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Opioid Agent(s) | Prescriber Name* | Quantity | Dosage Regimen/Duration
---|---|---|---

*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:
- Are you requesting PA for: Benzodiazepine Agent(s) □ Opioid Agent(s) □ Both □
- Is/are the other prescriber(s) aware of the request for concurrent therapy? □ Yes □ No
- Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? □ Yes □ No

PA Requirements:

Patient diagnosis/diagnoses for use of benzodiazepine therapy:

Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
</tr>
</thead>
</table>

Do you plan to continue benzodiazepine therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Patient diagnosis/diagnoses for use of opioid therapy:

Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
</tr>
</thead>
</table>
Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, ________________________________________, hereby attest to the following:

(Prescriber Name)

• The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
• I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
• If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
• I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber
Signature:___________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**

CONFIDENTIAL INFORMATION
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REFERENCES

- Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016; 65(1);1-49. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

CONTINUED ON NEXT PAGE
REFERENCES (CONTINUED)

- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).
GUIDELINES FOR USE

The guideline named LORLATINIB (Lorbrena) requires a diagnosis of anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC). In addition, approval requires that the patient has experienced disease progression on at least ONE of the following regimens:

- Crizotinib and at least one other ALK inhibitor for metastatic disease
- Alectinib as the first ALK inhibitor therapy for metastatic disease
- Ceritinib as the first ALK inhibitor therapy for metastatic disease

RATIONALE
Promote appropriate utilization and dosing of Lorbrena for its FDA approved indication

FDA APPROVED INDICATIONS
Lorbrena is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on

- Crizotinib and at least one other ALK inhibitor for metastatic disease; or
- Alectinib as the first ALK inhibitor therapy for metastatic disease; or
- Ceritinib as the first ALK inhibitor therapy for metastatic disease

DOSAGE AND ADMINISTRATION
The recommended dosage is 100 mg orally once daily.

AVAILABLE STRENGTHS
Tablets: 25 mg or 100 mg

REFERENCES

Created: 09/19
Effective: 01/01/20
Client Approval: 10/14/19
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named LUSUTROMBOPAG (Mulpleta) requires a diagnosis of thrombocytopenia. In addition, the following criteria must be met.

- The patient is 18 years of age or older
- The patient has chronic liver disease
- The patient is scheduled to undergo a procedure 8 to 14 days following initiation of Mulpleta (lusutrombopag) therapy

RATIONAL

To ensure appropriate utilization of Mulpleta based on FDA-approved indication and dosing.

FDA APPROVED INDICATION

Mulpleta (lusutrombopag) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

DOSAGE AND ADMINISTRATION

Begin Mulpleta therapy 8 to 14 days before the scheduled procedure. The recommended dose is 3 mg once per day with or without food for 7 consecutive days. Patients should undergo their procedure 2 to 8 days after the last dose of Mulpleta.

REFERENCES


Created: 11/18
Effective: 11/23/18
Client Approval: 11/06/18
P&T Approval: N/
Our guideline for **MEBENDAZOLE** indicates it will be approved for treatment of *Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (common roundworm), *Ancylostoma duodenale* (common hookworm), or *Necator americanus* (American hookworm). Additional criteria are required for the four aforementioned parasitic worm infections:

- Documented confirmed diagnosis of *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (common roundworm), *Ancylostoma duodenale* (common hookworm), or *Necator americanus* (American hookworm).

**RATIONALE**
To ensure appropriate use of **MEBENDAZOLE** consistent with FDA approved use and CDC treatment guidelines.

Emverm is a member of the benzimidazole drug class, which also includes the branded product, Albenza (albendazole). Besides Emverm and Albenza, other anthelmintics include ivermectin and pyrantel pamoate. Ivermectin does not share any of the same indications as Emverm but could be considered as an equally efficacious off-label treatment alternative for roundworm. Pyrantel pamoate is only approved for the treatment of pinworms and is the standard of care due to its low cost and over-the-counter (OTC) availability. Alternatively, Emverm and Albenza may also be used for pinworm due to comparable efficacy; however, of the two benzimidazoles, only Emverm is FDA approved for this indication. For whipworm and roundworm, Emverm is the drug of choice for treatment; however, Albenza may be used off-label. Finally, for hookworm, Albenza has the highest cure rate and is the preferred treatment regimen despite not being FDA approved for this indication.

***Enterobius vermicularis* (pinworm)**
Pinworm is the most common helminthic parasite infection in the United States with an estimated prevalence of 40 million cases each year. Infection most commonly occurs among children aged 5-10 years, institutionalized persons, and within families. Transmission usually occurs through the fecal-oral route but may also spread through contaminated surfaces (including clothing and bedding) or airborne transmission. Due to the ease of transmission, all members of a family should be treated if one member has a confirmed infection. While infections are usually asymptomatic, the worms, eggs, and larvae may also cause perianal itching. Treatment options include, Albenza (albendazole), Emverm (mebendazole) and pyrantel pamoate. All of these agents are comparable in efficacy and have high cure rates, with a near 100% cure rate with two doses. **Reinfection is frequent; the CDC recommends a second dose of any of the three treatment options to prevent re-infection by adult worms that hatch from any eggs not killed by the first treatment.**

CONTINUED ON NEXT PAGE
MEBENDAZOLE

RATIONALE (CONTINUED)

Soil-transmitted helminth (STH) infections

Trichuris trichiura (whipworm), Ascaris lumbricoides (common roundworm), Ancylostoma duodenale (common hookworm), and Necator americanus (American hookworm) are soil-transmitted helminths that are seen primarily in tropical climates. Infections with these organisms are rare overall in the United States but are more common in the rural Southeast. Infection is associated with poor hygiene and is more common in children due to high exposure to soil compared to adults. STH infections are usually asymptomatic. Patients may experience abdominal discomfort, loose stools with blood or mucus, and episodes of nocturnal stools. Rarely, heavy infections with high worm burden can progress to colitis, intestinal blockage, rectal inflammation, cough, peripheral eosinophilia, impaired growth in children, and secondary anemia. Also, hookworm infections may cause rash at the site of cutaneous penetration.

According to the CDC, Albenza (albendazole) and Emverm (mebendazole) are the drugs of choice for whipworm and roundworm infection. Multiple studies have demonstrated that higher cure rates are achieved with the use of Albenza (albendazole) compared to Emverm (mebendazole) when treating hookworm infection. With all agents, three day treatment is required to achieve significant cure rates.

FDA APPROVED INDICATION

Emverm (mebendazole) is indicated for the treatment of Enterobius vermicularis (pinworm), Trichuris trichiura (whipworm), Ascaris lumbricoides (common roundworm), Ancylostoma duodenale (common hookworm), Necator americanus (American hookworm) in single or mixed infections.

DOSAGE

- Treatment of Enterobius vermicularis (pinworm)
  - 1 tablet (100mg), once.
  - If the patient is not cured three weeks after treatment, a second course of treatment is advised.

- Treatment of Trichuris trichiura (whipworm), Ascaris lumbricoides (common roundworm), Ancylostoma duodenale (common hookworm), Necator americanus (American hookworm)
  - 1 tablet (100mg) twice daily for three consecutive days.
  - If the patient is not cured three weeks after treatment, a second course of treatment is advised.

AVAILABLE STRENGTHS:

- Mebendazole 100mg chewable tablet

REFERENCES

REFERENCES (CONTINUED)

GUIDELINES FOR USE

Our guideline for approval requires that Vecamyl be used for the management of moderately severe to severe essential (or primary) hypertension or in uncomplicated cases of malignant hypertension; and a trial or a contraindication to at least three of the following: angiotensin converting enzyme (ACE) inhibitor or ACE-I combination, angiotensin receptor blocker (ARB) or ARB combination, Beta Blocker, or Calcium Channel Blocker, such as benazepril, benazepril-HCTZ, captopril, captopril-HCTZ, enalapril, enalapril-HCTZ, fosinopril, fosinopril-HCTZ, lisinopril, lisinopril-HCTZ, quinapril, ramipril, moexipril, moexipril-HCTZ, perindopril erbumine, quinapril, quinapril-HCTZ, trandolapril, trandolapril/verapamil, losartan, losartan-HCTZ, irbesartan, irbesartan-HCTZ, olmesartan, olmesartan-HCTZ, olmesartan-amlodipine-HCTZ, valsartan, valsartan-HCTZ, diltiazem HCL, diltiazem sustained release (generics only), verapamil, verapamil sustained release (generics only), atenolol, atenolol-chlorthalidone, bisoprolol, bisoprolol-HCTZ, carvedilol, metoprolol tartrate, nadolol, acebutolol, betaxolol, labetalol, metoprolol succinate, metoprolol-HCTZ, pindolol, propranolol, propranolol-HCTZ, sotalol, timolol maleate, or nebivolol.

RATIONALE

To ensure appropriate use aligned with FDA approved indication.

Therapy is usually started with one 2.5 mg tablet of Vecamyl twice a day. This initial dosage should be modified by increments of one 2.5 mg tablet at intervals of not less than 2 days until the desired blood pressure response occurs (the criterion being a dosage just under that which causes signs of mild postural hypotension).

The average total daily dosage of Vecamyl is 25 mg, usually in three divided doses. However, as little as 2.5 mg daily may be sufficient to control hypertension in some patients. Since the blood pressure response to antihypertensive drugs is increased in the early morning, the larger dose should be given at noontime and perhaps in the evening.

Vecamyl joins several different agents used in the treatment of hypertension. The most commonly prescribed drug classes for primary hypertension include thiazide-type diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and beta blockers; all of which have generic formulations available. Each category of antihypertensive agent has similar levels of efficacy in lowering the blood pressure, producing a good antihypertensive response in 30 to 50 percent of patients. Malignant hypertension most often occurs in patients with long-standing uncontrolled hypertension, many of whom have discontinued antihypertensive therapy. The oral drug of choice in uncomplicated malignant hypertension is the ACE inhibitor, captopril, since it can substantially lower the BP within 10 to 30 minutes for most patients and has a relatively short duration that facilitates dose titration.

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

In more recent years, there has been considerable interest in evaluating Vecamyl for the treatment of other clinical indications, including smoking cessation and depression. The principal focus of research on other clinical indications largely involves Vecamyl’s potent blockade of brain nicotinic receptors at doses that do not have a significant effect on parasympathetic function (2.5-10 mg/day). Recently Vecamyl was studied as an add-on treatment to existing anti-depressants. However, it failed two short-term Phase 3 clinical trials in 2011, showing no significant difference in patients when compared to a placebo.

The package insert for Vecamyl does not include any clinical trials as it was approved using an abbreviated new drug application (ANDA) of the innovator product, Inversine (mecamylamine). The distribution of Inversine was discontinued in 2009. Approved on March 1, 1956, Inversine was available prior to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (commonly referred to as the Kefauver-Harris Amendments) which established a framework requiring drug manufacturers to prove scientifically that a medication was not only safe, but effective. Since drugs approved between 1938 and 1962 were approved only on the grounds of safety, the FDA’s Drug Efficacy Study Implementation (DESI) program has been retrospectively evaluating the effectiveness of these medications.

The Journal of the American Medical Association published a study in 1957 examining the effects of mecamylamine alone on 17 patients with sustained blood pressure above 150/100 mm Hg. Each patient was initiated on mecamylamine 2.5mg twice daily before undergoing a set dose titration. Treatment response was defined as a decrease in mean blood pressure by at least 20 mm Hg or a reduction of blood pressure to the normotensive level (defined by the investigators as less than 150/100 mm Hg). A little more than half of this small group responded to mecamylamine alone. Among the responders, the average dose was 34mg daily. However, there were some patients, who despite doubling this average dose, did not respond satisfactorily to mecamylamine.

Vecamyl is contraindicated in those with coronary insufficiency or recent myocardial infarction, uremia, glaucoma, organic pyloric stenosis as well as patients with hypersensitivity to the product.

Vecamyl should be given with great discretion, if at all, in patients with renal insufficiency. Patients receiving antibiotics and sulfonamides should generally not be treated with ganglion blockers such as Vecamyl.

Vecamyl should not be used in mild, moderate, labile hypertension and may prove unsuitable in uncooperative patients. When ganglion blockers or other potent antihypertensive drugs are discontinued suddenly, hypertensive levels return. For some patients, particularly those with malignant hypertension, this may occur abruptly and may cause fatal cerebral vascular accidents or acute congestive heart failure. Vecamyl should be gradually discontinued and substituted with other antihypertensive therapy.

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

At therapeutic antihypertensive doses (30 to 90 mg per day), Vecamyl has parasympathetic-blocking activity which results in side effects such as constipation, urinary retention, dryness of the mouth and skin, dilation of the pupils, and loss of visual accommodation in some patients. Since urinary retention may occur, caution is required in patients with prostatic hypertrophy, bladder neck obstruction, and urethral stricture. Vecamyl should be discontinued immediately if a patient is showing signs of paralytic ileus (for example frequent loose bowel movements with abdominal distention and decreased bowel sounds).

Since Vecamyl readily penetrates into the brain, it can cause central nervous system effects such as tremor, choreiform movements, mental aberrations, and convulsions. Although rare in nature, these effects have occurred most often when large doses of Vecamyl were used, especially in patients with cerebral or renal insufficiency.

Vecamyl is pregnancy category C. Because of the potential for serious adverse reactions in nursing infants from Vecamyl, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

FDA APPROVED INDICATIONS
For the management of moderately severe to severe essential (or primary) hypertension and in uncomplicated cases of malignant hypertension.

REFERENCES
• Vecamyl [Prescribing Information]. Fort Collins, CO: Manchester Pharmaceuticals; February 2012.
GUIDELINES FOR USE

Approval requires an age of less than 18 years old; supervision by a pediatric endocrinologist or nephrologist; a diagnosis of growth failure in children with primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to GH; a height standard deviation score less than or equal to -3.0, basal IGF-1 standard deviation score less than or equal to -3.0, and normal or elevated growth hormone [serum growth hormone level of greater than or equal to 10ngm/mL to at least 2 stimuli (insulin, levodopa, arginine, clonidine or glucagon)]; and the patient's epiphyses (bone growth plates) are open (as confirmed by radiograph of the wrist and hand).

RATIONALE
To ensure appropriate use of mecasermin. Mecasermin is contraindicated in patients with closed epiphyses (bone growth plates). The recommended starting dose of mecasermin is 0.04 to 0.08 mg/kg twice daily. If well tolerated the dose may be increased to a maximum of 0.12 mg/kg twice daily. The approval quantity in the guideline allows for a patient weighing up to 50 kg to receive 0.12 mg/kg twice daily. Clinical review is required for patients weighing over 50 kg or those requesting a dose greater than 0.12 mg/kg twice daily.

FDA APPROVED INDICATIONS
Long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/11
GUIDELINES FOR USE

Approval requires a diagnosis of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (CTCLs) and prior skin-directed therapy (such as corticosteroids, carmustine, topical retinoids (Targretin, Tazorac), imiquimod, or local radiation therapy).

MECHLORETHAMINE GEL

RATIONALE
To promote appropriate utilization of Valchlor based on FDA approved indication and NCCN guidelines.

Valchlor is for topical dermatological use only. Apply a thin film of Valchlor gel once daily to affected areas of the skin. Stop treatment with Valchlor for any grade of skin ulceration, blistering, or moderately - severe or severe dermatitis (i.e., marked skin redness with edema). Upon improvement, treatment with Valchlor can be restarted at a reduced frequency of once every 3 days. If reintroduction of treatment is tolerated for at least one week, the frequency of application can be increased to every other day for at least one week and then to once daily application if tolerated.

Warnings and precautions include: mucosal or eye injury; secondary exposure to Valchlor; dermatitis; non-melanoma skin cancer; embryo-fetal toxicity; and flammable gel. The most common adverse reactions (≥5%) are dermatitis, pruritus, bacterial skin infection, skin ulceration or blistering, and hyperpigmentation. Valchlor is contraindicated in patients with severe hypersensitivity to mechlorethamine.

Valchlor is pregnancy category D. No drug interaction studies have been performed with Valchlor. Systemic exposure has not been observed with topical administration of Valchlor; therefore, systemic drug interactions are not likely.

Valchlor is a gel formulation of mechlorethamine (nitrogen mustard), an alkylating agent which inhibits rapidly proliferating cells. Mechlorethamine was previously approved as an intravenous formulation for the treatment of mycosis fungoides. Prior to the approval of Valchlor, there were no FDA-approved topical mechlorethamine products; only pharmacy-compounded petroleum ointment or aqueous-based topical preparations were available.

Developed primarily in the skin, CTCLs may progress to involve lymph nodes, blood and visceral organs. They account for about 5 percent of all non-Hodgkin lymphomas (NHL). There will be an estimated 69,740 new cases of NHL and 19,020 deaths from NHL in 2013. The overall 5-year relative survival rate for patients with NHL is 68 percent.

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RATIONALE (CONTINUED)

The National Comprehensive Cancer Network (NCCN) recommends skin-directed therapies for the initial treatment of patients with patch/plaque mycosis fungoides-type CTCL with the addition of milder systemic therapy. Localized skin-directed therapies include topical therapy with corticosteroids, mechlorethamine (previously compounded formulations and now Valchlor), carmustine, topical retinoids (Targretin, Tazorac), imiquimod, or local radiation therapy. Generalized skin directed therapies such as phototherapy (UVB or PUVA) and total skin electronic beam therapy are indicated for patients with widespread skin involvement. Systemic therapies with extracorporeal photopheresis, interferons, systemic retinoids, or histone deacetylase inhibitors are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies. They include oral Targretin and intravenous formulations Istodax and Ontak.

The efficacy of Valchlor was assessed in a randomized, active-controlled, non-inferiority clinical trial of 260 patients with Stage IA, IB, and IIA mycosis fungoides-type cutaneous T-cell lymphoma (CTCL) who had received at least one prior skin-directed therapy. Qualifying prior therapies included topical corticosteroids, phototherapy, Targretin gel, and topical nitrogen mustard. Patients were not required to be refractory to or intolerant of prior therapies.

Patients were stratified based on Stage (IA vs. IB and IIA) and then randomized to receive Valchlor 0.016% (equivalent to 0.02% mechlorethamine HCL) or Aquaphor-based Mechlorethamine HCL 0.02% ointment (comparator). Eighteen patients were excluded from the efficacy analysis due to protocol violations involving randomization at a single site. Study drug was to be applied topically on a daily basis for 12 months. Concomitant use of topical corticosteroids was not permitted during the study. Dosing could be suspended or continued with reduced frequency for dermatitis. The mean daily usage of Valchlor gel was 2.8 g (1 to 2 tubes per month). The maximum daily usage was 10.5 g (5 to 6 tubes per month). Patients were evaluated for a response on a monthly basis for the first 6 months and then every 2 months for the last 6 months using the Composite Assessment of Index Lesion Severity (CAILS) score. The CAILS score is obtained by adding the severity score of each of the following categories for up to 5 index lesions: erythema, scaling, plaque elevation, and surface area. Severity was graded from 0 (none) to 8 (severe) for erythema and scaling; 0 to 3 for plaque elevation; and 0 to 9 for surface area. A response was defined as greater than or equal to 50% reduction in baseline CAILS score which was confirmed at the next visit at least 4 weeks later. A complete response was defined as a confirmed CAILS score of 0. Non-inferiority was considered to have been demonstrated if the lower bound of the 95% confidence interval (CI) around the ratio of response rates (Valchlor/Comparator) was greater than or equal to 0.75. Patients were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (%BSA) and multiplying it by a severity weighting factor (1=patch, 2=plaque, 3=tumor or ulcer). A response was defined as greater than or equal to 50% reduction in baseline SWAT score which was confirmed at the next visit at least 4 weeks later. The baseline demographics and disease characteristics were balanced between treatment arms. The median age was 57 years in the Valchlor arm and 58 years in the comparator arm. The majority of the patients were male (60% in Valchlor arm, 59% in Comparator arm) and white (75% in both treatment arms).

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

The median number of prior therapies was 2 in both treatment arms. The most common prior therapy was topical corticosteroids (used in 86% of patients in both treatment arms). The median body surface area (BSA) involvement at baseline was 8.5% (range 1%, 61%) in the Valchlor arm and 9% (range 1%, 76%) in the comparator arm.

Sixty percent (60%) of the patients on the Valchlor arm and 48% of patients on the comparator arm achieved a response based on the CAILS score. Valchlor was non-inferior to the comparator based on a CAILS overall response rate ratio of 1.24 (95% CI 0.98, 1.58). Complete responses constituted a minority of the CAILS or SWAT overall responses. The onset of CAILS overall response for both treatment arms showed a wide range from 1 to 11 months.

Efficacy in Patients with Mycosis Fungoides - Type CTCL (From Valchlor Prescribing Information)

<table>
<thead>
<tr>
<th>Response Rates</th>
<th>VALCHLOR N=119</th>
<th>Comparator N=123</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAILS Overall Response (CR+PR), % (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>45%</td>
<td>37%</td>
</tr>
<tr>
<td>SWAT Overall Response (CR+PR), % (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>43%</td>
<td>43%</td>
</tr>
</tbody>
</table>

FDA APPROVED INDICATIONS
Valchlor (mechlorethamine) is an alkylating drug indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (CTCLs) in patients who have received prior skin-directed therapy.

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/13
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for MEPOLIZUMAB requires a diagnosis of severe asthma with an eosinophilic phenotype or eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome. In addition, the following criteria must also be met:

For patients with a diagnosis of severe asthma with eosinophilic phenotype, approval requires:
- The requested medication is prescribed by or in consultation with a physician specializing in pulmonary medicine or allergy medicine
- Patient must be 6 years of age or older
- Patient must have a documented blood eosinophil level of at least 300 cells/mcL within the past 6 months
- Patient must be adherent to a maximally tolerated inhaled corticosteroids and at least one other maintenance medication (e.g., long-acting inhaled beta2-agonist, long-acting muscarinic antagonist, a leukotriene receptor antagonist, theophylline, or oral corticosteroid)
- The patient has experienced at least 2 or more asthma exacerbations within the past 12 months (exacerbation is defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days)
- The patient has ONE of the following:
  - Asthma Control Test (ACT) score of less than 20
  - Asthma Control Questionnaire (ACQ) score of at least 1.5 or more
  - Asthma Therapy Assessment Questionnaire (ATAQ) score of at least 1 or more
- Nucala will be used as add-on maintenance treatment
- The patient is not being concurrently treated with Xolair, Dupixent, or another anti-IL-5 asthma biologic (e.g., Cinqair, Fasenra)

For patients with a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA), approval requires:
- Patient must be 18 years of age or older
- Patient must have a documented blood eosinophil level of at least 300 cells/mcL within the last 6 months

CONTINUED ON NEXT PAGE
MEPOLIZUMAB

GUIDELINES FOR USE (CONTINUED)
RENEWAL CRITERIA

Our guideline for MEPOLIZUMAB requires a diagnosis of eosinophilic asthma or eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome for renewal. In addition, the following criteria must also be met:

For the diagnosis of eosinophilic asthma, approval requires:

- The patient has experienced a reduction in asthma exacerbations (defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days) from baseline
- The patient has experienced an improvement in the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Asthma Therapy Assessment Questionnaire (ATAQ) score from baseline
- The patient has reduced their total daily oral corticosteroid dose from baseline, if the patient was on maintenance therapy with oral corticosteroids prior to initiation of Nucala

For the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss, approval requires:

- The patient has experienced remission or a longer time to relapse since initiation of Nucala

RATIONALE
Promote appropriate utilization of Nucala (mepolizumab) based on FDA approved indication.

Nucala (mepolizumab) is a humanized monoclonal antibody that binds to and inactivates interleukin-5 (IL-5), resulting in a reduction in the number of circulating blood and sputum eosinophils. IL-5 is a proinflammatory mediator that promotes eosinophil production and infiltration into airway, as well as the release of immunoglobulin E (IgE). Eosinophilia, as well as increased serum IgE concentrations can potentiate worsening asthma symptoms and asthma exacerbations.

FDA APPROVED INDICATIONS
Nucala (mepolizumab) is indicated for:

- the add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype
- the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)

Limitation of use: Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.

In clinical trials, Nucala (mepolizumab) was shown to reduce the rates of asthma exacerbations by approximately 50%, as well as significantly reduce the daily dose of oral corticosteroids patients were on for maintenance therapy for asthma control. Nucala’s (mepolizumab) ability to control asthma symptoms and reduce exacerbations can allow for the reduction or “stepping down” of doses of oral and inhaled corticosteroids, which will reduce the risk of experiencing adverse events related to steroid use. In clinical trials, blood eosinophil counts rebounded to pre-treatment levels or higher upon the discontinuation of Nucala (mepolizumab) therapy, indicating that this drug should be used as a maintenance medication to control asthma symptoms.

CONTINUED ON NEXT PAGE
MEPOLIZUMAB

FDA APPROVED INDICATIONS (CONTINUED)

DOSE

Asthma:
Adults and Adolescents Aged 12 Years and Older:
The recommended dosage of Nucala (mepolizumab) is 100mg given by subcutaneous injection every four weeks into the upper arm, thigh, or abdomen.

Pediatric Patients Aged 6 to 11 Years:
The recommended dosage of NUCALA in children aged 6 to 11 years is 40 mg administered once every 4 weeks by SC injection into the upper arm, thigh, or abdomen.

Eosinophilic granulomatosis with polyangiitis (EGPA):
The recommended dosage of Nucala is 300mg given every four weeks by subcutaneous injection as three separate injections into the upper arm, thigh, or abdomen, administered by a healthcare provider.

HOW SUPPLIED

- 100 mg of lyophilized powder in a single-dose vial for reconstitution
- 100 mg/mL, single-dose, prefilled autoinjector or single-dose prefilled syringe

REFERENCES


Created: 01/16
Effective: 01/01/20
Client Approval: 10/14/19
P&T Approval: N/A
GUIDELINES FOR USE

RENEWAL CRITERIA will apply in the following scenarios only:

- For patients active with MDwise for 90 days or longer AND previous prior authorization approval for the same medication with the same strength AND recent paid pharmacy claims for the requested medication. Chart notes and/or cash pay for opioid use is not accepted.
- For patients new to MDwise within the past 90 days AND chart notes are provided that document the patient is stable on the requested medication.

All other requests will be reviewed against the INITIAL CRITERIA.

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline named METHADONE for patients with past use of opioid dependency agents (i.e., buprenorphine/naloxone SL tablets/films or buprenorphine SL tablets) requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid analgesic will be authorized.

Our guideline named METHADONE does not permit concurrent use with carisoprodol-containing products.

Our guideline named METHADONE requires its use be for the treatment of pain or pain management only, and not for opioid dependence therapy. Our guideline does not allow for approval of methadone 40mg tablet for oral suspension (Diskets dispersible tablet) and methadone oral concentrate 10mg/mL as they are FDA (Food and Drug Administration)-indicated for opioid dependence therapy only.

CONTINUED ON NEXT PAGE
METHADONE

INITIAL CRITERIA (CONTINUED)

Our guideline named METHADONE requires its use be for the treatment of pain or pain management only, and not for opioid dependence therapy. In addition, ALL of the following criteria must be met:

- You have a diagnosis of moderate to severe pain
- You have had a trial and failure of generic MS Contin and TWO non-preferred long-acting opioid analgesics (such as Duragesic, Nucynta, OxyContin, Zohydro)
- You meet the definition of opioid tolerance [defined as those who are taking, for one week or longer, at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid]. Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted.
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

Our guideline named METHADONE for concurrent use of more than one long-acting opioid requires patients to meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You experience refractory pain (pain that continues or returns) despite concurrent therapy with one short-acting opioid and one long-acting opioid as documented in chart notes or claim history
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan. Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
METHADONE

INITIAL CRITERIA (CONTINUED)

Our guideline named METHADONE for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
  - For anxiolytic disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required:
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
  - For pain related to sickle cell disease, pain in patients receiving palliative care, no additional criteria applies
  - For long-acting opioid therapy requested for chronic moderate to severe pain, ALL of the following are required:
    - You meet the definition of opioid tolerance (defined as those who are taking, for one week or longer, at least 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose (a dose of one pain medication that is the same in pain-relieving effects to that of another pain medication) of another opioid). Your plan requires that for patients active with MDwise for 90 days or longer, only previously paid claims for opioids may be considered for this criterion. If your prescriber indicates that you have been on opioid therapy, it must be verified in claims history. Chart notes and/or cash pay for opioid use is not accepted
    - You have had a trial and failure of generic MS Contin and TWO non-preferred long-acting opioid analgesics (e.g., Duragesic, Nucynta, OxyContin, Zohydro)
  - Your prescriber has signed an attestation as to ALL of the following:
    - Your prescriber will regularly review the patient’s controlled substance utilization contained within INSPECT
    - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
    - Both you and your provider accept the of using benzodiazepines and opioid analgesics together at the same time

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for METHADONE for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of methadone and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RENEWAL CRITERIA

Our guideline named METHADONE does not permit concurrent use with carisoprodol-containing products.

Our guideline named METHADONE for renewal of therapy requires that you meet ALL of the following criteria:

- Opioid therapy has resulted in a meaningful improvement in your pain and/or function
- Your doctor has developed an updated pain management plan with clear treatment goals
- A risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (e.g., INSPECT)
- Adherence to prescribed opioid regimen has been periodically assessed (e.g., urine drug screen, pill counts)

In addition, requests for renewal of concurrent use of (used at the same time with) more than one long-acting opioid requires that you meet ALL of the following rules:

- You have a diagnosis of moderate to severe pain
- You experience refractory pain (pain that continues or returns) despite concurrent therapy with one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals
- Exceptions may be granted if you have moderate to severe pain from cancer, have sickle cell disease (a type of red blood cell disorder) or you are receiving opioids as part of a palliative care plan (treatment for symptoms related to an illness).

Please note that additional rules apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA (CONTINUED)

Our guideline named METHADONE for patients with claims in history for benzodiazepines requires that your doctor submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)

- The diagnosis contributing to the need for renewal of the requested opioid analgesic therapy and that you meet the following:
  - Opioid therapy has resulted in a meaningful improvement in your pain and/or function
  - Your doctor has developed an updated pain management plan with clear treatment goals
  - A risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (e.g., INSPECT)
  - Adherence to prescribed opioid regimen has been periodically assessed (e.g., urine drug screen, pill counts)

- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the of using benzodiazepines and opioid analgesics together at the same time

Our guideline for METHADONE for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of methadone and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RATIONALE
To ensure opioid analgesics are used according to FDA approved indications with patient safety in mind, and to encourage the use of more cost-effective analgesics.
RATIONALE (CONTINUED)
From 2000-2014, almost half a million people died due to drug overdose, with 2014 being the highest year for deaths on record. In that time, the number of opioids prescribed, as well as the number of opioid overdoses, has risen exponentially. At least half of all opioid overdose deaths involve a prescription opioid. Indiana was among the states that had a statistically significant increase of overdose deaths from 2013-2014.

According to recent research, the opioid epidemic has a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed opioids at double the rate of non-Medicaid patients, and are subsequently at much higher risk of prescription opioid overdose.

Improving the way that opioids are prescribed can ensure safer and more effective pain treatment, and reduce the addiction, misuse, abuse, and overdose of these drugs. These guidelines are to ensure that the use of opioids is consistent with their FDA approved indications, and to initiate action combating the current opioid epidemic.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60mg oral morphine/day, 25mcg transdermal fentanyl/hour, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid for a week or longer.

### Opioid Conversion Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butorphanol</td>
<td>7</td>
<td>8.5mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
<td>400mg</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>0.12</td>
<td>0.5mg (500mcg)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Hydromorphone HCl</td>
<td>4</td>
<td>15mg</td>
</tr>
<tr>
<td>Meperidine HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>60mg</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
<td>1.5</td>
<td>40mg</td>
</tr>
<tr>
<td>Oxymorphone HCl</td>
<td>3</td>
<td>20mg</td>
</tr>
<tr>
<td>Pentazocine HCl</td>
<td>0.37</td>
<td>162mg</td>
</tr>
<tr>
<td>Tapentadol HCl</td>
<td>0.4</td>
<td>150mg</td>
</tr>
<tr>
<td>Tramadol HCl</td>
<td>0.1</td>
<td>600mg</td>
</tr>
</tbody>
</table>

### Methadone Conversion Table

<table>
<thead>
<tr>
<th>Methadone daily dose (mg/day)</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0, &lt;= 20</td>
<td>4</td>
<td>20mg</td>
</tr>
<tr>
<td>&gt;20, &lt;= 40</td>
<td>8</td>
<td>7.5mg</td>
</tr>
<tr>
<td>&gt;40, &lt;= 60</td>
<td>10</td>
<td>6mg</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>5mg</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
METHADONE

RATIONALED (CONTINUED)

Opioid Usage in Chronic Pain Management
Per systematic review in the CDC Guideline for Prescribing Opioids for Chronic Pain, long-term (> 1 year) efficacy of opioids in management of chronic pain, function, or quality of life is not established. Most randomized controlled trials present effectiveness within 6 weeks or less. Conversely, significant risks of adverse events are present with chronic opioid therapy, including opioid abuse and dependence, social role withdrawal, and increased risk of CNS depression, and withdrawal emergencies.

The CDC also recommends re-evaluating and re-establishing treatment goals, including realistic expectation for pain and function, as well as discontinuation strategies when benefits do not outweigh risks. The guideline provides the following recommendations for opioid selection, dosage, duration, follow-up and discontinuation:
- Immediate-release (IR) opioids are preferred over extended-release (ER) forms.
- The lowest effective dosage is preferred with initial opioid use. Caution is warranted at any dose and reassessing benefits and risks is recommended for 50 morphine milligram equivalents (MME) daily or more. 90 MME daily or more should be avoided if possible.
- Within 1 to 4 weeks of therapy, clinicians should evaluate benefits and harms of using opioids to treat chronic pain. Therapy continuation should be evaluated every 3 months or sooner. If benefits do not outweigh harms to continue opioid therapy, other therapies should be optimized and opioid tapering/discontinuation should be considered and encouraged.

Assessing Risk and Addressing Harms of Opioid Use
- Prior to and throughout opioid therapy, adverse events should be evaluated periodically. Factors that increase risk for opioid overdose include history of overdose or substance use disorder, 50 MME daily or more, and concurrent benzodiazepine use.
- Prescription drug monitoring program (PDMP) data (e.g., RXINSPECT) are useful to monitor total opioid dosage. PDMP data is helpful for initial and periodic opioid usage evaluations.
- Prescribing opioids and benzodiazepines concurrently should be avoided.
- For patients with substance use disorder, evidence-based treatment (medication-assisted and behavioral therapy) is recommended.

Analysis performed by the US Department of Health and Human Services Center for Disease Control and Prevention (CDC) determined the risk of harm to individuals increases as their opioid dose increases and as their length of opioid therapy increases. For example:
- Individuals taking opioid doses > 50 morphine milligram equivalents (MMEs) per day had twice the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking opioid doses > 90 (MMEs) per day had 10 times the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking an opioid for > 3 months (even at low doses) had 15 times the risk of addiction to those taking opioids for < 3 months.

CONTINUED ON NEXT PAGE
APPENDIX 1: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM
INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY
PRIOR AUTHORIZATION REQUEST FORM

Today’s Date

Note: This form must be completed by the prescribing provider.
**All sections must be completed or the request will be denied.**

<table>
<thead>
<tr>
<th>Patient’s Medicaid #</th>
<th>Date of Birth / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Name</td>
<td>Prescriber’s Name</td>
</tr>
<tr>
<td>Prescriber’s IN License #</td>
<td>Specialty</td>
</tr>
<tr>
<td>Prescriber’s NPI #</td>
<td>Prescriber’s Signature: <strong>Required below within attestation section.</strong></td>
</tr>
<tr>
<td>Return Fax #</td>
<td>Return Phone #</td>
</tr>
</tbody>
</table>

PA is required for the following:
- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).

<table>
<thead>
<tr>
<th>Benzodiazepine Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
### Opioid Agent(s) Prescriber Name* Quantity Dosage Regimen/Duration

*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:

- Are you requesting PA for: Benzodiazepine Agent(s) ☐ Opioid Agent(s) ☐ Both ☐
- Is/are the other prescriber(s) aware of the request for concurrent therapy? □ Yes □ No
- Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? □ Yes □ No

### PA Requirements:

Patient diagnosis/diagnoses for use of benzodiazepine therapy:

Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Do you plan to continue benzodiazepine therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Patient diagnosis/diagnoses for use of opioid therapy:

Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, __________________________________________, hereby attest to the following:

(Prescriber Name)

• The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
• I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
• If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
• I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber Signature: ______________________________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**

CONFIDENTIAL INFORMATION
This facsimile transmission (and attachments) may contain protected health information from the Indiana Health Coverage Programs (IHCP), which is intended only for the use of the individual or entity named in this transmission sheet. Any unintended recipient is hereby notified that the information is privileged and confidential, and any use, disclosure, or reproduction of this information is prohibited.
METHADONE

REFERENCES

- Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016; 65(1);1-49. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

CONTINUED ON NEXT PAGE
METHADONE

REFERENCES (CONTINUED)

- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).
GUIDELINES FOR USE

The guideline named METHOTREXATE ORAL SOLUTION (Xatmep) requires a diagnosis of acute lymphoblastic leukemia (ALL) or polyarticular juvenile idiopathic arthritis (PJIA). The following criteria must also be met:

For patients with acute lymphoblastic leukemia (ALL), approval requires:
- Patient is < 18 years of age
- For patients ≥ 12 years old, patient must have previous trial of or contraindication to oral methotrexate tablet
- The requested medication will be used as part of a combination chemotherapy maintenance regimen

For patients with polyarticular juvenile idiopathic arthritis (PJIA), approval requires:
- Patient is < 18 years of age
- For patients ≥ 12 years old, patient must have previous trial of or contraindication to oral methotrexate tablet
- The patient has an insufficient therapeutic response or was intolerant to a minimum 2-month trial of first-line therapy (i.e., full dose non-steroidal anti-inflammatory agent)

CONTINUED ON NEXT PAGE
RATIONALE
Promote appropriate utilization of Xatmep based on FDA approved indication.

FDA APPROVED INDICATIONS
Xatmep is a folic acid analog metabolic inhibitor indicated for:
- The treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as a component of a combination chemotherapy maintenance regimen
- Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

DOSAGE AND ADMINISTRATION
Xatmep is intended for oral use only. Use another formulation of methotrexate for alternative dosing in patients who require dosing via other routes of administration. Instruct patients and caregivers that the recommended dose should be taken weekly, as directed, and that mistaken daily use of the recommended dose has led to fatal toxicity.

Acute Lymphoblastic Leukemia (ALL)
The recommended starting dose of Xatmep, in multi-agent combination chemotherapy maintenance regimens, is 20 mg/m² given one time weekly. After initiating Xatmep, continuation of appropriate dosing requires periodic monitoring of absolute neutrophil count (ANC) and platelet count to assure sufficient drug exposure (that is to maintain ANC at a desirable level) and to adjust for excessive hematological toxicity.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)
The recommended starting dose of Xatmep is 10 mg/m² given one time weekly. Dosages should be tailored to the individual patient and adjusted gradually to achieve an optimal response. Although there is experience with doses up to 30 mg/m²/week in pediatric patients, doses greater than 20 mg/m²/week may result in a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression. Doses between 20 and 30 mg/m²/week (0.65 to 1 mg/kg/week) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered by an alternative route using another formulation. Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more. Certain side effects such as mouth sores may be reduced by folate supplementation with methotrexate in PJIA.

REFERENCES
GUIDELINES FOR USE

Our guideline for METHYLNALTREXONE (Relistor) requires that the patient have a diagnosis of opioid-induced constipation. For patients receiving palliative care for an advanced (terminal) illness, only Relistor injection may be approved. In addition, the following criteria must be met.

- **For patients with chronic non-cancer pain, approval requires all of the following criteria:**
  - The patient has been taking opioids for at least four weeks
  - The patient had a previous trial of or contraindication to naloxegol (Movantik) AND lubiprostone (Amitiza)

METHYLNALTREXONE

RATIONAL

Promote cost-effective and clinically appropriate utilization of methylnaltrexone for its FDA approved indications and dosing. In pivotal trials, methylnaltrexone was studied in patients with advanced illness with a life expectancy of less than 6 months who were receiving care to control their symptoms.

FDA APPROVED INDICATIONS

- Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.
- Treatment of opioid-induced constipation (OIC) in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.
- Limitation of Use: Use beyond four months has not been studied in the advanced illness population.

DOISING

**Opioid-induced constipation in adult patients with chronic non-cancer pain**

- The recommended dosage of Relistor tablets is 450 mg taken orally once daily in the morning.
- The recommended dosage of Relistor injection is 12 mg administered subcutaneously once daily.

**Opioid-induced constipation in adult patients with advanced illness**

- The pre-filled syringe is only for patients who require a Relistor injection dose of 8 mg or 12 mg. Use the vial for patients who require other doses of Relistor injection.
- The recommended dosage regimen is one administered subcutaneously every other day, as needed (see Table 1). Do not administer more frequently than one dose per 24-hour period.

Table 1. Weight-based dosing of Relistor injection and corresponding injection volume for adult patients with OIC and advanced illness

<table>
<thead>
<tr>
<th>Weight of adult patient</th>
<th>Subcutaneous dose</th>
<th>Injection volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 38 kg</td>
<td>0.15 mg/kg</td>
<td>See below*</td>
</tr>
<tr>
<td>38 kg to less than 62 kg</td>
<td>8 mg</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>62 kg to 114 kg</td>
<td>12 mg</td>
<td>0.6 mL</td>
</tr>
<tr>
<td>More than 114 kg</td>
<td>0.15 mg/kg</td>
<td>See below*</td>
</tr>
</tbody>
</table>

*Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.0075 and then rounding up the volume to the nearest 0.1 mL.
REFERENCES


Created: 05/15
Effective: 10/20/17
Client Approval: 09/26/17
P&T Approval: 05/15
GUIDELINES FOR USE

The guideline named MIFEPRISTONE (Korlym) requires a diagnosis of endogenous Cushing’s syndrome. In addition, the following criteria must be met:

- The patient also has a diagnosis of type 2 diabetes mellitus OR glucose intolerance
- Patient has failed surgical treatment for Cushing’s syndrome OR is not a candidate for surgery

MIFEPRISTONE

RATIONALE
To ensure appropriate use of Korlym.

FDA APPROVED INDICATIONS

- Korlym is a cortisol receptor antagonist indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing’s syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.
- Korlym should not be used for the treatment of diabetes type 2 unrelated to endogenous Cushing’s syndrome.

REFERENCE


Created: 06/15
Effective: 03/09/18
Client Approval: 02/19/18
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named MIDOSTAURIN (Rydapt) requires a diagnosis of newly diagnosed acute myeloid leukemia (AML), aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL). The following criteria must also be met:

For newly diagnosed acute myeloid leukemia (AML), approval requires all of the following:
- The patient is FLT3 mutation-positive as detected by an FDA-approved diagnostic test
- The requested medication will be used in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
- The requested medication will not be used as a single-agent induction therapy for the treatment of patients with AML

RATIONALE
Promote appropriate utilization of MIDOSTAURIN based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS
Rydapt is a kinase inhibitor indicated for the treatment of adult with:
- Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL)

CONTINUED ON NEXT PAGE
Limitations of Use:
Rydapt is not indicated as a single-agent induction therapy for the treatment of patients with AML.

DOSAGE AND ADMINISTRATION
Rydapt is available as 25 mg capsules. Rydapt should be taken twice daily with food. Rydapt capsules should not be opened or crushed.

Recommended Dosage in Acute Myeloid Leukemia
The recommended dose of Rydapt for patients with acute myeloid leukemia is 50 mg orally twice daily with food on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with high-dose cytarabine.

FLT3 mutation status must be reported using the FDA-approved, in-vitro companion diagnostic LeukoStrat® CDx FLT3 Mutation Assay to ensure correct selection of patients eligible to be treated with Rydapt.

Recommended Dosage in ASM, SM-AHN, and MCL
The recommended dose of Rydapt for patients with ASM, SM-AHN, and MCL is 100 mg orally twice daily with food. Continue treatment until disease progression or unacceptable toxicity occurs. Dose modifications for therapy-related toxicities can be found in the prescribing information.

REFERENCES
• Rydapt [Prescribing Information]. East Hanover, New Jersey: Novartis Pharmaceuticals; April 2017.
GUIDELINES FOR USE

The guideline named MIGALASTAT (GALAFOLD) requires a diagnosis of Fabry disease. In addition, the following criteria must be met.

- The patient is 18 years of age or older
- The patient has an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data

RATIONALE
To ensure appropriate use of Galafold (migalastat) consistent with FDA-approved indications.

FDA-APPROVED INDICATIONS
Galafold is an alpha-galactosidase A (a-Gal A) pharmacological chaperone indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data.

This indication is approved under accelerated approval based on reduction in kidney interstitial capillary cell globotriaosylceramide (KIC GL-3) substrate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION
Galafold is dosed at 123 mg orally once every other day at the same time of day. Galafold should not be taken on two consecutive days. Doses should be taken on an empty stomach. Food should not be consumed for at least two hours before and two hours after taking Galafold, to give a minimum 4-hour fast. However, clear liquids can be consumed during this fasting window.

REFERENCES

Created: 11/18
Effective: 11/23/18
Client Approval: 11/06/18
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires a diagnosis of type 1 Gaucher disease in patients 18 years of age or older for whom enzyme replacement therapy is not an option.

RATIONALE

Ensure that Zavesca is being used to treat patients with type 1 Gaucher disease.

FDA APPROVED INDICATION

ZAVESCA® is indicated for the treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access).

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/12
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

The guideline named MIPOMERSEN SODIUM (Kynamro) requires a diagnosis of homozygous familial hypercholesterolemia (HoFH). The following criteria must also be met:

- The diagnosis of homozygous familial hypercholesterolemia (HoFH) is determined by meeting ONE of the following criteria:
  - Simon Broome diagnostic criteria (definite)
  - Dutch Lipid Network criteria with a score of at least 8
  - A clinical diagnosis based on a history of an untreated LDL-cholesterol level greater than 500 mg/dL, in combination with either (1) xanthoma before 10 years of age OR (2) evidence of heterozygous familial hypercholesterolemia (HeFH) in both parents
- The agent is prescribed by or given in consultation with a cardiologist, endocrinologist, or lipidologist
- The patient has a LDL-cholesterol level greater than or equal to 70 mg/dL while on maximally tolerated drug treatment
- The patient has had a previous trial of Repatha (evolocumab) unless the patient lacks functional LDL receptors

For statin tolerant patients, approval also requires the following:

- The patient meets ONE of the following criteria:
  - The patient has been taking a high-intensity statin (i.e., atorvastatin 40-80 mg daily, rosuvastatin 20-40 mg daily) for a duration of at least 8 weeks, OR
  - The patient has been taking a maximally tolerated dose of any statin for a duration of at least 8 weeks given that the patient cannot tolerate a high-intensity statin (i.e., atorvastatin 40-80 mg daily, rosuvastatin 20-40 mg daily)
- The patient will continue statin treatment in combination with Kynamro

For statin intolerant patients, approval also requires ONE of the following:

- The patient has an absolute contraindication to statin therapy (e.g., active decompensated liver disease, nursing female, pregnancy or plans to become pregnant, hypersensitivity reaction)
- The patient has complete statin intolerance as defined by severe and intolerable adverse effects (e.g., creatine kinase elevation greater than or equal to 10 times the upper limit of normal, liver function test elevation greater than or equal to 3 times the upper limit of normal, rhabdomyolysis, severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group) that have occurred with trials of at least two separate statins and have improved with the discontinuation of each statin

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA

The guideline named MIPOMERSEN SODIUM (Kynamro) renewal requires that the patient has had at least 26 weeks of therapy, with a LDL reduction of at least 20% from baseline after Kynamro (mipomersen) therapy for 26 weeks. Patient must also be adherent to Kynamro (mipomersen) and statin therapy (or Kynamro and other lipid-lowering agent, if the patient is statin intolerant).

RATIONALE

To ensure appropriate use of Kynamro based on FDA approved indication dosing, and national treatment guidelines.

FDA APPROVED INDICATION

Kynamro (mipomersen) is indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Limitations of Use:

• The safety and effectiveness of Kynamro have not been established in patients with hypercholesterolemia who do not have HoFH.
• The effect of Kynamro on cardiovascular morbidity and mortality has not been determined.
• The use of Kynamro as an adjunct to LDL apheresis is not recommended.

DOSAGE AND ADMINISTRATION

The recommended dose of Kynamro is 200 mg once weekly as a subcutaneous injection.

Kynamro is intended for subcutaneous use only. Do not administer intramuscularly or intravenously. The injection should be given on the same day every week, but if a dose is missed, the injection should be given at least 3 days from the next weekly dose.

REFERENCES

• Kynamro (mipomersen) [Prescribing Information]. Cambridge, MA: Genzyme Corp.; May 2016.
GUIDELINES FOR USE

Our guideline for EVZIO requires current use of an opioid, a medical reason (other than rhinorrhea) why Narcan Nasal Spray cannot be used, and one of the following risk factors for overdose:

- History of emergency medical care involving opioid overdose
- History of substance abuse
- Daily prescription opioid doses ≥ 60 mg morphine equivalents
- Concomitant use with benzodiazepines, antidepressants, alcohol, or muscle relaxants
- Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma)
- Sleep apnea
- Renal impairment
- Chronic cirrhosis or hepatitis
- Mental illness (e.g., bipolar disorder, schizophrenia)
- Cognitive impairment

NALOXONE

RATIONALÉ

To ensure use of EVZIO is consistent with indication.

FDA APPROVED INDICATIONS

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

DOSSING AND ADMINISTRATION

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present. Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of EVZIO and its instructions for use. Each EVZIO autoinjector contains a single dose of naloxone, either as 0.4mg/0.4mL or 2mg/0.4mL. EVZIO is administered intramuscularly or subcutaneously into the thigh.

REFERENCES


Created: 04/16
Effective: 02/16/17
Client Approval: 02/02/17
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named NATALIZUMAB (Tysabri) requires a diagnosis of moderate to severe Crohn's disease or relapsing form of multiple sclerosis (MS). The following criteria must also be met:

For patients with moderate to severe Crohn's disease, approval requires:
- Therapy is initiated by or given in consultation with a gastroenterologist
- Previous trial of at least ONE of the following conventional agents: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
- The patient is 18 years of age or older
- Previous trial of the preferred formulary TNF (tumor necrosis factor) inhibitor: Cimzia

For patients with a relapsing form of multiple sclerosis (MS), approval requires:
- The patient is 18 years of age or older
- Previous trial of at least TWO preferred MS agents (oral or injectable): Aubagio, Avonex, Copaxone, Gilenya, Rebif, or Tecfidera. (Please note: other MS agents may also require prior authorization.)

RENEWAL CRITERIA

The guideline named NATALIZUMAB (Tysabri) renewal requires a diagnosis of moderate to severe Crohn's disease or relapsing form of multiple sclerosis. The following criteria must also be met:

Renewal for the diagnosis of moderate to severe Crohn's disease requires:
- Documentation that the patient has not required more than 3 months of corticosteroid use within the past 12 months to control their Crohn's disease while on Tysabri (natalizumab) OR
- Documentation that the patient has taper off corticosteroids during the first 24 weeks of Tysabri (natalizumab) therapy.

CONTINUED ON NEXT PAGE
RATIONAL
To promote formulary alternatives and ensure appropriate utilization of Tysabri per FDA approved
dosing and indication.

NOTE: Only prescribers registered in the TOUCH™ Prescribing Program may prescribe TYSABRI.

TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic
viral infection of the brain that usually leads to death or severe disability. Risk factors for the
development of PML include duration of therapy, prior use of immunosuppressants, and presence of
anti-JCV antibodies. These factors should be considered in the context of expected benefit when
initiating and continuing treatment with TYSABRI. Monitor patients, and withhold TYSABRI immediately
at the first sign or symptom suggestive of PML.

FDA APPROVED INDICATIONS
Multiple Sclerosis
TYSABRI is indicated as monotherapy for the treatment of patients with relapsing forms of multiple
sclerosis. Tysabri increases the risk of PML. When initiating and continuing treatment with Tysabri,
physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. See
important information regarding the risk of PML with TYSABRI.

Crohn's Disease
TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with
moderately to severely active Crohn’s disease (CD) with evidence of inflammation who have had an
inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.
TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine,
azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α.

DOSING
Multiple Sclerosis
The recommended dose of TYSABRI for multiple sclerosis is 300 mg intravenous infusion over one
hour every four weeks.

Crohn's Disease
The recommended dose of TYSABRI for Crohn’s disease is 300 mg intravenous infusion over one hour
every four weeks. TYSABRI should not be used with concomitant immunosuppressants (e.g., 6-
mercaptopurine, azathioprine, cyclosporine, or methotrexate) or concomitant inhibitors of TNF-α.
Aminosalicylates may be continued during treatment with TYSABRI.
NATALIZUMAB

FDA APPROVED INDICATIONS (CONTINUED)

If the patient with Crohn’s disease has not experienced therapeutic benefit by 12 weeks of induction therapy, discontinue TYSABRI. For patients with Crohn’s disease that start TYSABRI while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of TYSABRI has occurred; if the patient with Crohn’s disease cannot be tapered off oral corticosteroids within six months of starting TYSABRI, discontinue TYSABRI. Other than the initial six-month taper, prescribers should consider discontinuing TYSABRI for patients who require additional steroid use that exceeds three months in a calendar year to control their Crohn’s disease.

REFERENCES

- Yoursry T et al., Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. NEJM 2006; 354:924-33.
NERATINIB

GUIDELINES FOR USE

The guideline named NERATINIB (Nerlynx) requires a diagnosis of breast cancer. The following criteria must also be met:

- The patient is 18 years of age or older
- The tumor is early-stage (stage I-II)
- The tumor is HER2-overexpressed/amplified (i.e., HER2-positive)
- The requested medication will be used as extended adjuvant therapy following Herceptin- (trastuzumab-) based therapy

RATIONALE

Promote appropriate utilization of NERATINIB based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS

Nerlynx is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

DOSAGE AND ADMINISTRATION

Nerlynx is available as 40 mg tablets. Nerlynx should be taken once daily with food. Nerlynx tablets should not be crushed, chewed, or split prior to swallowing.

The recommended dose of Nerlynx is 240 mg (6 tablets) orally once daily with food, continuously for one year.

Antidiarrheal prophylaxis is recommended during the first 8 weeks (56 days) of treatment and should be initiated with the first dose of Nerlynx. Patients should be instructed to take Imodium (loperamide) as outlined in Table 1 and adjust dose to maintain 1-2 bowel movements per day. Additional antidiarrheal agents, Nerlynx dose interruptions, and dose reductions may be required to manage diarrhea in patients with loperamide-refractory diarrhea. Dose modifications for diarrhea, other toxicities, hepatic impairment, and drug interactions may be found in the Nerlynx prescribing information.

<table>
<thead>
<tr>
<th>Time on Nerlynx</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-2 (days 1 - 14)</td>
<td>4 mg</td>
<td>Three times daily</td>
</tr>
<tr>
<td>Weeks 3-8 (days 15 - 56)</td>
<td>4 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Weeks 9-52 (days 57 - 365)</td>
<td>4 mg</td>
<td>As needed (not to exceed 16 mg per day)</td>
</tr>
</tbody>
</table>

REFERENCES


Created: 08/17
Effective: 02/23/18
Client Approval: 09/01/17
P&T Approval: N/A
The guideline named **NILOTINIB (Tasigna)** requires a diagnosis of newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, OR Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic or accelerated phase. In addition, the following criteria must be met:

**For patients with newly diagnosed Ph+ CML in chronic phase,** approval requires:
- The patient is 1 year of age or older

**For patients with resistant or intolerant Ph+ CML in accelerated phase,** approval requires:
- The patient is 18 years of age or older
- The patient is resistant or intolerant to prior therapy including imatinib (Gleevec)
- The patient has a Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) mutational analysis confirming that the following mutations are NOT present: T315I, Y253H, E255K/V, or F359V/C/I

**For patients with resistant or intolerant Ph+ CML in chronic phase,** approval requires:
- The patient has a Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) mutational analysis confirming that the following mutations are NOT present: T315I, Y253H, E255K/V, or F359V/C/I
- The patient must also meet **ONE** of the following criteria:
  - The patient is between 1 and 17 years of age AND has resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib)
  - The patient is 18 years of age or older AND has resistance or intolerance to prior therapy including imatinib (Gleevec)

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**NILOTINIB RATIONALE**

Ensure appropriate utilization of nilotinib based on its FDA approved indications.

**FDA APPROVED INDICATIONS**

Tasigna is a kinase inhibitor indicated for the following:
- Newly diagnosed adults and pediatric patients with greater than or equal to 1 year of age with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase.
- Adult patients with chronic phase (CP) or accelerated phase (AP) Philadelphia chromosome-positive chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.
- Pediatric patients greater than or equal to 1 year of age with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy
NILOTINIB

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION
Tasigna should be taken twice daily at approximately 12-hour intervals and must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. Advise patients to swallow the capsules whole with water.

For patients who are unable to swallow capsules, the contents of each capsule may be dispersed in 1 teaspoon of applesauce (puréed apple). The mixture should be taken immediately (within 15 minutes) and should not be stored for future use.

Adult patients with Newly diagnosed Ph+ CML in chronic phase
• The recommended dose of Tasigna is 300 mg orally twice daily.

Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP
• The recommended dose of Tasigna is 400 mg orally twice daily.

Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP
• The recommended dose of Tasigna for pediatric patients is 230 mg/m² orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).
• If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

REFERENCE

Created: 06/15
Effective: 06/01/18
Client Approval: 05/04/18
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires that Nymalize be used in patients who have had a subarachnoid hemorrhage (SAH) from a ruptured intracranial berry aneurysm within the past 21 days. Nymalize has comparable bioavailability to nimodipine oral capsules and should only be used in patients who are unable to swallow nimodipine oral capsules.

NIMODIPINE SOLUTION

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIMODIPINE</td>
<td>NYMALIZE</td>
<td></td>
<td>34794</td>
<td></td>
</tr>
</tbody>
</table>

RATIONALE

Ensure cost-effective use of Nymalize with FDA approved indication and dosing.

Treatment courses of Nymalize are started within 96 hours of the onset of SAH. The approved dosage is 20 mL (60 mg) given enterally (orally or via feeding tube) every 4 hours for 21 consecutive days. The dosage can be reduced to 10 mL (30mg) every 4 hours in patients with cirrhosis.

Patients who require administration through a feeding tube should use the supplied oral syringe labeled “ORAL USE ONLY.” After each dose is administered, the syringe should be refilled with 20 mL of 0.9% saline solution in order to flush any remaining contents from nasogastric or gastric tube into the stomach. Nymalize should not be administered intravenously or using other parenteral routes.

Nymalize (nimodipine oral solution) joins nimodipine oral, liquid-filled, gel capsules in the reduction of poor outcomes associated with vasospasm, a complication that can follow SAH. Subarachnoid hemorrhage is a type of stroke with serious, life threatening bleeding that evades the subarachnoid space (the area between the brain and the thin tissues that cover the brain). It is believed that during the lysis of subarachnoid blood clots, spasmogenic substances are generated which cause arterial narrowing with subsequent ischemia and infarction. Typically beginning no earlier than day three after hemorrhage and reaching a peak at days seven to eight, clinical or symptomatic vasospasm is seen in 20 to 30 percent of patients with SAH. Symptomatic vasospasm is associated with a clinical decline in neurologic status and may not be identifiable on cerebral angiography. It is the leading cause of death and disability after aneurysm rupture. However, it is important to note that nimodipine does not prevent or treat the vasospasm itself but instead reduces the risk for poor outcomes. The mechanism behind how nimodipine works to prevent further disability is uncertain. A potential advantage of Nymalize over nimodipine gel capsules is that it may reduce the serious and sometimes fatal medication errors due to intravenous (IV) injection of the liquid contents of oral nimodipine capsules. Often patients with SAH are unable to swallow safely and may subsequently have feeding tubes placed; there have been at least 25 instances where the liquid from the nimodipine capsule was extracted with a syringe and erroneously administered intravenously instead of enterally. This medication error has resulted in five reported deaths and five near-death events. In efforts to minimize the risk for accidental intravenous administration, many hospital pharmacies extemporaneously prepare a liquid formulation from the capsules and dispense the product in an oral syringe labeled “ORAL USE ONLY.”

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)
Some hospitals that employ computerized order entry systems have utilized its potential to alert health care providers on the proper administration technique of nimodipine.

The safety and efficacy of Nymalize (nimodipine oral solution) in the treatment of patients with SAH is based on adequate and well-controlled studies of nimodipine oral capsules in patients with SAH. Nymalize (nimodipine oral solution) has comparable bioavailability to nimodipine oral capsules.

Nimodipine has been shown in 4 randomized, double-blind, placebo-controlled trials to reduce the severity of neurological deficits resulting from vasospasm in patients who have had a recent SAH (Studies 1, 2, 3, and 4). The trials used doses ranging from 20-30 mg to 90 mg every 4 hours, with drug given for 21 days in 3 studies, and for at least 18 days in the other. A dose-ranging study comparing 30 mg, 60 mg, and 90 mg doses found a generally low rate of spasm-related neurological deficits but no dose response relationship. Three of the four trials followed patients for 3-6 months. Three of the trials studied less severe cases, with all or most patients in Hunt and Hess Grades I - III (essentially free of focal deficits after the initial bleed). Study 4 studied much sicker patients with Hunt and Hess Grades III - V.

Besides sharing a similar design, Studies 1 and 2 had a relatively unimpaired study population who were randomized to nimodipine or placebo. In each, a judgment was made as to whether any late-developing deficit was due to spasm or other causes. Deficits subsequently were graded on severity. As shown below, both studies showed significantly fewer severe deficits due to spasm in the nimodipine group (referenced in package insert as Table 2). No effect was seen on deficits not related to spasm. In addition, Study 2 showed fewer spasm-related deficits of all severities.

### Deficits in Patients with Hunt and Hess Grades I to III in Study 1 and Study 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Grade*</th>
<th>Treatment</th>
<th>Patients</th>
<th>Number Analyzed</th>
<th>Number of Patients with Any Deficit Due to Spasm</th>
<th>Numbers with Sever Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>I-III</td>
<td>Nimodipine 20-30 mg every 4 hours</td>
<td>56</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>60</td>
<td>16</td>
<td>8**</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>I-III</td>
<td>Nimodipine 60 mg every 4 hours</td>
<td>31</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>39</td>
<td>11</td>
<td>10**</td>
<td></td>
</tr>
</tbody>
</table>

*Hunt and Hess Grade
** p=0.03

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

Study 3 was a 554-patient trial that included SAH patients with all grades of severity (89% were in Hunt and Hess Grades I-III). In Study 3, patients were treated with placebo or 60 mg of nimodipine every 4 hours. Outcomes were not defined as spasm related or pertaining to other causes. However, there was a significant reduction in the overall rate of brain infarction and severely disabling neurological outcome at 3 months. Study 4 enrolled much sicker patients, (Hunt and Hess Grades III-V), who had a high rate of death and disability, and used a dose of 90 mg every 4 hours, but was otherwise similar to Study 1 and Study 2. Delayed ischemic deficits were analyzed and many were due to spasm. Results (referenced in the package insert as Table 4) presented below show a significant reduction in spasm-related deficits.

<table>
<thead>
<tr>
<th>Neurological Ischemic Deficits with Hunt and Hess Grades III to V in Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delayed Ischemic Deficits (DID)</strong></td>
</tr>
<tr>
<td>Nimodipine 90 mg every 4 hours n (%)</td>
</tr>
<tr>
<td>DID Spasm Alone</td>
</tr>
<tr>
<td>DID Spasm Contributing</td>
</tr>
<tr>
<td>DID Without Spasm</td>
</tr>
<tr>
<td>No DID</td>
</tr>
</tbody>
</table>

*p = 0.001, Nimodipine vs. placebo

To analyze patients with Hunt and Hess Grades IV or V, data from Study 3 and Study 4 was combined. Nimodipine tends to improve good recovery of SAH patients with poor neurological status post-ictus, while decreasing the numbers with severe disability and vegetative survival. Pooled results are shown below (referenced in the package insert as Table 5).

<table>
<thead>
<tr>
<th>Glasgow Outcome *</th>
<th>Nimodipine (n=87)</th>
<th>Placebo (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Recovery</td>
<td>22 (25.3%)</td>
<td>11 (10.9%)</td>
</tr>
<tr>
<td>Moderate Disability</td>
<td>8 (9.2%)</td>
<td>12 (11.9%)</td>
</tr>
<tr>
<td>Sever Disability</td>
<td>6 (6.9%)</td>
<td>15 (14.9%)</td>
</tr>
<tr>
<td>Vegetative Survival</td>
<td>4 (4.6%)</td>
<td>9 (8.9%)</td>
</tr>
<tr>
<td>Death</td>
<td>47 (54.0%)</td>
<td>54 (53.5%)</td>
</tr>
</tbody>
</table>

*p = 0.001, Nimodipine vs. placebo

FDA APPROVED INDICATIONS

Nymalize is a dihydropyridine calcium channel blocker indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V).

CONTINUED ON NEXT PAGE
NIMODIPINE SOLUTION

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/13
**NINTEDANIB**

<table>
<thead>
<tr>
<th>Generic</th>
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<td>NINTEDANIB</td>
<td>OFEV</td>
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**GUIDELINES FOR USE**

Our guideline for **NINTEDANIB** requires a diagnosis of idiopathic pulmonary fibrosis (IPF). IPF is defined by the American Thoracic Society with the following criteria: a) Exclusion of other known causes of interstitial lung disease (ILD) (e.g., connective tissue disease, drug toxicity, asbestos or beryllium exposure, hypersensitivity pneumonitis, systemic sclerosis, rheumatoid arthritis, radiation, sarcoidosis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV) infection, viral hepatitis, or cancer) **AND** b) The presence of usual interstitial pneumonia (UIP) pattern as evidenced by high-resolution computed tomography (HRCT) alone or via a combination of surgical lung biopsy and HRCT. In addition, our guideline requires:

- treatment is prescribed by or in consultation with a pulmonologist
- patient must obtain liver function tests prior to the start of NINTEDANIB
- patient has a predicted forced vital capacity (FVC) of at least 50%, and patient must obtain liver function test prior to the start of nintedanib

**RATIONALE**

Promote appropriate utilization of Ofev based on FDA approved indication and dosage.

Ofev (NINTEDANIB) is one of the first drugs to be approved by the FDA to treat idiopathic pulmonary fibrosis (IPF). Esbriet (pirfenidone), the other agent for the treatment of IPF, was also approved on the same day. These two drugs were granted Breakthrough Therapy Designation as well as Orphan Drug status since there are no other drugs to date for the treatment of IPF, a disease that affects an estimated 100,000 people (mostly adults over the age of 40) in the United States. IPF is a chronic, progressive disorder of the lower respiratory tract in which lung tissue becomes scarred or fibrotic over time. As a result, patients with IPF experience shortness of breath, cough, and difficulty participating in everyday physical activities.

The American Thoracic Society guidelines state the diagnosis of IPF requires:

- a) Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)
- b) The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy
- c) Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

There is no cure for IPF; many people live only about 3 to 5 years, with the most common cause of death related to IPF being respiratory failure. The exact cause of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

**CONTINUED ON NEXT PAGE**
RATIONAL (CONTINUED)

Treatment options for IPF have been extremely limited, mainly consisting of supportive care (e.g., oxygen therapy, pulmonary rehabilitation) and lung transplantation. Systemic glucocorticoid monotherapy, combination therapy with azathioprine, prednisone, and N-acetylcysteine, and monotherapy with N-acetylcysteine have been tried, but were unsuccessful in demonstrating efficacy and may in fact cause potential harm. Many other pharmacological treatments (e.g.; sildenafil, endothelin receptor antagonist, TNFs and chemotherapeutic agents) have been studied in IPF but were found to be ineffective or have inconclusive evidence to routinely support their use in IPF. The approval of Ofev provides a new treatment option that may slow disease progression for patients with IPF. Ofev is a kinase inhibitor that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Ofev has been shown to inhibit platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR) which are associated with IPF pathogenesis.

Liver function tests (ALT, AST, and bilirubin) should be conducted prior to initiation of treatment and monthly for 3 months, and every 3 months thereafter and as clinically indicated. In clinical trials, Ofev was associated with elevations of liver enzymes that were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. Ofev also associated with increases in bilirubin.

Ofev is classified as a pregnancy category D and can cause fetal harm when administered to pregnant women. Women of childbearing age should avoid becoming pregnant during treatment with Ofev and should be advised to use adequate contraception during and at least 3 months after the last dose of Ofev.

Other warnings and precautions include gastrointestinal distress, gastrointestinal perforation, arterial thromboembolic events and increased risk of bleeding.

Most common adverse reactions (≥5%) of Ofev treated patients and more commonly than placebo are: diarrhea (62% vs. 18%), nausea (24% vs. 7%), abdominal pain (15% vs. 6%), vomiting (12% vs. 3%), liver enzyme elevation (14% vs. 3%), decreased appetite (11% vs. 5%), headache (8% vs. 5%), weight decreased (10% vs. 3%), and hypertension (5% vs. 4%).

DOSAGE

The recommended dosage of Ofev is 150 mg twice daily administered approximately 12 hours apart. Do not exceed the recommended maximum daily dosage of 300 mg. If a dose of Ofev is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose.

Ofev capsules should be taken with food and swallowed whole with liquid. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known.

CONTINUED ON NEXT PAGE
DOSAGE (CONTINUED)

Dose reduction (100mg twice daily) or temporary interruption maybe necessary for management of adverse events until the specific adverse reaction resolves to levels that allow continuation of therapy. If a patient cannot tolerate 100 mg twice daily treatment with Ofev should be discontinued. In patients with aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce Ofev to 100 mg twice daily. Discontinue Ofev for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

FDA APPROVED INDICATION
Ofev is a kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named **NITISINONE (Orfadin, Nityr)** requires a documented diagnosis of hereditary tyrosinemia type 1 (HT-1) as confirmed by elevated urinary or plasma succinylacetone (SA) levels or a mutation in the fumarylacetoacetate hydrolase (FAH) gene. In addition, the following criteria must also be met:

- The medication must be prescribed by or given in consultation with a prescriber specializing in inherited metabolic diseases.
- The patient must be counseled on maintaining dietary restriction of tyrosine and phenylalanine.
- For requests for Orfadin capsules, the patient must have tried Nityr tablets.
- For requests for Orfadin oral suspension, the patient must have tried Orfadin capsules or Nityr tablets. For patients who have difficulties swallowing capsules, Orfadin capsules may be opened and the contents suspended in a small amount of water, formula, or applesauce immediately before use.

RENEWAL CRITERIA

The renewal guideline named **NITISINONE (Orfadin, Nityr)** requires a diagnosis of hereditary tyrosinemia type 1 (HT-1). In addition, the following renewal criterion must be met:

- The patient's urinary or plasma succinylacetone (SA) levels have decreased from baseline while on treatment with nitisinone.

NITISINONE

RATIONALE

Promote appropriate utilization of **NITISINONE** based on FDA approved indication.

FDA APPROVED INDICATION

Orfadin (nitisinone) is a 4-hydroxyphenylpyruvate dioxygenase inhibitor indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Nityr is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

CONTINUED ON NEXT PAGE
DOSAGE

Recommended Dosage:
- The recommended initial dosage is 0.5 mg/kg orally twice daily.
- Titrate the dose based on biochemical and/or chemical response, as described in the full prescribing information.
- The maximum dosage is 1 mg/kg orally twice daily.

Preparation and Administration Instructions for Orfadin:
- For instructions on preparing, measuring and administering the oral suspension, see the full prescribing information.
- Maintain dietary restriction of tyrosine and phenylalanine.
- Take Orfadin capsules at least one hour before, or two hours after a meal.
- For patients who have difficulties swallowing capsules and who are intolerant to the oral suspension, the capsules may be opened and the contents suspended in a small amount of water, formula or applesauce immediately before use.
- Take Orfadin oral suspension without regard to meals.

Preparation and Administration Instructions for Nityr:
- Take with or without food.
- For patients who have difficulties swallowing intact tablets, including pediatric patients, the tablets can be disintegrated in water and administered using an oral syringe. If patients can swallow semi-solid foods, the tablets can also be crushed and mixed with applesauce. For preparation and administration instructions, see the full prescribing information.

DOSAGE FORMS AND STRENGTHS

Orfadin:
- Capsules: 2 mg, 5 mg, 10 mg, 20 mg
- Oral suspension: 4 mg/mL

Nityr:
- Tablets: 2 mg, 5 mg, 10 mg

REFERENCES

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline for OBETICHOLIC ACID (Ocaliva) requires a diagnosis of primary biliary cholangitis, as confirmed by TWO of the following criteria:

- An alkaline phosphatase level of at least 1.5 times the upper limit of normal.
- The presence of antimitochondrial antibodies at a titer of 1:40 or higher.
- Histologic evidence of non-suppurative destructive cholangitis and destruction of interlobular bile ducts.

The following must also be met:

- The patient is at least 18 years of age and older.
- The requested agent will be used in combination with ursodeoxycholic acid (e.g., Ursodiol, Urso 250, Urso Forte) in adults with an inadequate response to ursodeoxycholic acid at a dosage of 13-15 mg/kg/day for at least 1 year, OR as monotherapy in adults unable to tolerate ursodeoxycholic acid.
- The patient does not have complete biliary obstruction.
- The medication is being prescribed by or in consultation with a gastroenterologist or hepatologist.

RENEWAL CRITERIA

The renewal guideline for OBETICHOLIC ACID (Ocaliva) requires a diagnosis of primary biliary cholangitis and meet ALL of the following: the patient's alkaline phosphatase levels are less than 1.67-times the upper limit of normal OR have decreased by at least 15% from baseline while on treatment with obeticholic acid. The following criteria must also be met:

- The patient has not developed complete biliary obstruction.

CONTINUED ON NEXT PAGE
OBETICHOLIC ACID

RATIONALE
Promote appropriate utilization of OBETICHOLIC ACID based on FDA approved indication.

DOSEAGE
- **Starting Dosage:** The recommended starting dosage of Ocaliva is 5 mg orally once daily in adults who have not achieved an adequate response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA.
- **Dosage Titration:** If adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of Ocaliva 5 mg once daily and the patient is tolerating Ocaliva, increase dosage to 10 mg once daily.
- **Maximum Dosage:** 10 mg once daily
- **Administration Instructions:** Take with or without food. For patients taking bile acid binding resins (e.g., cholestyramine, colestipol, colesevelam), take Ocaliva at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible.

FDA APPROVED INDICATION
Ocaliva (obeticholic acid), a farnesoid X receptor (FXR) agonist, is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

REFERENCES

Created: 05/17
Effective: 07/01/17
Client Approval: 05/02/17
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named OCRELIZUMAB (Ocrevus) requires a diagnosis of primary progressive multiple sclerosis (PPMS) or a relapsing form of multiple sclerosis (MS). In addition, the following criteria must be met:

For the diagnosis of primary progressive multiple sclerosis (PPMS), approval requires:
- The patient is 18 years of age or older

For the diagnosis of a relapsing form of multiple sclerosis (MS), approval requires:
- The patient is 18 years of age or older
- The patient meets ONE of the following:
  - The patient had a previous trial of any TWO of the following preferred MS agents: Aubagio, Avonex, Copaxone, Gilenya, Rebif, or Tecfidera
  - Physician attestation that the patient shows signs of severe disease requiring high-efficacy disease modifying therapy (DMT) (e.g., high lesion volume and/or count, walking disability, or rapid decline)

RENEWAL CRITERIA

The guideline named OCRELIZUMAB (Ocrevus) renewal requires patient age of 18 years or older AND a diagnosis of primary progressive multiple sclerosis (PPMS) or a relapsing form of multiple sclerosis (MS).

RATIONALE
Promote appropriate utilization of Ocrevus (ocrelizumab) based on FDA approved indication and dosing.

FDA APPROVED INDICATIONS
Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of:
- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

**DOSAGE AND ADMINISTRATION**
Administer Ocrevus under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions.

- **Initial dose:** 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion.
- **Subsequent doses:** single 600 mg intravenous infusion every 6 months.

**HOW SUPPLIED**
Injection: 300 mg/10 mL (30 mg/mL) in a single-dose vial.

**REFERENCES**

Created: 02/18  
Effective: 11/29/19  
Client Approval: 11/06/19  
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Approval for Sandostatin requires a diagnosis of acromegaly with the failure to be treated with one of the following or the inability to be treated with any of the following: surgical resection, pituitary irradiation, or bromocriptine mesylate at maximally tolerated doses; a diagnosis of carcinoid tumors; or a diagnosis of vasoactive intestinal peptide tumors.

RATIONALE

To ensure appropriate use of Sandostatin and Sandostatin LAR based on FDA approved indications and dosing.

FDA APPROVED INDICATIONS

Sandostatin mimics natural somatostatin and is indicated:

- to reduce blood levels of growth hormone and IGF-I (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses
- for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.
- for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors
FDA APPROVED INDICATIONS (CONTINUED)

Sandostatin LAR is indicated for treatment in patients who have responded to and tolerated Sandostatin subcutaneous injection for acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, or profuse watery diarrhea associated with VIP-secreting tumors

INITIAL DOSAGE

Acromegaly: SubQ: Initial 50mcg SubQ, IV 3 times per day. IM Depot: 20mg IM Depot intraglutelally every 4 weeks for 3 months.

Carcinoid Tumors: SubQ: 100-600mcg/day SubQ, IV in 2 to 4 divided doses for initial 2 weeks. IM Depot: 20mg IM intraglutelally every 4 weeks for 2 months.

Vasoactive Intestinal Peptide Tumors: SubQ: 200-300mcg/day in 2 to 4 divided doses for initial 2 weeks. IM Depot: 20mg IM Depot intraglutelally every 4 weeks for 2 months.

DOSEAGE ADJUSTMENTS

Acromegaly

• SubQ: titrate initial 50mcg 3 times/day to achieve growth hormone levels <5ng/mL or IGF-I (somatostatin C) levels <1.9units/mL in males and <2.2 units/mL in females.
  o Should be withdrawn yearly for a 4-week interval (8 weeks for depot injection) in patients who have received irradiation.
• Depot dose adjustments: After 3 months of depot injections, the dosage may be continued or modified as follows:
  o GH ≤1 ng/mL, IGF-1 normal, and symptoms controlled: Reduce octreotide depot to 10 mg IM every 4 weeks
  o GH ≤2.5 ng/mL, IGF-1 normal, and symptoms controlled: Maintain octreotide depot at 20 mg IM every 4 weeks
  o GH >2.5 ng/mL, IGF-1 elevated, and/or symptoms uncontrolled: Increase octreotide depot to 30 mg IM every 4 weeks

Carcinoid tumors

• After 2 months of depot injections, the dosage may be continued or modified as follows:
  o Increase to 30 mg IM every 4 weeks if symptoms are inadequately controlled
  o Decrease to 10 mg IM every 4 weeks, for a trial period, if initially responsive to 20 mg dose
  o Dosage >30 mg is not recommended

Vasoactive intestinal peptide tumors

• After 2 months of depot injections, the dosage may be continued or modified as follows:
  o Increase to 30 mg IM every 4 weeks if symptoms are inadequately controlled
  o Decrease to 10 mg IM every 4 weeks, for a trial period, if initially responsive to 20 mg dose
  o Dosage >30 mg is not recommended

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OCTREOTIDE

FDA APPROVED INDICATIONS (CONTINUED)

HOW SUPPLIED
Sandostatin® (octreotide acetate) Injection is available in 1 mL ampules and 5-mL multi-dose vials as follows:
Ampules
- 50 mcg/mL octreotide (as acetate), package of 10 ampules
- 100 mcg/mL octreotide (as acetate), package of 10 ampules
- 500 mcg/mL octreotide (as acetate), package of 10 ampules
Multi-Dose Vials
- 200 mcg/mL octreotide (as acetate), box of one
- 1000 mcg/mL octreotide (as acetate), box of one

Sandostatin LAR Depot is available in single-use kits containing a 6-mL vial of 10 mg, 20 mg or 30 mg strength, a syringe containing 2 mL of diluent, one vial adapter, and one sterile safety injection needle.

REFERENCES
- Sandostatin LAR Depot (octreotide) [prescribing information]. East Hanover, NJ: Novartis; July 2016.

Created: 10/15
Effective: 11/23/18
Client Approval: 11/08/18
P&T Approval: 10/15
GUIDELINES FOR USE

Our guideline for OLAPARIB requires a diagnosis of advanced ovarian cancer, OR recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, OR advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, OR HER2-negative metastatic breast cancer. In addition, the following criteria must be met:

For patients with advanced ovarian cancer, approval requires:
- The requested medication will be used as monotherapy
- The patient has mutated BRCA genes as confirmed by an FDA-approved test such as BRACAnalysis CDx
- The patient has been treated with at least three prior lines of chemotherapy (e.g., paclitaxel, docetaxel, cisplatin, carboplatin)
- The patient is 18 years of age or greater

For patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, approval requires:
- The requested medication will be used as monotherapy
- The requested medication will be started no later than 8 weeks after the patient’s most recent platinum-containing regimen
- The patient is in complete or partial response to their most recent platinum based-chemotherapy
- The patient has completed at least 2 lines of platinum-based chemotherapy
- The requested medication will be used for maintenance treatment
- The patient is 18 years of age or greater

For patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, approval requires:
- The requested medication will be used as monotherapy
- The patient has mutated BRCA genes as confirmed by an FDA-approved test such as BRACAnalysis CDx
- The requested medication will be started no later than 8 weeks after the patient's first-line, platinum-containing regimen
- The patient is in complete or partial response to first-line, platinum based-chemotherapy
- The requested medication will be used for maintenance treatment
- The patient is 18 years of age or greater

(Denial text continued on next page)
OLAPARIB

GUIDELINES FOR USE (CONTINUED)

For patients with HER2-negative metastatic breast cancer, approval requires:
- The patient has deleterious or suspected deleterious germline BRCA mutation as confirmed by an FDA-approved test
- The patient has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting
- Patients with hormone receptor (HR)-positive breast cancer must have additional prior therapy with endocrine therapy or be considered inappropriate for endocrine therapy

RATIONALE
Promote appropriate utilization of OLAPARIB based on FDA approved indications.

FDA APPROVED INDICATION
- Lynparza is FDA approved for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
- Lynparza is FDA approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.
- Lynparza is FDA approved for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer for therapy based on an FDA-approved companion diagnostic for Lynparza.
- Lynparza is FDA approved for the treatment of patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

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OLAPARIB

DOSAGE AND ADMINISTRATION
The recommended dose is 300 mg (two 150 mg tablets) taken orally twice daily, with or without food, for a total daily dose of 600 mg. The tablets should be swallowed whole and should not be chewed, crushed, dissolved, or divided. Continue treatment until disease progression or unacceptable toxicity. When used for first-line maintenance treatment of BRCA-mutated advanced ovarian cancer, patients should be re-evaluated for treatment response at 2 years. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.

To manage adverse reactions, the dosage can be reduced to 250 mg (one 150 mg tablet and one 100 mg tablet) taken twice daily, for a total daily dose of 500 mg. If a further dose reduction is required, then reduce to 200 mg (two 100 mg tablets) taken twice daily, for a total daily dose of 400 mg.

If concurrent use with a CYP3A inhibitor cannot be avoided, reduce the Lynparza dose to 100 mg (one 100 mg tablet) taken twice daily for a strong CYP3A inhibitor or 150 mg (one 150 mg tablet) taken twice daily for a moderate CYP3A inhibitor.

In patients with moderate renal impairment (CrCl 31-50 mL/min) the recommended dose reduction is to 200 mg (two 100 mg tablets) twice daily, for a total daily dose of 400 mg. Patients with mild renal impairment (CLcr 51-80 mL/min) do not require an adjustment in Lynparza dosing.

REFERENCES

Created: 06/15
Effective: 09/13/19
Client Approval: 08/27/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named OMALIZUMAB (Xolair) requires a diagnosis of chronic idiopathic urticaria or moderate to severe persistent asthma. In addition, the following criteria must also be met:

For patients with chronic idiopathic urticaria (CIU), approval requires:
- The patient is 12 years of age or older
- The patient has tried at least THREE of the following for at least 2 weeks and still experiences hives on most days of the week:
  - High dose second generation H1 antihistamine (e.g., loratadine, fexofenadine, levocetirizine)
  - H2 receptor antagonist (e.g., ranitidine, famotidine)
  - Leukotriene receptor antagonist
  - High dose first generation H1 antihistamine (e.g., diphenhydramine, hydroxyzine)
  - Cyclosporine
- Treatment is prescribed by or given in consultation with a physician specializing in allergy or pulmonary medicine

For patients with moderate to severe persistent asthma, approval requires:
- The patient is 6 years of age or older
- The patient has a positive skin prick or RAST test to a perennial aeroallergen
- The patient has a documented baseline IgE serum level greater than or equal to 30 IU/mL
- The patient is currently adherent to a maximally tolerated inhaled corticosteroid plus at least one other maintenance medication (e.g., long-acting inhaled beta2-agonist, long-acting muscarinic antagonist, a leukotriene receptor antagonist, theophylline, or oral corticosteroid)
- The patient has experienced at least 2 asthma exacerbations within the past 12 months (exacerbation is defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days)
- The patient has ONE of the following:
  - Asthma Control Test (ACT) score of less than 20
  - Asthma Control Questionnaire (ACQ) score of at least 1.5
  - Asthma Therapy Assessment Questionnaire (ATAQ) score of at least 1
- Xolair will be used as add-on maintenance treatment
- The patient is not being concurrently treated with Dupixent or anti-IL5 asthma biologic (e.g., Nucala, Cinqair, Fasenra)
- Xolair is prescribed by or given in consultation with a physician specializing in allergy or pulmonary medicine

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OMALIZUMAB

GUIDELINES FOR USE

RENEWAL CRITERIA

Our guideline for OMALIZUMAB renewal requires a diagnosis of moderate to severe persistent asthma or chronic idiopathic urticaria. In addition, the following criteria must be met:

For moderate to severe persistent asthma, our guideline requires ALL of the following:

- The patient has experienced a reduction in asthma exacerbations (defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days) from baseline during the past 12 months of therapy.
- The patient has experienced an improvement in the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Asthma Therapy Assessment Questionnaire (ATAQ) score from baseline.
- The patient has decreased their total daily oral corticosteroid dose from baseline if the patient was on a maintenance regimen of oral corticosteroids prior to initiation of Xolair.

For chronic idiopathic urticaria, our guideline requires that the patient has experienced at least a 25% reduction in hives from their pre-Xolair baseline or that the patient been able to reduce their maintenance therapy medication (e.g., high dose second generation H1 antihistamine, H2 receptor antagonist, leukotriene receptor antagonist, high dose first generation H1 antihistamine, cyclosporine) dose from their pre-Xolair baseline.

RATIONALE

Ensure appropriate diagnostic and utilization criteria.

FDA APPROVED INDICATIONS

Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.

Adults and adolescents (6 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

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OMALIZUMAB

DOSAGE

**Chronic Idiopathic Urticaria:** Xolair 150 or 300 mg SC every 4 weeks. Dosing in CIU is not dependent on serum IgE level or body weight.

**Allergic Asthma:** Xolair 150 to 375 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts.

**Table 1**

Administration Every 4 Weeks
Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 4 Weeks for Adults and Adolescents 12 Years of Age and Older For Allergic Asthma

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE (IU/mL)</th>
<th>Body Weight (kg)</th>
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<tbody>
<tr>
<td></td>
<td>30-60</td>
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<td>≥ 30-100</td>
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<td>&gt; 300-400</td>
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<td>&gt; 400-500</td>
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<tr>
<td>&gt; 500-600</td>
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</tr>
</tbody>
</table>

SEE TABLE 2

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

Table 2
Administration Every 2 Weeks
Xolair Doses (milligrams) Administered by Subcutaneous Injection
Every 2 Weeks for Adults and Adolescents 12 Years of Age and Older
For Allergic Asthma

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE (IU/mL)</th>
<th>Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-60</td>
</tr>
<tr>
<td>≥ 30-100</td>
<td></td>
</tr>
<tr>
<td>&gt; 100-200</td>
<td></td>
</tr>
<tr>
<td>&gt; 200-300</td>
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<td>&gt; 300-400</td>
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<td>&gt; 400-500</td>
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<tr>
<td>&gt; 500-600</td>
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<tr>
<td>&gt; 600-700</td>
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</table>

SEE TABLE 1

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE (IU/mL)</th>
<th>Body Weight (kg)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
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</tr>
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</table>

Xolair Doses (milligrams) Administered by Subcutaneous Injection
Every 2 or 4 Weeks for Pediatric with Asthma
Who Begin Xolair Between Ages 6 to <12 Years

CONTINUED ON NEXT PAGE
REFERENCES


Created: 10/15
Effective: 01/01/20
Client Approval: 10/14/19
P&T Approval: N/A
## OPIOID AGENTS WITH PAST USE OF OPIOID DEPENDENCY AGENTS

<table>
<thead>
<tr>
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<th>GCN</th>
<th>Exception/Other</th>
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<td>FENTANYL-BUPIVACAINE-NS</td>
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<td>FENTANYL CITRATE-0.9 % NACL/PF</td>
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<tr>
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<tr>
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GPID ≠ 16051, 16060, 16063, 35166, 16070, 16052, 16062, 32719, 16054, 16071, 16053, 12939, 15868, 15869, 16078, 16212, 16213, 16640, 16641, 16642, 16643, 17189, 17191, 17192, 17193, 26490, 26494, 33158, 97508, 97534, 98135, 97535, 26492, 33159, 33162, 33164

BRAND ≠
GUIDELINES FOR USE

Our guideline for **OPIOID AGENTS** for patients with past use of opioid dependency agents requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid agent will be authorized and that opioid therapy is prescribed for less than or equal to 7 days.

Created: 08/15
Effective: 10/31/16
Client Approval: 10/21/16
P&T Approval: N/A
OSIMERTINIB

<table>
<thead>
<tr>
<th>Generic</th>
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<td>OSIMERTINIB</td>
<td>TAGRISSO</td>
<td>42803</td>
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</tr>
</tbody>
</table>

GUIDELINES FOR USE

Our guideline for OSIMERTINIB requires a diagnosis of an EGFR T790M or EGFR exon 19 deletions or exon 21 L858R mutation positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test. Patients with a positive T790M mutation must have had disease progression while on or after EGFR tyrosine kinase-inhibitor therapy (Tarceva [erlotinib], Iressa [gefitinib], or Gilotrif [afatinib dimaleate]) and not be currently receiving therapy with an EGFR tyrosine kinase-inhibitor.

RATIONALE

To ensure appropriate use of osimertinib (Tagrisso) consistent with FDA-approved indications.

DOSAGE

Recommended dose is 80 mg orally once daily, with or without food.

FDA-APPROVED INDICATIONS

Osimertinib (Tagrisso) is a kinase inhibitor indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, and for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

AVAILABLE STRENGTHS

- 40 mg tablets
- 80 mg tablets

REFERENCES

- Tagrisso [Prescribing Information]; Wilmington, DE: AstraZeneca Pharmaceuticals LP; April 2018.

Created: 01/16
Effective: 06/18/18
Client Approval: 05/29/18
P&T Approval: N/A
All requests for Ibrance (palbociclib) require review by a pharmacist prior to final approval.

GUIDELINES FOR USE

The guideline named PALBOCICLIB (Ibrance) requires a diagnosis of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. In addition, ONE of the following criteria must be met:

- Concurrent use with an aromatase inhibitor (i.e., anastrozole, letrozole, or exemestane) as initial endocrine based therapy in postmenopausal female patients
- Concurrent use with Faslodex (fulvestrant) in female patients who have experienced disease progression following endocrine therapy

CONTINUED ON NEXT PAGE
PALBOCICLIB

RATIONALE
Promote appropriate utilization of Ibrance based on FDA approved indication.

FDA APPROVED INDICATIONS
Ibrance is a kinase inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer in combination with:
- An aromatase inhibitor as initial endocrine based therapy in for postmenopausal women
- Fulvestrant in women with disease progression following endocrine therapy

DOSAGE
The recommended starting dose is 125 mg once daily taken with food for 21 days followed by 7 days off treatment (for complete 28 days cycle).

Ibrance capsules are taken orally with food in combination with the recommended dose of an aromatase inhibitor or fulvestrant.

Dosing interruption and/or dose reductions are recommended based on individual safety and tolerability.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended starting dose</td>
<td>125 mg/day</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>75 mg/day*</td>
</tr>
</tbody>
</table>

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

Avoid concomitant use of strong CYP3A inhibitors; if must be co-administered with strong CYP3A inhibitor reduce dose to 75 mg daily.

REFERENCES

Created: 05/15
Effective: 08/01/17
Client Approval: 07/07/17
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for PALIVIZUMAB requires that the patient is either less than 12 months old or less than 24 months at the start of respiratory syncytial virus (RSV) season. Additional guideline requirements apply.

For patients less than 12 months old, ONE of the following criteria must be met:

- Gestational age of less than 29 weeks
- Chronic lung disease of prematurity, as defined as gestational age of less than 32 weeks and requiring greater than 21% supplemental oxygen for at least the first 28 days after birth
- Profoundly immunocompromised during RSV season
- Solid-organ transplantation during RSV season
- Congenital heart disease conditions such as acyanotic heart disease requiring medication to control chronic heart failure, moderate to severe pulmonary hypertension, or cyanotic heart defect and medication made in consultation with a pediatric cardiologist
- Congenital abnormalities of the airways or neuromuscular disorder that compromises the handling of respiratory secretions
- American Navajo or American White Mount Apache infant, Alaska native infant born prematurely

For patients less than 24 months old, ONE of the following criteria must be met:

- Chronic lung disease of prematurity and require medical support (oxygen, bronchodilator, diuretic, or chronic steroid therapy) within 6 months prior to start of the second RSV season
- Solid-organ transplantation during RSV season
- Profoundly immunocompromised during RSV season.

RENEWAL CRITERIA

Our guideline for PALIVIZUMAB renewal requires that the patient is under 24 months of age and meets ONE of the following criteria:

- Patient underwent cardiopulmonary bypass surgery during RSV prophylaxis season, OR
- Patient has chronic lung disease of prematurity requiring medical support (for example, chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6 month period before the start of the second RSV season

CONTINUED ON NEXT PAGE
PALIVIZUMAB

RATIONALE
To ensure the optimal use of palivizumab in high-risk patients for the prophylaxis of RSV by following the most recent American Academy of Pediatrics guidelines for the use of palivizumab for the prevention of serious RSV infections. Variations in the onset and offset of the RSV season in different regions may affect the timing of palivizumab administration. A maximum of five monthly doses of palivizumab should be adequate for qualifying infants for most RSV seasons. RSV seasons within the continental United States may start in October/November and end in March/April.

The Indiana RSV Season is defined as November 1st through March 31st. The season may be extended at the discretion of the Office of Medicaid Policy and Planning (OMPP) based upon statewide virology data.

FDA APPROVED INDICATIONS
For the prevention of serious, lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease.

REFERENCES
- American Academy of Pediatrics, Subcommittee on Diagnosis and Management of Bronchiolitis. Pediatrics 2006; 118; 1774-1798.

Created: 01/16
Effective: 10/01/18
Client Approval: 08/22/18
P&T Approval: 3QTR
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for PAMIDRONATE (Aredia) requires that the patient have a diagnosis of moderate to severe hypercalcemia of malignancy, osteolytic bone metastases of breast cancer, osteolytic bone lesions of multiple myeloma, Paget's disease. Aredia will not be approved for use in hyperparathyroidism or non-tumor-related hypercalcemia. The following criteria must also be met:

For patients with a diagnosis of Paget's disease, approval requires:
  • Previous trial of or contraindication to an oral bisphosphonate (e.g. Fosamax, Actonel, Boniva)

RENEWAL CRITERIA

Our guideline for renewal of PAMIDRONATE (Aredia) requires that the patient have a diagnosis of hypercalcemia of malignancy, osteolytic bone metastases of breast cancer, osteolytic bone lesions of multiple myeloma, or Paget's disease.

RATIONALE
To ensure appropriate use of pamidronate based on FDA approved indications and dosing.

Aredia Dosing:
  • Hypercalcemia of malignancy:
    o Moderate hypercalcemia (12-13.5mg/dL): Administer 60 to 90mg single dose IV infusion over 2 to 24 hours.
    o Severe hypercalcemia (>13.5mg/dL): Administer 90mg single dose IV infusion over 2 to 24 hours.
  • Osteolytic bone metastases of breast cancer: Administer 90mg IV infusion over 2 hours once every 3 to 4 weeks.
  • Osteolytic bone lesions of multiple myeloma: Administer 90mg IV infusion over 4 hours once monthly.
  • Paget Disease: Administer 30mg IV infusion over 4 hours for 3 consecutive days (Maximum total dose is 90mg).
PAMIDRONATE

FDA APPROVED INDICATIONS
Aredia is an injectable bisphosphonate indicated for:
- Hypercalcemia of malignancy
- Osteolytic bone metastases of breast cancer
- Osteolytic bone lesions of multiple myeloma
- Paget Disease

REFERENCES
- Pamidronate disodium [prescribing information]. Lake Forest, IL: Hospira Inc; August 2012.

Created: 10/15
Effective: 10/01/18
Client Approval: 08/22/18
P&T Approval: 3QTR
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for **PANOBINOSTAT** requires the patient to have a diagnosis of multiple myeloma. Additional guideline requirements apply.

- Previously treated with at least 2 prior regimens; the patient must have had tried Velcade (bortezomib) and one of the following immunomodulatory agents: Thalomid, Revlimid, Pomalyst.
- Farydak to be used concurrently with Velcade (bortezomib) and dexamethasone.

RENEWAL CRITERIA

Our guideline for **PANOBINOSTAT** renewal permits patients with clinical benefit who do not experience unresolved severe or medically significant toxicity.

PANOBINOSTAT

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANOBINOSTAT</td>
<td>FARYDAK</td>
<td>41794</td>
<td>ROUTE = ORAL</td>
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</tbody>
</table>

RATIONALE

Promote appropriate utilization of **Farydak (panobinostat)** based on FDA approved indication. Initial dosing for up to 8 cycles. Renewal provided for patients with clinical benefit who do not experience unresolved severe or medically significant toxicity (maximum duration of therapy up to 16 cycles which allows up to 96 capsules in 48 weeks).

The most common prior antineoplastic therapies in the PANORAMA-1 (Panobinostat Oral in Multiple Myeloma) trial were corticosteroids (90%), melphalan (80%), thalidomide (53%), cyclophosphamide (47%), bortezomib (44%), and lenalidomide (19%).

Given the toxicity concerns, a regimen containing Farydak may be less preferred over other regimens for relapsed/refractory MM. As of March 2015, the NCCN lists the following as Category 1 recommendations (please check NCCN treatment guidelines for other possible regimens):

- Velcade
- Velcade with liposomal doxorubicin (i.e. Doxil, Lipodox)
- Revlimid/dexamethasone
- Kyprolis (carfilzomib)/Revlimid/dexamethasone

Farydak might also be reserved for patients less than 65 years of age with good performance status who either have not been exposed to or have been exposed to, but are not refractory to, proteasome inhibitors (i.e. Velcade and Kyprolis).

CONTINUED ON NEXT PAGE
**DOSAGE**
The recommended starting dose of Farydak is 20 mg, taken orally once every other day for 3 doses per week in Weeks 1 and 2 of each 21-day cycle for up to 8 cycles. Consider continuing treatment for an additional 8 cycles for patients with clinical benefit who do not experience unresolved severe or medically significant toxicity. The total duration of treatment may be up to 16 cycles (48 weeks). Farydak is administered in combination with bortezomib and dexamethasone.

![Schedule Table]

**FDA APPROVED INDICATIONS**
Indicated in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

**REFERENCES**
- Farydak [Prescribing Information]. East Hanover, NJ: Novartis; February 2015.
- NCCN Clinical Practice Guideline in Oncology: Multiple Myeloma Version 3.2015. National Comprehensive Cancer Network. Available at:

Created: 05/15
Effective: 11/01/15
Client Approval: 09/15
P&T Approval: 05/15
PARATHYROID HORMONE

<table>
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GUIDELINES FOR USE

Our guideline for PARATHYROID HORMONE requires a diagnosis of hypocalcemia secondary to hypoparathyroidism. Additional guideline requirements apply.

- Previous use of activated vitamin D (calcitriol) and calcium
- Patient's hypoparathyroidism is not due to a calcium sensing receptor (CSR) mutation
- Patient's hypoparathyroidism is not considered acute post-surgical hypoparathyroidism (surgery in past 30 days)
- Therapy initiated by or in consultation with an endocrinologist

RATIONALE

Promote appropriate utilization of parathyroid hormone based on FDA approved indication, dosing and best practices.

DOSSAGE

The starting dose of Natpara is 50 mcg injected once daily in the thigh.

The dose of Natpara may be increased in increments of 25 mcg every four weeks up to a maximum daily dose of 100 mcg if serum calcium cannot be maintained above 8 mg/dL without an active form of vitamin D and/or oral calcium supplementation.

FDA APPROVED INDICATIONS

Natpara is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

Limitations of Use

- Because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone.
- Natpara was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.
- Natpara was not studied in patients with acute post-surgical hypoparathyroidism.

REFERENCES

GUIDELINES FOR USE

Approval requires a diagnosis of Cushing’s disease for which the patient has undergone pituitary surgery or pituitary surgery is not an option, and a trial of ketoconazole, metyrapone, or cabergoline.

RATIONALE
To ensure appropriate use of Signifor consistent with FDA approved indication and dose.

Signifor’s recommended dosage range is 0.3 mg to 0.9 mg twice a day. The recommended initial dose is either 0.6 mg or 0.9 mg injected subcutaneously twice a day. For patients with moderate hepatic impairment (Child Pugh B), the recommended initial dosage is 0.3 mg twice a day and the maximum dosage is 0.6 mg twice a day. Avoid the use of SIGNIFOR in patients with severe hepatic impairment (Child Pugh C).

Cushing’s disease is caused by a pituitary gland tumor that produces adrenocorticotropic hormone (ACTH). This additional ACTH acts as a signal to the adrenal glands to make excess cortisol. Signifor binds and activates the human somatostatin receptor subtype 5 resulting in inhibition of ACTH secretion by the pituitary tumor cells, which leads to decreased cortisol secretion. First line treatment for Cushing’s disease is transsphenoidal surgery and resection of the pituitary tumor. If surgery is delayed, contraindicated, or unsuccessful, adjunct medical therapy is usually required. Adrenal enzyme inhibitors, ketoconazole, and metyrapone (not FDA approved for this indication) are most commonly prescribed, followed by cabergoline (also not FDA approved for this indication) which targets the corticotrophin tumor. Combination therapy, such as Signifor, cabergoline, and/or ketoconazole, may be necessary to achieve an acceptable response.

A total of 162 patients were enrolled in a Phase III, multicenter, randomized study over a 6-month treatment period to evaluate the safety and efficacy of Signifor in patients with Cushing’s disease. The majority of clinical trial subjects (83%) had persistent or recurrent disease despite pituitary surgery whereas surgery was not indicated or surgery was refused in the remaining subjects. Patients with a baseline 24-hour urine free cortisol (UFC) >1.5 x upper limit of normal (ULN) were randomized to receive a twice-daily, subcutaneous injection of either Signifor 0.6 mg or 0.9 mg. The primary efficacy endpoint was the proportion of patients who achieved normalization of mean 24-hour UFC levels after six months of treatment and did not dose increase during this period. At Month 6, the percentages of responders for the primary endpoint were 15% and 26% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively. Signifor resulted in a decrease in the mean 24-hour UFC after 1 month of treatment. For patients (n=78) who stayed in the trial, similar UFC lowering was observed at Month 12.

CONTINUED ON NEXT PAGE
RATIONALI (CONTINUED)
Most common adverse reactions occurring in ≥20% of patients are diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus.

Other clinically significant adverse reactions include hypocortisolism, bradycardia and QT prolongation, liver test elevations, and pituitary hormone deficiency.

Treatment with Signifor leads to suppression of adrenocorticotropic hormone (ACTH) secretion in Cushing’s disease. Suppression of ACTH may lead to a decrease in circulating levels of cortisol and potentially hypocortisolism. Pituitary hormones other than ACTH may also be inhibited since Signifor mimics the acts of somatostatin. Monitoring of pituitary function (e.g., TSH/free T4, GH/IGF-1) should occur prior to initiation of therapy with Signifor and periodically during treatment. Patients who have undergone transsphenoidal surgery and pituitary irradiation are particularly at increased risk for deficiency of pituitary hormones.

Drug interactions include cyclosporine (decreased cyclosporine levels), bromocriptine (increased bromocriptine levels), and anti-arrhythmic drugs or other medications that prolong QT interval (additive effects on QT interval prolongation).

Signifor is Pregnancy Category C.

FDA APPROVED INDICATIONS
Signifor is a somatostatin analog indicated for the treatment of adult patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative.

REFERENCES
• Signifor [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2012.
• UpToDate, Inc. Medical therapy of hypercortisolism (Cushing’s syndrome). UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated January 18, 2013.

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 05/13
Our guideline for PATIROMER (Veltassa) requires a diagnosis of hyperkalemia. In addition, the following criteria must also be met:

- The requested drug is not being used as an emergency treatment for life-threatening hyperkalemia.
- The requested drug will not be approved for patients currently receiving dialysis.
- The requested drug is being prescribed by or in consultation with a nephrologist or cardiologist.
- The patient has attempted any ONE of the following approaches in an effort to reduce the modifiable risks for hyperkalemia:
  - Angiotensin converting enzyme inhibitor (ACE-I)
  - Angiotensin receptor blocker (ARB)
  - Consideration of dose reduction of renin-angiotensin-aldosterone system (RAAS) inhibitors (e.g., ACE-I's, ARB's, aldosterone antagonists)
- The patient has tried to treat hyperkalemia with loop diuretics (e.g., bumetanide, ethacrynic acid, furosemide, torsemide) if estimated glomerular filtration rate (eGFR) is below 30 mL/min/1.73 m², or with loop diuretics or thiazide diuretics (e.g., chlorthalidone, hydrochlorothiazide, metolazone) if eGFR is 30 mL/min/1.73 m² or above

### PATIROMER RATIONALE
Promote appropriate utilization of PATIROMER based on FDA approved indication.

Hyperkalemia, typically defined as a serum potassium concentration of >5 or >5.5 meq/L, is a serious medical condition that can lead to life-threatening cardiac arrhythmias and sudden cardiac death. There are often no warning signs and a patient can unknowingly experience spikes in potassium levels and be at risk for these cardiac events. Those at highest risk are patients with diabetes, advanced CKD, kidney transplant recipients, and patients taking renin angiotensin aldosterone system (RAAS) inhibitors such as angiotensin receptor blockers (ARBs), aldosterone antagonists (AAs), and angiotensin-converting-enzyme inhibitors (ACE-I)s. The risk of RAAS inhibitor monotherapy-related hyperkalemia occurs infrequently (<2%); however in patients with CKD or HF the risk increases to 5 to 10%. Although controversial, physicians may prescribe dual therapy (ACEI and ARB) for delay in CKD progression; however, the NKF-KDOQI (National Kidney Foundation Kidney Disease Outcomes Quality Initiative) does not recommend the combination of ACEI and ARB as dual blockade since this greatly increases the risk of hyperkalemia.

CONTINUED ON NEXT PAGE
PATIROMER

According to the National Kidney Foundation (NKF), the goal of chronic management of hyperkalemia is to prevent the development or recurrence of hyperkalemia. The first step is to identify and reduce or eliminate modifiable causes, such as dietary potassium intake and hyperkalemia-inducing medications. The NKF recommends reducing the dose or discontinuing RAAS inhibitors to reduce hyperkalemia, if possible. However, since discontinuation of a RAAS inhibitor forfeits the well-documented benefits of these agents in CKD and HF, the historically available options for treatment of chronic hyperkalemia in patients that need to continue RAAS inhibitors included loop or thiazide diuretics, sodium polystyrene sulfonate (SPS), and dialysis. Although data is limited, chronic diuretic therapy in conjunction with a low potassium diet has been the mainstay of therapy in patients with mild to moderate CKD, especially in those who are treated with ACEIs or ARBs. The available modalities for removing potassium include: diuretics, cation exchange resins, dialysis, and Veltassa. Veltassa administration in patients who are receiving dialysis may be considered a duplicative therapy. Both a low-potassium diet and the use of loop or thiazide diuretics can be long-term strategies to prevent hyperkalemia in many patients with CKD who are treated with ACE inhibitors or ARBs.

Due to the progressive nature of CKD, however, diuretics may lose effectiveness over time. SPS is a common treatment for acute hyperkalemia, but there is limited data on its safety and efficacy for chronic management. In addition, the use of SPS with or without sorbitol can produce severe side effects, particularly intestinal necrosis, which although rare, can be fatal. Veltassa may have a more favorable safety profile since there were no severe GI side effects reported in the clinical trials, although there were reports of other GI adverse effects (constipation and decrease in gastric motility). The long-term safety of Veltassa is unknown.

CONTINUED ON NEXT PAGE
Patiromer

**Dosage**
The recommended starting dose of Veltassa is 8.4 grams administered orally once daily with food. Based on serum potassium levels, the dose can be increased or decreased to reach the target range. The dose can be increased at one-week intervals in increments of 8.4g up to a maximum dose of 25.2g once daily.

Veltassa is supplied as single use, powder for oral suspension packets.

**Available strengths:**
- 8.4g powder for oral suspension packet
- 16.8g powder for oral suspension packet
- 25.2g powder for oral suspension packet

**FDA approved indication**
Veltassa is a potassium binder indicated for the treatment of hyperkalemia. Veltassa should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

**References**
- Veltassa [Prescribing Information]. Relypsa, Inc.: Redwood City, CA; October 2015.
- UpToDate, Inc. Treatment and prevention of hyperkalemia in adults. UpToDate [database online]. Waltham, MA. Current through November 2015.
GUIDELINES FOR USE

Approval requires a diagnosis of advanced renal cell carcinoma (RCC) or advanced soft tissue sarcoma (STS) and previous chemotherapy. Votrient is not covered for adipocytic soft tissue sarcoma (STS) and gastrointestinal stromal tumors (GIST).

PAZOPANIB

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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<tr>
<td>PAZOPANIB</td>
<td>VOTRIENT</td>
<td>36709</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RATIONALE

Ensure appropriate utilization of pazopanib based on FDA approved indication and NCCN guidelines.

FDA APPROVED INDICATIONS

Pazopanib is indicated for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma (STS) in patients who have received prior chemotherapy.

Limitation of use: the efficacy of pazopanib for the treatment of patients with adipocytic STS or gastrointestinal stromal tumors (GIST) has not been demonstrated.

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/12
GUIDELINES FOR USE

Our guideline for **PDE5 INHIBITORS FOR PULMONARY ARTERIAL HYPERTENSION** requires that the prescriber is a cardiologist or a pulmonologist and the patient has a diagnosis of pulmonary arterial hypertension. Additional guideline requirements apply.

**Requests for Revatio suspension** require documentation that the patient is unable to swallow tablets and has tried crushed Revatio tablets.

**Requests for Adcirca** require a trial or contraindication to the use of Revatio tablets.

**RATIONALE**

Ensure appropriate utilization of PDE5 inhibitors, Revatio and Adcirca. FDA indicated dosage for Revatio tablets in the treatment of PAH is 20mg three times daily. For Adcirca, the dosage is 40mg once daily.

**FDA APPROVED INDICATIONS**

Revatio and Adcirca are indicated for treatment of pulmonary artery hypertension (WHO Group 1) to improve exercise capacity and delay clinical worsening.

World Health Organization Classification of Pulmonary Hypertension Group 1:

- Idiopathic (familial)
- Congenital systemic-to-pulmonary shunts
- HIV infection
- Collagen vascular disease
- Portal Hypertension
- Drugs and toxins

**REFERENCES**


Created: 09/15
Effective: 07/22/17
Client Approval: 07/10
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named PEGVALIASE (Palynziq) requires a diagnosis of phenylketonuria. In addition, the following criteria must be met:
- The patient is 18 years of age or older.
- The patient has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.

RATIONALE

To ensure appropriate use of Palynziq (pegvaliase) consistent with FDA-approved indications and dosing.

FDA-APPROVED INDICATION

Palynziq is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.

DOSAGE AND ADMINISTRATION

Treatment with Palynziq should be managed by a healthcare provider experienced in the management of phenylketonuria. Before initiating treatment, baseline blood phenylalanine concentrations should be obtained. After initiating treatment with Palynziq, blood phenylalanine concentrations should be obtained every 4 weeks until a maintenance dosage is established. After a maintenance dosage is established, periodic blood phenylalanine monitoring is recommended to assess blood phenylalanine control.

For hypersensitivity reactions, premedication may be considered with an H1-receptor antagonist, H2-receptor antagonist, and/or antipyretic prior to Palynziq administration based upon individual patient tolerability.

Induction:
The recommended initial induction dosage for Palynziq is 2.5 mg subcutaneously once weekly for 4 weeks. The initial dose should be administered under the supervision of a healthcare provider.

Titration:
Palynziq doses should be titrated in a stepwise manner based on tolerability, over at least 5 weeks, to achieve a dosage of 20 mg subcutaneously once daily.

CONTINUED ON NEXT PAGE
PEGVALIASE

DOSAGE AND ADMINISTRATION (CONTINUED)

Maintenance:
Therapeutic response may not be achieved until the patient is titrated to an effective maintenance dosage. The lowest effective and tolerated dosage of Palynziq should be used. Palynziq should be maintained at a dosage of 20 mg subcutaneously once daily for at least 24 weeks. Increasing the dosage to a maximum of 40 mg subcutaneously once daily may be considered in patients who have been maintained continuously on 20 mg once daily for at least 24 weeks and who have not achieved either a 20% reduction in blood phenylalanine concentrations from pre-treatment baseline levels or blood phenylalanine concentrations ≤600 micromol/L. Patient tolerability, blood phenylalanine concentrations, and dietary protein and phenylalanine intake should be assessed throughout treatment.

Discontinuation:
Palynziq should be discontinued in patients who have not achieved a response (at least a 20% reduction in blood phenylalanine concentrations from pre-treatment baseline levels or blood phenylalanine concentrations ≤600 micromol/L) after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily.

<table>
<thead>
<tr>
<th>Phase of Treatment</th>
<th>Palynziq Dosing Regimen</th>
<th>Duration a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>2.5 mg SC once weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Titration</td>
<td>2.5 mg SC twice weekly</td>
<td>1 week</td>
</tr>
<tr>
<td></td>
<td>10 mg SC once weekly</td>
<td>1 week</td>
</tr>
<tr>
<td></td>
<td>10 mg SC twice weekly</td>
<td>1 week</td>
</tr>
<tr>
<td></td>
<td>10 mg SC four times per week</td>
<td>1 week</td>
</tr>
<tr>
<td>Maintenance b</td>
<td>10 mg SC once daily</td>
<td>1 week</td>
</tr>
<tr>
<td></td>
<td>20 mg SC once daily</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

a Additional time may be required prior to each dosage escalation based on patient tolerability.
b Treatment should be individualized to the lowest effective and tolerated dosage. Increasing Palynziq to a maximum dosage of 40 mg once daily may be considered in patients who have not achieved a therapeutic response with at least 24 weeks of 20 mg once daily.

REFERENCES

Created: 06/18
Effective: 08/20/18
Client Approval: 07/06/18
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of acromegaly?
   
   If yes, continue to #2.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

2. Was the patient unable to be treated with **ANY** of the following or inadequately treated with **ONE** of the following: surgical resection, pituitary irradiation, or a dopamine agonist (e.g. cabergoline or bromocriptine) at maximally tolerated doses?
   
   If yes, **approve for 12 months by HICL with a quantity limit of #30 vials per 30 days.**
   If no, do not approve.
   **DENIAL TEXT:** Approval for Somavert requires a diagnosis of acromegaly with the failure to be treated with one of the following or the inability to be treated with any of the following: surgical resection, pituitary irradiation, or a dopamine agonist (e.g. cabergoline or bromocriptine) at maximally tolerated doses.

RATIONALE
To ensure appropriate use of Somavert based on FDA approved indication and dosing.

FDA APPROVED INDICATION
Somavert is a growth hormone receptor antagonist indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery or radiation therapy, or for whom these therapies are not appropriate. The goal of treatment is to normalize serum insulin-like growth factor-I (IGF-I) levels.

DOSING AND ADMINISTRATION
The recommended loading dose of Somavert is 40 mg given subcutaneously, under healthcare provider supervision. Provide proper training in subcutaneous injection technique to patients or their caregivers so they can receive once daily subcutaneous injections. On the next day following the loading dose, instruct patients or their caregivers to begin daily subcutaneous injections of 10 mg of Somavert.

**CONTINUED ON NEXT PAGE**
FDA APPROVED INDICATION (CONTINUED)

Titrate the dosage to normalize serum IGF-I concentrations (serum IGF-I concentrations should be measured every four to six weeks). The dosage should not be based on growth hormone (GH) concentrations or signs and symptoms of acromegaly. It is unknown whether patients who remain symptomatic while achieving normalized IGF-I concentrations would benefit from increased SOMAVERT dosage.

- Increase the dosage by 5 mg increments every 4 to 6 weeks if IGF-I concentrations are elevated.
- Decrease the dosage by 5 mg decrements every 4 to 6 weeks if IGF-I concentrations are below the normal range.
- IGF-I levels should also be monitored when a Somavert dose given in multiple injections is converted to a single daily injection.

REFERENCES

GUIDELINES FOR USE

Approval for Somavert requires a diagnosis of acromegaly with the failure to be treated with one of the following or the inability to be treated with any of the following: surgical resection, pituitary irradiation, or a dopamine agonist (e.g. cabergoline or bromocriptine) at maximally tolerated doses.

RATIONALE
To ensure appropriate use of Somavert based on FDA approved indication and dosing.

FDA APPROVED INDICATION
Somavert is a growth hormone receptor antagonist indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery or radiation therapy, or for whom these therapies are not appropriate. The goal of treatment is to normalize serum insulin-like growth factor-I (IGF-I) levels.

DOISING AND ADMINISTRATION
The recommended loading dose of Somavert is 40 mg given subcutaneously, under healthcare provider supervision. Provide proper training in subcutaneous injection technique to patients or their caregivers so they can receive once daily subcutaneous injections. On the next day following the loading dose, instruct patients or their caregivers to begin daily subcutaneous injections of 10 mg of Somavert.

Titrate the dosage to normalize serum IGF-I concentrations (serum IGF-I concentrations should be measured every four to six weeks). The dosage should not be based on growth hormone (GH) concentrations or signs and symptoms of acromegaly. It is unknown whether patients who remain symptomatic while achieving normalized IGF-I concentrations would benefit from increased SOMAVERT dosage.

- Increase the dosage by 5 mg increments every 4 to 6 weeks if IGF-I concentrations are elevated.
- Decrease the dosage by 5 mg decrements every 4 to 6 weeks if IGF-I concentrations are below the normal range.
- IGF-I levels should also be monitored when a Somavert dose given in multiple injections is converted to a single daily injection.

REFERENCES

Created: 02/18
Effective: 07/01/18
Client Approval: 05/21/18
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for PENICILLAMINE (Cuprimine, Depen) requires a diagnosis of Wilson's disease, cystinuria, or active rheumatoid arthritis unresponsive to conventional therapy. The following criteria must also be met:

For patients with Wilson's disease, approval requires:
- Known family history of Wilson's Disease OR physical examination consistent with Wilson's disease
- Plasma copper-protein ceruloplasmin less than 20 mg/dL
- Liver biopsy positive for an abnormally high concentration of copper (greater than 250 mcg/g dry weight) OR the presence of Kayser-Fleischer rings
- Maintenance of a reduced copper dietary intake (less than 2mg copper per day)
- Medication is prescribed by or given in consultation with a hepatologist
- For Cuprimine requests, the patient had a previous trial of or contraindication to Depen (penicillamine)

For patients with cystinuria, approval requires:
- Presence of nephrolithiasis and at least ONE of the following:
  - Stone analysis positive for cystine
  - Urinalysis positive for pathognomonic hexagonal cystine crystals
  - Family history of cystinuria with a positive cyanide-nitroprusside screen
- Daily cystine output greater than 300mg per 24 hours following urine cystine excretion testing
- Patient has failed to respond to an adequate trial of conventional therapy which includes ALL of the following (unless contraindicated):
  - Increased fluid intake
  - Modest reductions in sodium and protein intake
  - Urinary alkalinization
- Medication is prescribed by or given in consultation with a nephrologist
- For Cuprimine requests, the patient had a previous trial of or contraindication to Depen (penicillamine) AND Thiola (tiopronin)

For patients with active rheumatoid arthritis, approval requires:
- Medication is prescribed by or given in consultation with a rheumatologist
- Patient does not have a history of or other evidence of renal insufficiency
- Patient has failed to respond to an adequate trial of conventional therapy including at least one of the following DMARD (disease-modifying antirheumatic drug) agents: methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- For Cuprimine requests, the patient had a previous trial of or contraindication to Depen (penicillamine)

CONTINUED ON NEXT PAGE
RATIONAL
Promote appropriate utilization of PENICILLAMINE based on FDA approved indication and to ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for penicillamine.

Per the Cuprimine prescribing information regarding Wilson's disease: Wilson's disease (hepatolenticular degeneration) occurs in individuals who have inherited an autosomal recessive defect that leads to an accumulation of copper far in excess of metabolic requirements. The excess copper is deposited in several organs and tissues, and eventually produces pathological effects primarily in the liver, where damage progresses to postnecrotic cirrhosis, and in the brain, where degeneration is widespread. Copper is also deposited as characteristic, asymptomatic, golden-brown Kayser-Fleischer rings in the corneas of all patients with cerebral symptomatology and some patients who are either asymptomatic or manifest only hepatic symptomatology. The diagnosis, if suspected on the basis of family or individual history or physical examination, can be confirmed if the plasma copper-protein ceruloplasmin is <20 mg/dL and either a quantitative determination in a liver biopsy specimen shows an abnormally high concentration of copper (>250 mcg/g dry weight) or Kayser-Fleischer rings are present.

Treatment has two objectives: 1) to minimize dietary intake of copper; 2) to promote excretion and complex formation (i.e., detoxification) of excess tissue copper. The first objective is attained by a daily diet that contains no more than one or two milligrams of copper. For the second objective, a copper chelating agent is used.

Per the Cuprimine prescribing information regarding cystinuria: Normal daily output of cystine is 40 to 80 mg. In cystinuria, output is greatly increased and may exceed 1 g/day. At 500 to 600 mg/day, stone formation is almost certain. When it is more than 300 mg/day, treatment is indicated. Conventional treatment is directed at keeping urinary cystine diluted enough to prevent stone formation, keeping the urine alkaline enough to dissolve as much cystine as possible, and minimizing cystine production by a diet low in methionine (the major dietary precursor of cystine). Patients must drink enough fluid to keep urine specific gravity below 1.010, take enough alkali to keep urinary pH at 7.5 to 8, and maintain a diet low in methionine. This diet is not recommended in growing children and probably is contraindicated in pregnancy because of its low protein content.

When these measures are inadequate to control recurrent stone formation, CUPRIMINE may be used as additional therapy, and when patients refuse to adhere to conventional treatment, CUPRIMINE may be a useful substitute.

The American Urologic Association guidelines report, tiopronin is recommended as the agent of choice for the prevention of recurrent cystine stones in patients that are unresponsive to increased fluid intake, restriction of sodium and protein intake, and urinary alkalization or who have large recurrent stone burdens.

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

Cystinuria is diagnosed among patients with nephrolithiasis and one or more of the following findings:
- Stone analysis showing cystine
- Positive family history of cystinuria
- Identification of pathognomonic hexagonal cystine crystals on urinalysis (seen on initial urinalysis in about 25 percent of patients)

All patients presenting with new onset of nephrolithiasis should have stone composition determined when possible. Patients who do not have a stone available for analysis and in whom cystine crystals are not visualized in the urine should be screened for urine cystine using the cyanide-nitroprusside test.

Per the Cuprimine prescribing information regarding rheumatoid arthritis: Because CUPRIMINE can cause severe adverse reactions, its use in rheumatoid arthritis should be restricted to patients who have severe, active disease and who have failed to respond to an adequate trial of conventional therapy. Even then, benefit-to-risk ratio should be carefully considered.

DOSAGE

Wilson’s disease - Optimal dosage can be determined by measurement of urinary copper excretion and the determination of free copper in the serum. The urine must be collected in copper-free glassware, and should be quantitatively analyzed for copper before and soon after initiation of therapy with CUPRIMINE.

Determination of 24-hour urinary copper excretion is of greatest value in the first week of therapy with penicillamine. In the absence of any drug reaction, a dose between 0.75 and 1.5 g that results in an initial 24-hour cupriuresis of over 2 mg should be continued for about three months, by which time the most reliable method of monitoring maintenance treatment is the determination of free copper in the serum. This equals the difference between quantitatively determined total copper and ceruloplasmin-copper. Adequately treated patients will usually have less than 10 mcg free copper/dL of serum. It is seldom necessary to exceed a dosage of 2 g/day. If the patient is intolerant to therapy with CUPRIMINE, alternative treatment is trientine hydrochloride.

In patients who cannot tolerate as much as 1 g/day initially, initiating dosage with 250 mg/day, and increasing gradually to the requisite amount, gives closer control of the effects of the drug and may help to reduce the incidence of adverse reactions.

Cystinuria - The usual dosage of CUPRIMINE in the treatment of cystinuria is 2 g/day for adults, with a range of 1 to 4 g/day. For pediatric patients, dosage can be based on 30 mg/kg/day. The total daily amount should be divided into four doses. If four equal doses are not feasible, give the larger portion at bedtime. If adverse reactions necessitate a reduction in dosage, it is important to retain the bedtime dose.

CONTINUED ON NEXT PAGE
RATIONAL (CONTINUED)

Rheumatoid Arthritis - The currently recommended dosage regimen in rheumatoid arthritis begins with a single daily dose of 125 mg or 250 mg, which is thereafter increased at one to three month intervals, by 125 mg or 250 mg/day, as patient response and tolerance indicate. If a satisfactory remission of symptoms is achieved, the dose associated with the remission should be continued. If there is no improvement and there are no signs of potentially serious toxicity after two to three months of treatment with doses of 500-750 mg/day, increases of 250 mg/day at two to three month intervals may be continued until a satisfactory remission occurs or signs of toxicity develop. If there is no discernible improvement after three to four months of treatment with 1000 to 1500 mg of penicillamine/day, it may be assumed the patient will not respond and CUPRIMINE should be discontinued.

FDA APPROVED INDICATION
Wilson's disease, cystinuria, and in patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy.

REFERENCES
- Schilsky M, Runyon B, Travis A. Wilson disease: Treatment and prognosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 28, 2017.)
- Worcester E, Goldfarb S, Forman J. Cystine stones. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 28, 2017.)

Created: 10/16
Effective: 01/01/17
Client Approval: 10/24/16
P&T Approval: N/A
GUIDELINES FOR USE

The guideline for PEXIDARTINIB (Turalio) requires a diagnosis of symptomatic tenosynovial giant cell tumor (TGCT). In addition, the following criteria must be met:

- TGCT is associated with severe morbidity or functional limitations
- TGCT is NOT amenable to improvement with surgery
- The patient is 18 years of age or older

RATIONALE
Promote appropriate utilization and dosing of Turalio for its FDA approved indication.

FDA APPROVED INDICATIONS
Turalio is a kinase inhibitor indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

DOSAGE AND ADMINISTRATION
Recommended starting dosage is 400 mg orally twice daily

AVAILABLE STRENGTHS
200 mg capsules

REFERENCES

Created: 10/19
Effective: 10/21/19 Client Approval: 10/07/19 P&T Approval: N/A
PHENOXYBENZAMINE

<table>
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<td>DIBENZYL</td>
<td>02098</td>
<td></td>
<td>ROUTE = ORAL</td>
</tr>
</tbody>
</table>

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline for **PHENOXYBENZAMINE (DIBENZYLE)** requires a diagnosis of pheochromocytoma. In addition, the following criteria must also be met:

- The requested medication is used for the treatment of pheochromocytoma prior to pheochromocytoma resection/removal
- Therapy is prescribed by or in consultation with an endocrinologist, an endocrine surgeon, or a hematologist-oncologist
- The patient had a previous trial of or contraindication to an alpha-1 selective adrenergic receptor blockers (e.g. doxazosin, terazosin, or prazosin)

RATIONALE

Ensure appropriate utilization for phenoxybenzamine based on FDA approved indication and dosing.

FDA APPROVED INDICATIONS

Phenoxybenzamine is indicated for the treatment of pheochromocytoma, to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a beta-blocking agent concomitantly.

DOSAGE AND ADMINISTRATION

Initial dose for phenoxybenzamine is 10 mg orally twice a day. Dosage should be increased every other day, usually to 20 to 40 mg 2 or 3 times a day, until an optimal dosage is obtained, as judged by blood pressure control.

Dosage should be adjusted to fit the needs of each patient. Small initial doses should be slowly increased until the desired effect is obtained or the side effects from blockade become troublesome. After each increase, the patient should be observed on that level before instituting another increase. The dosage should be carried to a point where symptomatic relief and/or objective improvement are obtained, but not so high that the side effects from blockade become troublesome. Long-term use of phenoxybenzamine is not recommended.

REFERENCES

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Our guideline for **PIMAVANSGERIN** requires a diagnosis of Parkinson’s disease.

**RATIONALE**
To ensure the appropriate use of Nuplazid.

**DOSAGE**
The recommended dosage of Nuplazid is 34mg orally once daily, without titration, taken with or without food. Reduce dose to 10mg once daily when administering with a strong CYP3A4 inhibitor.

**FDA APPROVED INDICATIONS**
PIMAVANSGERIN is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis.

**AVAILABLE STRENGTHS**
- 10 mg tablets
- 17 mg tablets
- 34 mg capsules

**REFERENCES**

Created: 08/18
Effective: 09/10/18
Client Approval: 08/28/18
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for **PIRFENIDONE** requires a diagnosis of idiopathic pulmonary fibrosis (IPF). IPF is defined by the American Thoracic Society with the following criteria: a) Exclusion of other known causes of interstitial lung disease (ILD) (e.g., connective tissue disease, drug toxicity, asbestos or beryllium exposure, hypersensitivity pneumonitis, systemic sclerosis, rheumatoid arthritis, radiation, sarcoidosis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV) infection, viral hepatitis, or cancer) AND b) The presence of usual interstitial pneumonia (UIP) pattern as evidenced by high-resolution computed tomography (HRCT) alone or via a combination of surgical lung biopsy and HRCT. In addition, our guideline requires:

- treatment is prescribed by or in consultation with a pulmonologist
- patient not currently smoke cigarettes
- patient must obtain liver function tests prior to the start of pirfenidone
- patient has a predicted forced vital capacity (FVC) of at least 50%

RATIONALE
Promote appropriate utilization of Esbriet based on FDA approved indication and dosage.

Esbriet (pirfenidone) is one of the first drugs to be approved by the FDA to treat idiopathic pulmonary fibrosis (IPF). Ofev (nintedanib), the other agent for the treatment of IPF, was also approved on the same day. These two drugs were granted Breakthrough Therapy Designation as well as Orphan Drug status since there are no other drugs to date for the treatment of IPF, a disease that affects an estimated 100,000 people (mostly adults over the age of 40) in the United States. IPF is a chronic, progressive disorder of the lower respiratory tract in which lung tissue becomes scarred or fibrotic over time. As a result, patients with IPF experience shortness of breath, cough, and difficulty participating in everyday physical activities.

The American Thoracic Society guidelines state the diagnosis of IPF requires:

a) Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)

b) The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy

c) Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

There is no cure for IPF; many people live only about 3 to 5 years, with the most common cause of death related to IPF being respiratory failure. The exact cause of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.
PIRFENIDONE

RATIONALE (CONTINUED)

Treatment options for IPF have been extremely limited, mainly consisting of supportive care (oxygen therapy, pulmonary rehabilitation) and lung transplantation. The approval of Esbriet provides a new treatment option that may slow disease progression for patients with IPF. It is an orally administered pyridine that exerts anti-inflammatory effects by interfering with the production of Transforming Growth Factor (TGF)-beta, a small protein in the body involved in how cells grow, and Tumor Necrosis Factor (TNF)-alpha, a small protein that is involved in inflammation. In addition, it behaves as an antifibrotic by directly altering the expression, synthesis, and possibly accumulation of collagen.

Esbriet is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1. The concomitant administration of Esbriet and fluvoxamine or other strong CYP1A2 inhibitors is not recommended because it significantly increases exposure to Esbriet. Concomitant administration of Esbriet and ciprofloxacin moderately increases exposure to Esbriet. Conversely, concomitant use of Esbriet and a CYP1A2 inducer may decrease the exposure of Esbriet and decrease efficacy; this interaction may be particularly important for smokers. Hydrocarbons found in cigarettes are potent CYP1A2 inducers, and for smokers, the AUC and Cmax of Esbriet were 46% and 68% that of non-smokers (respectively). Patients should be instructed to stop smoking prior to and during treatment with Esbriet.

Increases in ALT and AST greater than three times the upper limit of normal have been reported, with rare occasions of concomitant elevations in bilirubin. Increases in these liver enzymes were reversible with dose medication or treatment discontinuation. Prior to starting Esbriet, patients should obtain liver function tests.

The most common adverse reactions (≥10%) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

DOSAGE

The recommended daily maintenance dose of Esbriet is 801mg (three 267mg capsules) three times a day with food for a total of 2403mg/day. Doses should be taken at the same time each day.

Upon initiation of treatment, titrate to the full dosage of 9 capsules per day over a 14-day period as follows:

<table>
<thead>
<tr>
<th>TREATMENT DAYS</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 through 7</td>
<td>1 capsule three times a day with food</td>
</tr>
<tr>
<td>Days 8 through 14</td>
<td>2 capsules three times a day with food</td>
</tr>
<tr>
<td>Days 15 onward</td>
<td>3 capsules three times a day with food</td>
</tr>
</tbody>
</table>

Patients who miss 14 or more days of Esbriet should re-initiate treatment by undergoing the initial 2-week titration regimen up to the full maintenance dosage.

CONTINUED ON NEXT PAGE
PIRFENIDONE

DO dosage (CONTINUED)

Temporary dosage reductions or interruptions of Esbriet may be considered if patients experience significant adverse reactions or elevations in liver enzyme and bilirubin. Modifications in dosage should also be considered when Esbriet is administered concurrently with CYP1A2 inhibitors.

FDA APPROVED INDICATION
Esbriet is a pyridine indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

REFERENCES
GUIDELINES FOR USE

Approval requires a diagnosis of multiple myeloma and prior trial with at least two therapies including Revlimid and Velcade.

RATIONALE

To ensure appropriate use of pomalidomide aligned with FDA approved indication.

The recommended starting dose is 4 mg once daily orally on days 1-21 of repeated 28-day cycles until disease progression. Pomalyst may be given in combination with dexamethasone and/or with water. The capsules should not be broken, chewed, or opened. Pomalyst should be taken at least 2 hours before or 2 hours after a meal. Dose interruption and modification to 1mg less than the previous dose is recommended in the presence of neutropenia, thrombocytopenia, or any other Grade 3 or 4 toxicity.

Pomalyst is a second generation oral, once-daily thalidomide analogue that may be administered in combination with low-dose dexamethasone for treatment of relapsed and refractory multiple myeloma (MM) patients who have received at least two prior therapies. Both Thalomid (thalidomide) and Revlimid (lenalidomide) are thalidomide analogues with FDA approval for MM; Thalomid as first line therapy and Revlimid as second line therapy. Velcade (bortezomib) and Kyprolis (carfilzomib) are proteasome inhibitors also approved for MM (Kyprolis as third line only) given intravenously. Additionally there are multiple traditional chemotherapy agents used in the treatment of MM. MM is a plasma cell neoplasm characterized by the presence of monoclonal (or myeloma) protein, also known as M protein. The malignant proliferation of plasma cells, or activated B cells, leads to accumulation in the bone marrow resulting in bone marrow failure and also bone destruction. It is estimated that in 2012 there were 21,270 new cases of MM and 10,710 deaths in the United States. The majority of MM patients are over 60 years old. The 5 year survival rate for MM has improved with the availability of newer therapies and was estimated to be 34% in 2003.

Pomalyst inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, Pomalyst inhibited the proliferation of Revlimid-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalyst enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalyst demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model. Thalomid and Revlimid work in a similar fashion. The proteasome inhibitors increase the sensitization of malignant cells to apoptosis.

CONTINUED ON NEXT PAGE
POMALIDOMIDE

RATIONALE (CONTINUED)
The National Comprehensive Cancer Network (NCCN) guidelines do not include Pomalyst at the time of this review. They do list several preferred regimens for MM, categorized by stage in therapy and transplant candidacy.

Treatment regimens utilizing alkylating agents such as melphalan should be avoided in stem cell transplant candidates since they compromise marrow hemopoiesis and may make the harvesting of adequate numbers of hemopoietic stem cells impossible. The preferred primary therapy regimens for transplant candidates are:
- Velcade (bortezomib) with dexamethasone
- Velcade with cyclophosphamide and dexamethasone
- Velcade with doxorubicin and dexamethasone
- Velcade with Revlimid and dexamethasone
- Velcade with Thalomid and dexamethasone
- Revlimid with dexamethasone

The preferred primary therapy regimens for non-transplant candidates are:
- Velcade with dexamethasone
- Revlimid with low-dose dexamethasone
- Melphalan with prednisone and Velcade
- Melphalan with prednisone and Revlimid
- Melphalan with prednisone and Thalomid

The preferred primary therapies for maintenance therapy are:
- Velcade
- Revlimid
- Thalomid

The preferred primary therapy regimens for salvage therapy are:
- Velcade
- Velcade with dexamethasone
- Velcade with Revlimid and dexamethasone
- Velcade with liposomal doxorubicin
- Velcade with Thalomid and dexamethasone
- Kyprolis
- Velcade with cyclophosphamide and dexamethasone
- Revlimid with cyclophosphamide and dexamethasone
- Dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP)
- Dexamethasone with Thalomid, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE) with or without Velcade (VTD-PACE)
- High-dose cyclophosphamide
- Revlimid with dexamethasone
- Thalomid with dexamethasone

CONTINUED ON NEXT PAGE
POMALIDOMIDE

RATIONALE (CONTINUED)

Pomalyst is being studied in combination with Velcade and low-dose dexamethasone (OPTIMISMM trial) and Kyprolis with dexamethasone for relapsed and refractory MM. It is also being investigated for the treatment of graft vs. host disease, myelofibrosis, and several other cancers. Pomalyst will likely be used as salvage therapy in practice, which is aligned with its FDA approved indication.

The pivotal trial (trial 1 included in the prescribing information) was a phase 2, multicenter, randomized open label study in patients with relapsed MM who were refractory to their last myeloma therapy and had received both Revlimid and Velcade. Patients were considered relapsed if they had achieved at least stable disease for at least one cycle of treatment to at least one prior regimen and then developed progressive disease. Patients were considered refractory if they experienced disease progression on or within 60 days of their last therapy. Patients (N=221) were randomized to receive Pomalyst (4mg once daily for 21 of 28 days, until disease progression) alone or in combination with low dose dexamethasone (40 mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients 75 years or younger, or 20mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients greater than 75 years of age). Patients in the Pomalyst alone arm were allowed to add dexamethasone upon disease progression.

Baseline characteristic for the Pomalyst alone and Pomalyst with low dose dexamethasone were as follows: age (61 vs. 64 years), male (57 vs. 62 percent), Caucasian (86 vs. 92 percent), number of prior therapies (5 in both groups), and refractory to bortezomib and lenalidomide (59.3 vs. 61.1 percent).

The overall response rate was greater among patients treated with Pomalyst and low dose dexamethasone compared to Pomalyst alone (29.2 vs. 7.4 percent).

Pomalyst was also studied in the phase III, open-label MM-003 study, which examined Pomalyst plus low-dose dexamethasone (given weekly) compared with high-dose dexamethasone alone (given on days 1-4, 9-12 and 17-20 of each 28-day cycle) in patients (N=455) with refractory multiple myeloma who have failed therapy with both Revlimid and Velcade, administered either alone or in combination. The top line results demonstrated significantly longer progression free survival in patients who received Pomalyst plus low-dose dexamethasone compared with those who received high-dose dexamethasone (median 3.6 months vs. 1.8 months).

Pomalyst has boxed warnings for embryo-fetal toxicity and venous thromboembolism. It is only available through a restricted program called the Pomalyst REMS program, which includes prescriber certification, pharmacy certification, and a signed patient-presenter agreement. Pomalyst is contraindicated in pregnancy (pregnancy category X) and nursing mothers are advised to discontinue either Pomalyst or nursing. It should also be avoided in patients with serum creatinine >3.0 mg/dL. Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide may be at higher risk of hypersensitivity. No formal drug interaction studies have been conducted with Pomalyst. It is primarily metabolized by CYP1A2 and CYP3A. It is also a substrate for P-glycoprotein (P-gp).

CONTINUED ON NEXT PAGE
POMALIDOMIDE

RATIONALE (CONTINUED)
The most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain and pyrexia. Neutropenia was the most frequently reported Grade 3/4 adverse event. Monitor patients for hematologic toxicities, especially neutropenia.

FDA APPROVED INDICATIONS
Pomalyst (pomalidomide) is indicated for patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

REFERENCES
GUIDELINES FOR USE

Approval requires that one of the following conditions are met: 1) a diagnosis of T315I-positive chronic myeloid leukemia (CML), or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL); or 2) a diagnosis of chronic myeloid leukemia (CML), or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) with a previous trial of Gleevec, Sprycel, Tasigna, or Bosulif, which may also require prior authorization.

PONATINIB

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONATINIB HCL</td>
<td>ICLUSIG</td>
<td>39859</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RATIONALE

Ensure appropriate utilization of ponatinib based on FDA approved indication and dosage. The recommended dosage is 45mg once daily with or without food. Tablets should be swallowed whole. Continue treatment as long as the patient does not show evidence of disease progression or unacceptable toxicity. Dose modifications to 30mg and then 15mg daily are recommended for neutropenia and thrombocytopenia unrelated to leukemia; hepatic toxicity; or pancreatitis and lipase elevation. The recommended dose should be reduced to 30 mg once daily when administering Iclusig with strong CYP3A inhibitors.

Iclusig (ponatinib) is the fifth tyrosine kinase inhibitor (TKI) approved for the treatment of CML. It blocks the activity of ABL (including the T315I mutation) to treat CML and Ph+ALL. Iclusig also inhibited the in vitro activity of additional kinases involved in the growth and development of cancer cells. These include members of the VEGFR, PDGFR, FGFR, EPH receptors, the SRC families of kinases, and KIT, RET, TIE2, and FLT3.

CML is a malignant clonal disorder that results in rapid growth of myeloid stem cells in the bone marrow. It is usually associated with a chromosomal abnormality that results from the fusion of the BCR and ABL1 genes, called the Philadelphia (Ph) chromosome. Normally, the ABL1 gene produces a protein with tyrosine kinase catalytic activity that is tightly regulated. The fused BCR-ABL1 gene in the Ph chromosome however, produces a protein with deregulated and constitutively active kinase activity that is fundamental to the pathogenesis of CML. The presence of the T315I “gatekeeper” mutation has been associated with resistance to currently approved TKIs including Gleevec, Sprycel, Tasigna, and Bosulif.

CONTINUED ON NEXT PAGE
RATIONAL (CONTINUED)

The mainstay of treatment in CML over the last decade has been inhibition of the enzymatic activity of those proteins, and thus the TKIs Gleevec, Sprycel, and Tasigna are designated as first line treatment of CML in the National Comprehensive Cancer Network clinical practice guidelines. NCCN recommends that Bosulif, another TKI, be considered as a second line treatment. It is currently being studied in the phase III open-label BELA trial versus Gleevec for patients with newly diagnosed CML. Synribo, a first-in-class cephalotaxine that inhibits protein synthesis independently of direct BCR-ABL1 binding, was also approved in 2012 for patients that fail, cannot tolerate, or are resistant to TKI therapy. NCCN recommends its use for patients who failed two or more TKIs or have a T315I mutation. EPIC is an ongoing randomized trial comparing Iclusig to Gleevec in patients with newly diagnosed CML. EPIC began in June 2012 and has an estimated study completion date of June 2021. Initially Iclusig will likely be used as a second line agent (similar to Bosulif) except for those patients with the T315I mutation where it may be considered as a first line therapy (similar to Synribo). Depending on the results of the EPIC trial, Iclusig may be considered a first line agent for all patients regardless of mutation type.

The PACE trial (n=444) studied Iclusig in patients with CML and Ph+ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy. This was a single-arm, open-label, international, multicenter trial. All patients were administered a starting dose of 45 mg of Iclusig once daily. Patients were assigned to one of six cohorts based on disease phase (chronic phase CML [CP-CML]; accelerated phase CML [AP-CML]; or blast phase CML [BP-CML]/Ph+ALL), resistance or intolerance (R/I) to prior TKI therapy, and the presence of the T315I mutation. All patients had previously been on at least one FDA approved or investigational TKI therapy: 7% had 1 TKI therapy, 37% had 2 TKI therapies, and 56% had 3 or more TKI therapies.

Resistance in CP-CML while on prior TKI therapy, was defined as failure to achieve either a complete hematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months). Patients with CP-CML who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on prior TKI therapy were also considered resistant. Resistance in AP-CML, BP-CML, and Ph+ALL was defined as failure to achieve either a major hematologic response (by 3 months in AP-CML, and by 1 month in BP-CML and Ph+ALL), loss of major hematologic response (at any time), or development of a kinase domain mutation in the absence of a complete major hematologic response while on prior TKI therapy. Intolerance was defined as the discontinuation of prior TKI therapy due to toxicities despite optimal management in the absence of a complete cytogenetic response in patients with CP-CML or major hematologic response for patients with AP-CML, BP-CML, or Ph+ALL.

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PONATINIB

RATIONALE (CONTINUED)

The primary endpoint of major cytogenetic response (which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses) for CP-CML was 54% overall and 70% in the T315I cohort. At the time of analysis, the median duration of Iclusig treatment was 281 days in patients with CP-CML and the median duration of major cytogenetic response was not reached.

The results of the primary endpoint of overall major hematologic response (which combines complete hematologic responses and no evidence of leukemia) for AP-CML, BP-CML, and Ph+ALL were 52%, 31% and 41%, respectively. At the time of analysis, the median duration of Iclusig treatment was 286 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ALL. The median time to overall major hematologic response in patients with AP-CML, BP-CML, and Ph+ALL was 21 days, 29 days, and 20 days, respectively. The median duration of overall major hematologic response for patients with AP-CML, BP-CML, and Ph+ALL was 9.5 months, 4.7 months, and 3.2 months, respectively.

Iclusig has a boxed warning for vascular occlusion, heart failure and hepatotoxicity. Patients should be monitored for signs and symptoms of congestive heart failure, hypertension, pancreatitis, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression, tumor lysis syndrome, gastrointestinal perforation, and compromised wound healing. The most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. Hematologic adverse reactions included thrombocytopenia, anemia, neutropenia, lymphopenia, and leukopenia. Iclusig is pregnancy category D and can cause fetal harm.

FDA APPROVED INDICATIONS

Iclusig (ponatinib) is a kinase inhibitor indicated for the:
- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) and T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated. These indications are based upon response rate [see Clinical Studies (14)]. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.

CONTINUED ON NEXT PAGE
REFERENCES

- Center for Drug Evaluation and Research. Application Number: 203469Orig1s000 Summary Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203469Orig1s000SumR.pdf [Accessed January 2, 2013].
- Tefferi, A. Overview of the myeloproliferative neoplasms. In: UpToDate, Schrier, SL (Ed), UpToDate, Waltham, MA, 2012.
GUIDELINES FOR USE

The guideline named **PREGABALIN (LYRICA CR)** requires that the patient have a diagnosis of neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia. A 30 day trial of immediate-release Lyrica (pregabalin) within the past 120 days is required unless the patient has been on Lyrica CR (at least 30 days Lyrica CR in the previous 60 days).

RATIONALE

Ensure appropriate utilization of Lyrica CR based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS

Lyrica CR is indicated for the management of:

- Neuropathic pain associated with diabetic peripheral neuropathy (DPN)
- Postherpetic neuralgia (PHN)

Efficacy of Lyrica CR has not been established for the management of fibromyalgia or as adjunctive therapy for adult patients with partial onset seizures.

DOSAGE AND ADMINISTRATION

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPN Pain (2.2)</td>
<td>Single dose per day</td>
<td>165 mg/day</td>
<td>330 mg/day within 1 week.</td>
</tr>
<tr>
<td>PHN (2.3)</td>
<td>Single dose per day</td>
<td>165 mg/day</td>
<td>330 mg/day within 1 week. Maximum dose of 660 mg/day.</td>
</tr>
</tbody>
</table>

Conversion from Lyrica Capsules or Oral Solution to Lyrica CR

<table>
<thead>
<tr>
<th>LYRICA Total Daily Dose (dosed 2 or 3 times daily)</th>
<th>LYRICA CR Dose (dosed once a day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg/daily</td>
<td>82.5 mg/day</td>
</tr>
<tr>
<td>150 mg/daily</td>
<td>165 mg/day</td>
</tr>
<tr>
<td>225 mg/daily</td>
<td>247.5 mg/day</td>
</tr>
<tr>
<td>300 mg/daily</td>
<td>330 mg/day</td>
</tr>
<tr>
<td>450 mg/daily</td>
<td>495 mg/day</td>
</tr>
<tr>
<td>600 mg/daily</td>
<td>660 mg/day</td>
</tr>
</tbody>
</table>

a. 247.5 mg = 3 × 82.5 mg tablets taken once a day.
b. 495 mg = 3 × 165 mg tablets taken once a day.
c. 660 mg = 2 × 330 mg tablets taken once a day.
DOSAGE FORMS AND STRENGTHS
- Extended-release tablets: 82.5 mg, 165 mg, and 330 mg

REFERENCES

Created: 05/18
Effective: 07/01/18
Client Approval: 05/21/18
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline for PREGABALIN IMMEDIATE-RELEASE (Lyrica) requires that Lyrica (pregabalin) is prescribed for the treatment of generalized anxiety disorder (GAD), neuropathic pain associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), partial onset seizures, fibromyalgia, or neuropathic pain associated with spinal cord injury. Approval of the liquid formulation requires that the patient is unable to swallow regular capsules or has difficulty swallowing that requires use of a liquid formulation. For patients new to therapy, the following criteria must also be met:

For patients with neuropathic pain associated with diabetic peripheral neuropathy (DPN), our guideline requires that the patient has had a previous trial of ONE of the following medications within the past 120 days:
- Serotonin-norepinephrine reuptake inhibitor antidepressant (SNRI) (e.g., duloxetine, venlafaxine)
- Tricyclic antidepressant (e.g., amitriptyline, desipramine, nortriptyline)
- Gabapentin

For patients with postherpetic neuralgia (PHN), our guideline requires that the patient has had a previous trial of ONE of the following medications within the past 120 days:
- Lidocaine patch
- Tricyclic antidepressant (e.g., amitriptyline, desipramine, nortriptyline)
- Gabapentin

(Denial text continued on next page)

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For patients with partial onset seizures, our guideline requires that **ALL** of the following criteria are met:
- The patient is 4 years of age or older
- The patient is using Lyrica as adjunctive therapy
- The patient has had a previous trial of **TWO** of the following anticonvulsants within the past 365 days: carbamazepine, gabapentin, lamotrigine, levetiracetam IR or ER, oxcarbazepine, valproic acid or divalproex, topiramate, or zonisamide

For patients with fibromyalgia, our guideline requires that the patient has had a previous trial of **TWO** of the following medications within the past 365 days:
- Tricyclic antidepressant (e.g., amitriptyline, desipramine, nortriptyline)
- Gabapentin
- Cyclobenzaprine
- Selective serotonin reuptake inhibitor (SSRI) (e.g., fluoxetine)
- Duloxetine HCl
- Savella (milnacipran HCl)

For patients with neuropathic pain from spinal cord injury, our guideline requires that the patient has had a previous trial of **ONE** of the following medications within the past 120 days:
- Tricyclic antidepressant (e.g., amitriptyline, desipramine, nortriptyline)
- Gabapentin
PREGABALIN IMMEDIATE-RELEASE

RATIONALE
Ensures appropriate utilization of Lyrica based on indication and dosage.

The American Academy of Neurology guidelines suggest that pregabalin should be offered for diabetic peripheral neuropathy if clinically appropriate (evidence level A), and that gabapentin and amitriptyline should also be considered for the treatment of diabetic peripheral neuropathy (level B). The evidence level A for pregabalin does not indicate that the medication is better tolerated or more effective than other neuropathy medications, only that the number and quality of clinical studies for pregabalin use are higher.

The Expert Panel on Diabetic Neuropathy (international) recommends current first line agents for diabetic peripheral neuropathy: tricyclic antidepressants, duloxetine, pregabalin, and gabapentin. The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain and the European Federation of Neurological Societies Task Force recommend the following first-line agents for neuropathic pain: tricyclic antidepressants, dual reuptake inhibitors of serotonin/norepinephrine, calcium channel alpha-2 delta ligands (gabapentin and pregabalin), and topical lidocaine.

FDA APPROVED INDICATIONS
Lyrica is indicated for:
• Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN)
• Management of postherpetic neuralgia (PHN)
• Adjunctive therapy for the treatment of partial onset seizures in patients 4 years of age and older
• Management of fibromyalgia
• Management of neuropathic pain associated with spinal cord injury

OFF-LABEL INDICATION
• Generalized anxiety disorder (GAD)

DOSAGE AND ADMINISTRATION

Neuropathic Pain associated with Diabetic Peripheral Neuropathy:
The maximum recommended dose of LYRICA is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended.

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PREGABALIN IMMEDIATE-RELEASE

RATIONALE (CONTINUED)

Postherpetic Neuralgia:
The recommended dose of LYRICA is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 75 mg two times a day, or 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, reserve dosing above 300 mg/day for those patients who have on-going pain and are tolerating 300 mg daily.

Adjunctive Therapy for Partial Onset Seizures in Patients 4 Years of Age and Older:
The recommended dosage for adults and pediatric patients 4 years of age and older is included in Table 1. Administer the total daily dosage orally in two or three divided doses. In pediatric patients 4 years of age and older, the recommended dosing regimen is dependent upon body weight. Based on clinical response and tolerability, dosage may be increased, approximately weekly.

Table 1: Recommended Dosage for Adults and Pediatric Patients 4 Years and Older

<table>
<thead>
<tr>
<th>Age and Body Weight</th>
<th>Recommended Initial Dosage (administer in two or three divided doses)</th>
<th>Recommended Maximum Dosage (administer in two or three divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (17 years and older)</td>
<td>150 mg/day</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Pediatric patients weighing 30 kg or more</td>
<td>2.5 mg/kg/day</td>
<td>10 mg/kg/day (not to exceed 600 mg/day)</td>
</tr>
<tr>
<td>Pediatric patients weighing 11 kg to less than 30 kg</td>
<td>3.5 mg/kg/day</td>
<td>14 mg/kg/day</td>
</tr>
</tbody>
</table>

Management of Fibromyalgia:
The recommended dose of LYRICA for fibromyalgia is 300 to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended.

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Neuropathic Pain Associated with Spinal Cord Injury:
The recommended dose range of LYRICA for the treatment of neuropathic pain associated with spinal cord injury is 150 to 600 mg/day. The recommended starting dose is 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient pain relief after 2 to 3 weeks of treatment with 150 mg two times a day and who tolerate LYRICA may be treated with up to 300 mg two times a day.

DOSAGE FORMS AND STRENGTHS
- Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg
- Oral Solution: 20 mg/mL

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

Our guideline for PYRIMETHAMINE (Daraprim) will be approved for acute treatment of toxoplasmosis or chronic maintenance therapy for toxoplasmosis with HIV. For prophylaxis of toxoplasmosis with HIV, a previous trial of or contraindication to Bactrim (SMX/TMP) is required.

Our guideline for PYRIMETHAMINE (Daraprim) renewal requires the following:
- **For continued treatment of acute toxoplasmosis**, approval requires that patient has persistent clinical disease (headache, neurological symptoms, or fever) and persistent radiographic disease (one or more mass lesions on brain imaging).
- **For chronic maintenance therapy of toxoplasmosis in patients with HIV**, approval requires the patient's CD4 count is less than 200 cells/mm³ and the patient is currently taking ART (anti-retroviral therapy).
- **For continued treatment of primary prophylaxis of toxoplasmosis in patients with HIV**, approval requires the patient's CD4 count is less than 200 cells/mm³ and the patient must currently be taking ART (anti-retroviral therapy).

RATIONALE
Promote appropriate utilization of Daraprim based on FDA approved indications and infectious disease guidelines.

**Toxoplasmosis Background**

Toxoplasmosis is an infection with a worldwide distribution that is caused by the parasite Toxoplasma gondii (T. gondii), which can be found in feline feces and undercooked meats. Once a person is infected, the parasite lies dormant in neural and muscle tissue and can never be eliminated. Up to 90% of immunocompetent patients are asymptomatic and if symptoms do occur, they are generally non-specific (fever, chills, night sweats, generalized lymphadenopathy). Chorioretinitis is the most frequent manifestation in immunocompetent patients and affects up to 1% of infected individuals. Congenital toxoplasmosis, a condition where the infection is passed to the unborn baby, can result in mental retardation, blindness, seizures and death. There is a risk of reactivation of the infection if the individual becomes immunocompromised, especially in patients with HIV/AIDS. The risk of developing reactivated toxoplasmosis is as high as 30% among patients with HIV not receiving appropriate prophylaxis and with a CD4 count <100 cells/mm³.

**Acute and maintenance Toxoplasmosis**
The Infectious Diseases Society of America (IDSA) recommends Daraprim, in combination with sulfadiazine and leucovorin as the preferred regimen for the treatment of acute toxoplasmosis encephalitis (TE) and chronic maintenance in patients with HIV. Definitive diagnosis of TE requires clinical symptoms, which include headache, neurological symptoms, or fever; identification of one or more mass lesions by CT, MRI or other radiographic testing; and detection of the organism in a clinical sample (brain biopsy, CSF stain).

CONTINUED ON NEXT PAGE
PYRIMETHAMINE

RATIONALE (CONTINUED)

Since obtaining a clinical sample can pose many risks, most physicians rely on empiric diagnosis with subsequent symptom and radiological improvement. Most HIV infected patients with TE will have positive antibodies to toxoplasma but the absence does not rule out the disease. Without treatment, disease progression results in seizures, stupor, and coma.

IDSA recommends Daraprim in combination with sulfadiazine and leucovorin as the preferred regimen for acute treatment and chronic maintenance therapy of toxoplasmosis. Second line treatments include Daraprim plus clindamycin, Bactrim (SMX/TMP), or Atovaquone with or without Daraprim or sulfadiazine. A small trial and open label observational study suggest Bactrim is as effective and better tolerated than Daraprim plus sulfadiazine; however, Bactrim has less in vitro activity against toxoplasma and experience is very limited using Bactrim for treatment. IDSA considers Bactrim an option if there is no valid reason not to use daraprim plus sulfadiazine. The remaining second line treatments previously mentioned have been shown to be effective in treating TE in at least two nonrandomized, uncontrolled trials, although their relative efficacy compared to the previous treatments is unknown.

IDSA recommends continuing treatment for acute TE for at least six weeks or longer if clinical or radiologic disease is extensive or response is incomplete at six weeks, in patients with HIV. Once acute treatment is complete, the patient will need to begin chronic maintenance therapy until the CD4 count > 200 mm$^3$ for >6 months in response to ART and clinical symptoms have fully resolved. Patients can restart maintenance therapy (secondary prophylaxis) if the CD4 count is <200 mm$^3$.

**PCP and toxoplasmosis prophylaxis**

IDSA recommends Bactrim (SMX/TMP) as first line treatment for primary prophylaxis of PCP and toxoplasmosis due to the dual coverage of both PCP and toxoplasmosis. Primary prophylaxis of PCP should be initiated when CD4 count <200 mm$^3$, oropharyngeal candidiasis is present, CD4 %< 14%, or if the patient has a history of an AIDS defining illness. Primary prophylaxis of PCP can be discontinued when the CD4 count >200 mm$^3$ for at least 3 months in response to ART. Secondary prophylaxis of PCP should be resumed if CD4 count <200 mm$^3$ unless the patient developed PCP when CD4 >200 mm$^3$. Second line treatments for PCP prophylaxis are dapsone with/without Daraprim, aerosolized pentamidine, or atovaquone with/without Daraprim. IDSA recommends initiating primary prophylaxis of toxoplasmosis when the CD4 count <100 mm$^3$ with or without a positive antibody to toxoplasma or when the patient seroconverts. Primary prophylaxis of toxoplasmosis can be discontinued when the CD4 count >200 mm$^3$ for > 3 months in response to ART. Consider restarting primary prophylaxis of toxoplasmosis when the CD4 count is <100 to 200 mm$^3$, especially in patients with a significant HIV viral load or if the patient is positive for the toxoplasma antibody. Second line treatment for toxoplasmosis prophylaxis includes atovaquone with/without Daraprim and dapsone with/without Daraprim. Patients will not need additional PCP coverage if they are receiving appropriate toxoplasmosis coverage. Of note, aerosolized pentamidine and dapsone monotherapy do not cover toxoplasmosis.

CONTINUED ON NEXT PAGE
PYRIMETHAMINE

FDA APPROVED INDICATION
Daraprim, in combination with a sulfonamide, is approved for treatment of toxoplasmosis.

NON-FDA APPROVED INDICATIONS
Toxoplasmosis prophylaxis in patients with HIV who are unable to tolerate Bactrim. Chronic maintenance therapy (secondary prophylaxis) of toxoplasmosis.

DOSAGE

• Acute toxoplasmosis treatment:
  - Adults 50 to 75mg PO daily, with a sulfonamide, for one to three weeks depending on patient's tolerance and response; then may reduce dose by 50% and continue for four to five weeks.
  - Pediatric dosage is 1mg/kg divided into 2 equal daily doses; after 2 to 4 days this dose may be reduced to one half and continued for approximately one month. The usual pediatric sulfonamide dosage is used in conjunction.

• Acute toxoplasmosis encephalitis treatment in patients with HIV:
  - Daraprim 200mg PO once, followed by dose based on body weight
    1. <60kg: Daraprim 50mg PO daily + sulfadiazine 1000mg PO q 6 hours + leucovorin.
    2. ≥60kg: Daraprim 75mg PO daily + sulfadiazine 1500mg PO q 6 hours + leucovorin.

• Chronic maintenance treatment of toxoplasmosis encephalitis in patients with HIV:
  - Daraprim 25-50mg daily + sulfadiazine 2000-4000mg PO daily (in 2 to 4 divided doses) + leucovorin.

• Primary prophylaxis of toxoplasmosis for patients with HIV:
  - Daraprim at doses of 50mg-75mg weekly in combination with dapsone + leucovorin.
  - Daraprim 25mg daily + atovaquone + leucovorin.

AVAILABLE STRENGTHS:
• Daraprim (pyrimethamine) 25mg tablet

REFERENCES
REGORAFENIB

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
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<tbody>
<tr>
<td>REGORAFENIB</td>
<td>STIVARGA</td>
<td></td>
<td>33363</td>
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</tr>
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</table>

GUIDELINES FOR USE

Our guideline for **REGORAFENIB** requires a diagnosis of metastatic colorectal cancer; locally advanced, unresectable, or metastatic gastrointestinal stromal tumor (GIST); or hepatocellular carcinoma. Additional guideline requirements apply.

**For the diagnosis of metastatic colorectal cancer**, approval requires a trial of the following preferred therapies:
- An anti-VEGF therapy (such as Avastin or Zaltrap) **AND**
- A fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy (such as FOLFOX, FOLFIRI, FOLFOXIRI, CapeOx, or infusional 5-FU/LV or capecitabine)

**For patients with wild type KRAS metastatic colorectal cancer**, a trial of an anti-EGFR therapy (such as Erbitux or Vectibix) is required.

**For the diagnosis of locally advanced, unresectable, or metastatic gastrointestinal stromal tumor (GIST)**, approval requires a trial of Gleevec and Sutent.

**For the diagnosis of hepatocellular carcinoma**, approval requires a trial of Nexavar.

These prior therapies may be covered under the medical benefit and/or may require prior authorization.

RATIONALE

To ensure appropriate use of Stivarga consistent with FDA approved indication.

The recommended dose of Stivarga is 160 mg orally (four 40mg tablets), once daily for the first 21 days of each 28-day cycle with a low-fat breakfast. Do not take two doses of Stivarga on the same day to make up for a missed dose from the previous day. Treatment should be interrupted and dose reduction to 120mg and then 80mg daily should be considered in the presence of certain grade 2-4 adverse reactions.

Stivarga is a once daily oral medication for treatment-resistant metastatic colorectal cancer, treatment-resistant metastatic and/or unresectable gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma. It is an inhibitor of multiple kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. Stivarga is structurally similar to sorafenib, leading to its moniker of “son of Nexavar”.

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

Colorectal cancer originates in either the colon or rectum typically as a polyp that slowly develops over many years. About 50% to 60% of patients diagnosed with colorectal cancer will eventually develop metastases. The American Cancer Society estimates that there will be 103,170 new cases of colon cancer and 40,290 new cases of rectal cancer in 2012.

According to the National Comprehensive Cancer Network (NCCN) colon and rectal cancer guidelines, options for treatment of metastatic disease consist of 5-fluorouracil with leucovorin (5-FU/LV), irinotecan, capecitabine, oxaliplatin, bevacizumab, cetuximab, and panitumumab. Five chemotherapy regimens are recommended as initial treatment of metastatic disease: FOLFOX, FOLFIRI, CapeOx, infusional 5-FU/LV or capecitabine, or FOLFOXIRI.

Vascular endothelial growth factor (VEGF) inhibitor Avastin (bevacizumab), and the epidermal growth factor receptor (EGFR) antagonists Erbitux (cetuximab) and Vectibix (panitumumab) are newer biologic therapies that may also be used as part of initial therapy. KRAS gene mutation status is predictive of poor response to Erbitux and Vectibix. Stivarga is not yet included in the current version of the NCCN guidelines. Zaltrap (ziv-aflibercept), a novel VEGF inhibitor, was also recently approved for the treatment of metastatic colorectal cancer in patients who have been previously treated with other therapies.

Stivarga was evaluated in a trial that randomized 760 patients with previously treated metastatic colorectal cancer to receive 160 mg of regorafenib orally once daily (n=505) plus Best Supportive Care (BSC) or placebo (n=255) plus BSC for the first 21 days of each 28-day cycle. Stivarga was administered with a low-fat breakfast that contained less than 30% fat. Treatment continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS); supportive efficacy outcome measures included progression-free survival (PFS); and objective tumor response rate.

History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. Patients received a median of three prior lines of therapy for metastatic disease.

The median OS for Stivarga with BSC was 6.4 months compared to 5.0 months for placebo with BSC. Stivarga also improved PFS (2.0 vs. 1.7 months) and overall response rate (1% vs. 0.4%) as compared to placebo.

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in which patients with previously-treated HCC received either STIVARGA (n=374) 160 mg orally on days 1 21 of each 4 week treatment cycle or placebo (n=193). The median age was 63 years, 88% were men, 98% had Child-Pugh A cirrhosis, 66% had an ECOG performance status (PS) of 0 and 34% had PS of 1. The median duration of therapy was 3.5 months (range 1 day to 29.4 months) for patients receiving STIVARGA. Of the patients receiving STIVARGA, 33% were exposed to STIVARGA for greater than or equal to 6 months and 14% were exposed to STIVARGA for greater than or equal to 12 months. Dose interruptions for adverse events were required in 58.3% of patients receiving STIVARGA and 48% of patients had their dose reduced. The most common adverse reactions requiring dose modification (interruption or dose reduction) were HFSR/PPES (20.6%), blood bilirubin increase (5.9%), fatigue (5.1%) and diarrhea (5.3%). Adverse reactions that resulted in treatment discontinuation were reported in 10.4% of STIVARGA-treated patients compared to 3.6% of patients who received placebo; the most common adverse reactions requiring discontinuation of STIVARGA were HFSR/PPES (1.9%) and AST increased (1.6%).

Warnings and precautions include hepatotoxicity, hemorrhage, dermatological toxicity, hypertension, cardiac ischemia and infarction, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation or fistulae, and wound healing complications. The Stivarga label contains a Boxed Warning alerting patients and health care professionals that severe and fatal liver toxicity occurred in patients treated with Stivarga during clinical studies.

The most common side effects of Stivarga are asthenia/fatigue, decreased appetite and food intake, hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia (PPE)], diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia. Stivarga is Pregnancy Category D and can cause fetal harm when administered to a pregnant woman. Avoid concomitant use of strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John’s Wort) and strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole).

Stivarga is a kinase inhibitor indicated for the treatment of patients with:
- Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.
- Hepatocellular carcinoma who have been previously treated with sorafenib.

Anti-VEGF therapies approved for the treatment of colorectal cancer include Avastin and Zaltrap. Anti-EGFR therapies approved for the treatment of colorectal cancer include Erbitux and Vectibix.

CONTINUED ON NEXT PAGE
REGORAFENIB

REFERENCES

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named RESLIZUMAB (Cinqair) requires a diagnosis of severe asthma with an eosinophilic phenotype. In addition, the following criteria must also be met:

- The medication is prescribed by or given in consultation with a physician specializing in allergic or pulmonary medicine
- The patient is 18 years of age or older
- The patient is currently adherent to a maximally tolerated dose of an inhaled corticosteroid AND at least one other maintenance medication (e.g., long-acting inhaled beta2-agonist, long-acting muscarinic antagonist, a leukotriene receptor antagonist, theophylline, or oral corticosteroid)
- The patient has a documented blood eosinophil level of 300 cells/mcL or more within the past 6 months
- The patient has experienced at least 2 or more asthma exacerbations within the past 12 months (exacerbation is defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days)
- The patient has ONE of the following:
  - Asthma Control Test (ACT) score of less than 20
  - Asthma Control Questionnaire (ACQ) score of 1.5 or more
  - Asthma Therapy Assessment Questionnaire (ATAQ) score of 1 or more
- Cinqair will be used as add-on maintenance treatment
- The patient is not being concurrently treated with Xolair, Dupixent, or another anti-IL5 asthma biologic (e.g., Nucala, Fasenra)

RENEWAL CRITERIA

The guideline named RESLIZUMAB (Cinqair) requires a diagnosis of severe asthma with an eosinophilic phenotype. In addition, the following must be met:

- The patient has experienced a reduction in asthma exacerbations (defined as an asthma-related event requiring hospitalization, emergency room visit, or systemic corticosteroid burst lasting at least 3 days) from baseline
- The patient has experienced an improvement in the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Asthma Therapy Assessment Questionnaire (ATAQ) score from baseline
- The patient has decreased their total daily oral corticosteroid dose from baseline, if the patient was on maintenance therapy with oral corticosteroids prior to initiation of Cinqair

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RESLIZUMAB

RATIONALE
Promote appropriate utilization of RESLIZUMAB based on FDA approved indication.

Reslizumab is a humanized monoclonal antibody that binds to and inactivates interleukin-5 (IL-5), resulting in a reduction in the number of circulating blood and sputum eosinophils. Reslizumab is indicated for add-on therapy for patients with moderate-to-severe eosinophilic asthma that is not adequately controlled with other therapies.

IL-5 is a proinflammatory mediator that promotes eosinophil production and infiltration into airway, as well as the release of immunoglobulin E (IgE). Eosinophilia, as well as increased serum IgE concentrations can potentiate worsening asthma symptoms and asthma exacerbations. In clinical trials, reslizumab was shown to reduce the rate of asthma exacerbations and improve lung function.

In clinical trials, reslizumab was shown to reduce the rates of asthma exacerbations by 50 – 59%, as well as significantly reduce the incidence of asthma exacerbation episodes requiring treatment with systemic corticosteroids. Reslizumab also demonstrated improvement in lung function with increased FEV1 values. Reslizumab’s ability to control asthma symptoms and reduce exacerbations can allow for the reduction or "stepping down" of doses of oral and inhaled corticosteroids, which will reduce the risk of experiencing adverse events related to steroid use. In clinical trials, blood eosinophil counts rebounded to pre-treatment levels or higher upon the discontinuation of reslizumab therapy, indicating that this drug should be used as a maintenance medication to control asthma symptoms.

DOSAGE
The recommended dosage of Cinqair (reslizumab) is 3mg/kg administered by intravenous infusion once every four weeks by a healthcare provider.

FDA APPROVED INDICATION
Cinqair (reslizumab) is indicated as an add-on maintenance treatment of patients with severe asthma who are 18 years of age and older with an eosinophilic phenotype.

Limitations of Use:
Cinqair is not indicated for
• Treatment of other eosinophilic conditions
• Relief of acute bronchospasm or status asthmaticus

REFERENCES
• Cinqair [Prescribing Information]. Frazer, PA. Teva Pharmaceutical Industries Ltd. May 2016.
GUIDELINES FOR USE

The guideline named RIBOCICLIB (Kisqali, Kisqali/Femara co-pack) requires a diagnosis of advanced or metastatic breast cancer that is hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative. In addition, the following criteria must be met:

For Kisqali-Femara Co-Pack request, approval requires:
- The patient is female and pre/perimenopausal OR post-menopausal
- The patient has not received prior endocrine-based therapy for metastatic breast cancer (e.g., letrozole, anastrozole, tamoxifen, fulvestrant, exemestane)
- The patient has NOT experienced disease progression following prior CDK inhibitor therapy

For Kisqali request, approval requires ONE of the following:
- Kisqali will be used in combination with an aromatase inhibitor and meet all of the following:
  - The patient is female and pre/perimenopausal OR post-menopausal
  - The patient has NOT received prior endocrine-based therapy for metastatic breast cancer (e.g., letrozole, anastrozole, tamoxifen, fulvestrant, exemestane)
  - The patient has NOT experienced disease progression following prior CDK inhibitor therapy
- Kisqali will be used in combination with Faslodex (fulvestrant) and meet all of the following:
  - The patient is female and post-menopausal
  - The patient has not received prior endocrine-based therapy for metastatic breast cancer (e.g., letrozole, anastrozole, tamoxifen, fulvestrant, exemestane) OR patient has experienced disease progression on endocrine therapy
  - The patient has NOT experienced disease progression following prior CDK inhibitor therapy

RATIONALE
Promote appropriate utilization of RIBOCICLIB (Kisqali) based on FDA approved indication and dosing. The Kisqali/Femara co-pack indications have been updated based on the most current Prescribing Information for Kisqali.

FDA APPROVED INDICATION
KISQALI/FEMARA CO-PACK:
- Kisqali/Femara co-pack, a co-packaged product containing ribociclib, a kinase inhibitor, and letrozole, an aromatase inhibitor, is indicated as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

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FDA APPROVED INDICATION (CONTINUED)

KISQALI, a kinase inhibitor indicated in combination with:
• An aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer as initial endocrine-based therapy, OR
• Fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, either as initial endocrine therapy or following disease progression on endocrine therapy

DOSAGE AND ADMINISTRATION

KISQALI/FEMARA CO-PACK:
• The Kisqali/Femara co-pack, is comprised of ribociclib tablets copackaged with letrozole tablets, to provide a 28-day treatment regimen.
• The Kisqali/Femara co-pack, should be coadministered, with or without food
• The recommended starting dose is KISQALI 600 mg (three 200 mg tablets) taken orally, once daily for 21 consecutive days followed by 7 days off KISQALI treatment resulting in a complete cycle of 28 days, and Femara 2.5 mg (one tablet) taken once daily throughout the 28-day cycle.

KISQALI:
• The recommended starting dose is 600 mg orally (three 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment (for complete 28 day cycle).
• Pre/perimenopausal women treated with the combination KISQALI plus an aromatase inhibitor or fulvestrant should be treated with a luteinizing hormone-releasing hormone (LHRH) agonist according to current clinical practice standards.

Patients should take Kisqali, Kisqali/Femara co-pack, and the aromatase inhibitor at approximately the same time each day, preferably in the morning.

If the patient vomits after taking the dose, or misses a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time. Kisqali tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

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DOSAGE AND ADMINISTRATION (CONTINUED)

Dose interruption, reduction, and/or discontinuation may be required based on individual safety and tolerability.

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<thead>
<tr>
<th>Dose Level</th>
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<tbody>
<tr>
<td>Recommended starting dose</td>
<td>600 mg/day</td>
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<tr>
<td>First dose reduction</td>
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<tr>
<td>Second dose reduction</td>
<td>200 mg/day*</td>
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</table>

*If further dose reduction below 200 mg/day is required, discontinue the treatment.

Avoid concomitant use of strong CYP3A inhibitors; if must be co-administered with strong CYP3A inhibitor reduce Kisqali dose to 400 mg once daily.

REFERENCES

- Kisqali [Prescribing Information]. East Hanover, NJ. Novartis; July 2018.
- Kisqali/Femara Co-Pack [Prescribing Information]. East Hanover, NJ. Novartis; May 2018.

Created: 04/17
Effective: 03/18/19
Client Approval: 02/26/19
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

XIFAXAN 550MG TABLETS

Our guideline for RIFAXIMIN 550mg TABLETS (Xifaxan) requires use for the reduction in risk of overt hepatic encephalopathy (HE) recurrence or for the diagnosis of irritable bowel syndrome with diarrhea (IBS-D). In addition, the following criteria must be met.

For the reduction in risk of overt hepatic encephalopathy (HE) recurrence, approval requires:
- The patient is 18 years of age or older
- The medication is being prescribed by a hepatologist
- The patient had a trial of lactulose or is currently on lactulose monotherapy

For the diagnosis of irritable bowel syndrome with diarrhea (IBS-D), approval requires:
- The patient is 18 years of age or older
- The medication is being prescribed by a gastroenterologist
- The patient had a trial of or contraindication to a tricyclic anti-depressant and dicyclomine

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE (CONTINUED)

RIFAXIMIN

RENEWAL CRITERIA

Our guideline for RIFAXIMIN 550mg (Xifaxan) renewal requires use for the reduction in risk of overt hepatic encephalopathy (HE) recurrence or the diagnosis of irritable bowel syndrome with diarrhea (IBS-D). In addition, the following criteria must be met:

For the treatment of irritable bowel syndrome with diarrhea (IBS-D), ALL of the following criteria must be met:

- At least 10 weeks have passed since the last treatment course of rifaximin
- Patient has experienced at least a 30% decrease in abdominal pain (on a 0-10 pain scale)
- Patient has experienced at least a 50% reduction in the number of days per week with a stool consistency of mushy stool (Bristol Stool scale type 6) or entirely liquid stool (Bristol Stool scale type 7)

RATIONALE

To ensure appropriate utilization of Xifaxan.

FDA APPROVED INDICATIONS

Xifaxan is a rifamycin antibacterial indicated for:

- Treatment of travelers’ diarrhea (TD) caused by noninvasive strains of Escherichia coli in adult and pediatric patients 12 years of age and older
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults
- Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults

Limitations of Use

- TD: Do not use in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than Escherichia coli.

DOSING

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<thead>
<tr>
<th>Condition</th>
<th>Recommended Dosage Regimen</th>
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<tbody>
<tr>
<td>TD</td>
<td>One 200 mg tablet 3 times a day for 3 days</td>
</tr>
<tr>
<td>HE</td>
<td>One 550 mg tablet 2 times a day</td>
</tr>
<tr>
<td>IBS-D</td>
<td>One 550 mg tablet 3 times a day for 14 days. Patients who experience recurrence can be retreated up to two times with the same regimen.</td>
</tr>
</tbody>
</table>

REFERENCES

GUIDELINES FOR USE

The guideline named RILONACEPT (Arcalyst) requires a diagnosis of Familial Cold Autoinflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS). In addition, the following criteria must be met:

- Prescribed by or supervised by a rheumatologist
- The patient is 12 years of age or older

RATIONALE

Ensure appropriate use of rilonacept.

FDA APPROVED INDICATIONS

Arcalyst is an interleukin-1β blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 12 years of age and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)

DOSAGE AND ADMINISTRATION

Injection for subcutaneous use only.

Adult patients 18 years and older: Treatment should be initiated with a loading dose of 320 mg delivered as two, 2 mL, subcutaneous injections of 160 mg each given on the same day at two different sites. Dosing should be continued with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. Arcalyst should not be given more often than once weekly.

Pediatric patients aged 12 to 17 years: Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. Arcalyst should not be given more often than once weekly.

REFERENCES


Created: 02/18
Effective: 06/01/18
Client Approval: 04/10/18
P&T Approval: N/A
RILUZOLE SUSPENSION

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GUIDELINES FOR USE

The guideline named **RILUZOLE SUSPENSION (Tiglutik)** requires a diagnosis of amyotrophic lateral sclerosis (ALS).

REFERENCES


Created: 12/18
Effective: 01/21/19
Client Approval: 12/20/18
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline for RIOCI GUAT (Adempas) requires a diagnosis of a persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4 or a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1) and the requested medication is prescribed by or given in consultation with a cardiologist or pulmonologist. The following criteria must also be met.

For a diagnosis of Pulmonary Arterial Hypertension, approval requires:
- The patient has NYHA-WHO Functional Class II to IV symptoms
- The patient previous trial of or contraindication to a phosphodiesterase-5 inhibitor (e.g. Revatio or Adcirca)
- The patient is not concurrently taking nitrates or nitric oxide donors (e.g. amyl nitrate), phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, or vardenafil), or non-specific phosphodiesterase inhibitors (e.g. dipyridamole, theophylline)

For a diagnosis of Chronic thromboembolic pulmonary hypertension, approval requires:
- The patient is not a candidate for surgery or has inoperable CTEPH
- The patient has persistent or recurrent disease after surgical treatment
- The patient has NYHA-WHO Functional Class II to IV symptoms
- The patient is not concurrently taking nitrates or nitric oxide donors (e.g. amyl nitrate), phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, or vardenafil), or non-specific phosphodiesterase inhibitors (e.g. dipyridamole, theophylline)

RENEWAL CRITERIA

The guideline named RIOCI GUAT (Adempas) requires that the patient has ONE of the following diagnoses:
- Persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO (World Health Organization) Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class
- Pulmonary arterial hypertension (PAH) (WHO Group 1)

In addition, the patient must show improvement from baseline in the 6-minute walk distance OR has a stable 6-minute walk distance with a stable or improved World Health Organization (WHO) functional class

RATIONALE

Ensure appropriate utilization of Adempas based on FDA approved indications.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS
Indicated for the treatment of adults with:
• Persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO (World Health Organization) Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.
• Pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

World Health Organization Classification of Pulmonary Hypertension Group 1:
• Idiopathic (familial)
• Congenital systemic-to-pulmonary shunts
• HIV infection
• Collagen vascular disease
• Portal Hypertension
• Drugs and toxins

World Health Organization Classification of Pulmonary Hypertension Group 4:
• Secondary to chronic thromboembolic disease

SAFETY
Adempas has a warning for hypotension, bleeding, and pulmonary edema. Adempas is pregnancy category X and contains a boxed warning regarding embryo-fetal toxicity. Adempas is only available to females through a restricted REMS program.

The most common adverse reactions (≥ 3%) in patients receiving Adempas were headache, dizziness, dyspepsia/gastritis, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation. Adempas is not recommended in patients with creatinine clearance <15 mL/min or on dialysis. Also not recommended in patients with severe (Child Pugh C) hepatic impairment.

DOSAGE
The dose is 1mg three times daily to start, or 0.5mg three times daily for patients unlikely to tolerate the hypotensive effect of Adempas. After two weeks the dose may be increased by 0.5mg at two week intervals to a maximum daily dosage of 2.5mg three times daily.

For patients receiving strong CYP and P-gp/BCRP inhibitors, consider a starting dose of 0.5 mg three times a day. Monitor for hypotension. Separate administration of antacids by at least 1 hour.

Among smokers, Adempas may require dosages higher than 2.5 mg three times a day if tolerated. Dose decrease may be required in patients who stop smoking.

Pregnancy must be prevented during treatment and for at least one month after treatment discontinuation.

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named **RISANKIZUMAB-RZAA (Skyrizi)** requires a diagnosis of moderate to severe plaque psoriasis (PsO). In addition, the following criteria must be met:

- The patient is 18 years of age or older
- Therapy is prescribed by or in consultation with a dermatologist
- The patient has psoriatic lesions involving greater than or equal to 10% of body surface area (BSA) or psoriatic lesions affecting the face, hands, feet, or genital area
- The patient has had a previous trial with one of the following conventional therapies: PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- The patient had a previous trial with TWO of the following preferred agents: Cosentyx, Enbrel, Cimzia, or Otezla

RENEWAL CRITERIA

The guideline named **RISANKIZUMAB-RZAA (Skyrizi)** requires a diagnosis of moderate to severe plaque psoriasis (PsO). In addition, the following criteria must be met:

- The patient has achieved or maintained clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50% or more

RATIONALE

For further information, please refer to the Prescribing Information and/or Drug Monograph for Skyrizi.

REFERENCES

GUIDELINES FOR USE
INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named ROMIPLOSTIM (Nplate) requires a diagnosis of chronic immune thrombocytopenia (ITP) and the patient is 1 year of age or older. In addition, the following criteria must be met.

- The patient had a trial of or contraindication to corticosteroids or immunoglobulins, or had an insufficient response to splenectomy

For patients between 1 and 17 years old, approval requires the patient has had ITP for at least 6 months

RENEWAL CRITERIA

The guideline named ROMIPLOSTIM (Nplate) requires a diagnosis of chronic immune thrombocytopenia (ITP) and ONE of the following criteria must be met:

- The patient had a clinical response, as defined by an increase in platelet count to at least $50 \times 10^9$/L
- The patient received the maximum dose of 10mcg/kg for 4 consecutive weeks with a clinical response

RATIONALE

Promote appropriate utilization and dosing of Nplate for its FDA approved indication.

FDA APPROVED INDICATIONS

Nplate is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in:

- Adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

DOSAGE AND ADMINISTRATION

The recommended initial dose is 1 mcg/kg once weekly as a subcutaneous injection.

AVAILABLE STRENGTHS

For injection: 125 mcg, 250 mcg, or 500 mcg of deliverable romiplostim as a lyophilized powder in single-dose vials.

REFERENCES

GUIDELINES FOR USE

The guideline named **RUCAPARIB (Rubraca)** requires a diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer OR recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. In addition, the following criteria must be met:

**For diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer, approval requires:**
- The patient is 18 years of age or older
- The requested medication will be used as monotherapy
- The patient has a deleterious BRCA mutation (germline and/or somatic) as confirmed by an FDA-approved test for Rubraca
- The patient has been treated with two or more chemotherapies (e.g., paclitaxel, docetaxel, cisplatin, carboplatin)

**For diagnosis of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, approval requires:**
- The patient is 18 years of age or older
- The patient is in complete or partial response to platinum-based chemotherapy
- The requested medication will be used for maintenance treatment

CONTINUED ON NEXT PAGE
RATIONALE
Promote appropriate utilization of RUCAPARIB based on FDA approved indication and dosage.

FDA APPROVED INDICATIONS
RUBRACA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:
- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA.

DOSAGE AND ADMINISTRATION
The recommended dose of Rubraca is 600 mg (two 300 mg tablets) taken orally twice daily with or without food. Continue treatment until disease progression or unacceptable toxicity. If a patient misses a dose of Rubraca, instruct the patient to take the next dose at its scheduled time. Vomited doses should not be replaced.

To manage adverse reactions, consider interruption of treatment or dose reduction. Recommended dose reductions are indicated in Table 1.

Table 1. Recommended Dose Adjustments

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<td>Third Dose Reduction</td>
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REFERENCES

Created: 07/17
Effective: 10/01/19
Client Approval: 09/04/19
P&T Approval: N/A
RUXOLITINIB

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This drug requires a written request for prior authorization.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named RUXOLITINIB (Jakafi) requires a diagnosis of intermediate or high-risk myelofibrosis, (such as primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis), polycythemia vera, or steroid -refractory acute graft-versus-host disease. The following criteria must also be met:

For patients with intermediate or high-risk myelofibrosis, such as primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis, approval requires:

- The patient is 18 years of age or older

For patients with polycythemia vera, approval requires:

- The patient is 18 years of age or older
- The patient has had a trial of or contraindication to hydroxyurea

For patients with steroid-refractory acute graft-versus-host disease, approval requires:

- The patient is 12 years of age or older

RENEWAL CRITERIA

The guideline named RUXOLITINIB (Jakafi) requires a diagnosis of intermediate or high-risk myelofibrosis, such as primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. In addition, renewal requires that the patient experience or maintain symptom improvement [such as a 50 percent or greater reduction in total symptom score on the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0], 50 percent or greater reduction in palpable spleen length, or spleen reduction of 35 percent or greater from baseline spleen volume after 6 months of therapy.

CONTINUED ON NEXT PAGE
RUXOLITINIB

RATIONALE
Promote appropriate utilization and dosing of Jakafi for its FDA approved indication.

FDA APPROVED INDICATIONS
Jakafi is a kinase inhibitor indicated for treatment of patients with:
- Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.
- Polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.
- Steroid-refractory acute graft-versus-host disease in adults and pediatric patients 12 years and older.

DOSAGE
Doses should be individualized based on safety and efficacy. Starting doses per indication are noted below.

Myelofibrosis
- The starting dose of Jakafi is based on patient's baseline platelet count:
  - Greater than 200 X 10^9/L: 20 mg given orally twice daily
  - 100 X 10^9/L to 200 X 10^9/L: 15 mg given orally twice daily
  - 50 X 10^9/L to less than 100 X 10^9/L: 5 mg given orally twice daily
- Monitor complete blood counts every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Modify or interrupt dosing for thrombocytopenia.

Polycythemia Vera
The starting dose of Jakafi is 10 mg given orally twice daily.

Steroid-Refractory Acute Graft-Versus-Host Disease
- The starting dose of Jakafi is 5 mg given orally twice daily.

REFERENCES

Created: 06/15
Effective: 09/13/19
Client Approval: 08/29/19
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires a diagnosis of genetically determined sucrose deficiency, or congenital sucrase-isomaltase deficiency (CSID).

RATIONALE

To ensure use of Sucraid based on its FDA approved indication and dosing.

FDA APPROVED INDICATIONS

Sucraid oral solution is indicated as oral replacement therapy of the genetically determined sucrose deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID).

REFERENCES


Created: 06/15
Effective: 07/01/17
Client Approval: 05/01/17
P&T Approval: 05/12
GUIDELINES FOR USE

Our guideline for SACUBITRIL/VALSARTAN requires a diagnosis of heart failure. In addition, the following criteria must also be met:

- Prescribed by or in consultation with a cardiologist
- Heart failure with NYHA Class II - IV
- Has a left ventricular ejection fraction of 40% or less
- Previous heart failure treatment with an ACE inhibitor (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril) or ARB (olmesartan, valsartan, azilsartan, candesartan, eprosartan, irbesartan, losartan, telmisartan)
- No history of angioedema related to previous ACE inhibitor or ARB therapy
- Discontinuation of ACE inhibitor or ARB prior to starting Entresto

RATIONALE

Promote appropriate utilization of sacubitril/valsartan based on FDA approved indication and current heart failure treatment guidelines. In accordance with clinical trial design and the population treated per inclusion criteria, patients must be stabilized on an ACEI or an ARB prior to therapy with sacubitril/valsartan. In PARADIGM-HF, the clinical trial assessing Entresto for treatment of HFrEF, patients were required to be receiving a stable dose of an ACEI or an ARB for at least 4 weeks to be eligible for trial enrollment.

The most recent ACCF/AHA guidelines recommend that ACE inhibitors should be used in all heart failure patients with a reduced EF to prevent symptomatic HF. The guidelines suggest that there is no difference among available ACEIs in their effects on symptoms or survival and they do not reference selection preference among the available ARBs. Entresto should not be used concurrently with an ACEI and this combination is contraindicated per the label due to an increased risk of angioedema. Patients with a history of angioedema were excluded from the clinical trial, PARADIGM-HF, and history of angioedema is a contraindication to use of Entresto per the product’s label.

FDA APPROVED INDICATIONS & DOSING

Entresto is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

The recommended starting dose of Entresto is 49/51mg (sacubitril/valsartan) twice-daily. Double the dose of Entresto after 2 to 4 weeks to the target maintenance dose of 97/103mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.

CONTINUED ON NEXT PAGE
SACUBITRIL/VALSARTAN

Reduce the starting dose to 24/26mg (sacubitril/valsartan) twice-daily for:
- patients not currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents
- patients with severe renal impairment
- patients with moderate hepatic impairment

Double the dose of Entresto every 2 to 4 weeks to the target maintenance dose of 97/103mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.

REFERENCES
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for SAPROPTERIN DIHYDROCHLORIDE requires a diagnosis of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU) and that the patient follows a phenylalanine-restricted diet.

RENEWAL CRITERIA

Our guideline for SAPROPTERIN DIHYDROCHLORIDE renewal requires a diagnosis of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU), in addition to the patient experiencing a greater than or equal to 30% decrease in blood phenylalanine from baseline after taking Kuvan (sapropterin dihydrochloride) and continuing to follow a phenylalanine-restricted diet.

RATIONALE

Promote appropriate utilization of SAPROPTERIN DIHYDROCHLORIDE based on FDA approved indication and dosing.

Phenylketonuria (PKU), in most cases, is caused by deficiency of phenylalanine hydroxylase (PAH). PAH is a hepatic enzyme that catalyzes the conversion of the essential amino acid phenylalanine to tyrosine. Tetrahydrobiopterin (BH4) is a cofactor required for PAH activity. PKU results in elevated blood and urine concentrations of phenylalanine and its metabolites, phenylacetate and phenyllactate. Tyrosine concentration is normal or low normal. Occasionally tyrosine concentrations are low.

Complete enzyme deficiency results in classic PKU, in which serum phenylalanine concentration exceeds 20 mg/dL (1200 micromol/L). Residual enzyme activity causes mild PKU (phenylalanine concentration 10 to 20 mg/dL, 600 to 1200 micromol/L) and hyperphenylalaninemia (HPA, phenylalanine concentration 2.5 to 10 mg/dL, 150 to 600 micromol/L).

Kuvan is a synthetic form of the cofactor BH4 (tetrahydrobiopterin) for the enzyme phenylalanine hydroxylase (PAH). BH4 activates residual PAH enzyme, improving normal phenylalanine metabolism and decreasing phenylalanine levels in Kuvan responders. Response to Kuvan treatment was defined in clinical trials as a ≥ 30% decrease in blood Phe from baseline. Approximately 25% to 50% of patients with PAH deficiency are responsive to sapropterin. The prevalence of responsiveness was 79 to 83% in patients with mild HPA, 49 to 60% in patients with mild PKU, and 7 to 10% in patients with classic PKU. Before routine treatment with Kuvan is initiated, a test should be conducted to determine if the patient is responsive.

CONTINUED ON NEXT PAGE
DO dosage

Patients 1 month to 6 years
• The recommended starting dose of Kuvan is 10 mg/kg taken once daily.

Patients 7 years and older
• The recommended starting dose of Kuvan is 10 to 20 mg/kg taken once daily.

Blood Phe levels should be checked after 1 week of Kuvan treatment and periodically for up to a month. If blood Phe does not decrease from baseline at 10 mg/kg per day, the dose may be increased to 20 mg/kg per day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg per day are nonresponders and treatment with Kuvan should be discontinued in these patients.

Once responsiveness to Kuvan has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg per day according to response to therapy. Periodic blood Phe monitoring is recommended to assess blood Phe control.

FDA APPROVED INDICATIONS
Kuvan is a phenylalanine hydroxylase activator indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe restricted diet.

REFERENCES
GUIDELINES FOR USE

This medication is not approved for the requested indication unless prescribed by a hematologist or oncologist.

RATIONALE
Ensure appropriate diagnostic usage criteria for sargramostim.

FDA APPROVED INDICATIONS
It is indicated for acute myelogenous leukemia following induction chemotherapy in older adult patients, bone marrow transplant engraftment delay or failure, mobilization of peripheral blood hematopoietic progenitor cells, myeloid reconstitution after autologous or allogenic bone marrow transplant, and neutropenia associated with chemotherapy, acute myelogenous leukemia, PBPC transplant, or peripheral blood stem cell transplantation.

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/10
The guideline named SARILUMAB (Kevzara) requires a diagnosis of moderate to severe rheumatoid arthritis. The following criteria must be met:

- Therapy prescribed by or in consultation with a rheumatologist
- Previous trial of at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine or sulfasalazine
- Patient is 18 years of age or older
- Previous trial of TWO preferred agents: Actemra SC, Cimzia, Enbrel, Ocrecia SC, Simponi, or Xeljanz/Xeljanz XR

RENEWAL CRITERIA

The guideline for SARILUMAB (Kevzara) renewal requires a diagnosis of moderate to severe rheumatoid arthritis. The following criteria must also be met:

Renewal for the diagnosis of moderate to severe rheumatoid arthritis requires:

- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender or swollen joint count while on therapy.

RATIONALE

Ensure appropriate use of Kevzara consistent with its FDA approved indications.

FDA APPROVED INDICATION

Kevzara is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).

DOSAGE AND ADMINISTRATION

Kevzara may be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs. The recommended dosage of Kevzara is 200 mg once every two weeks given as a subcutaneous injection. Reduce dose to 150 mg once every two weeks for management of neutropenia, thrombocytopenia and elevated liver enzymes.

DOSAGE FORMS AND STRENGTHS

Single-dose prefilled syringes are available for subcutaneous administration:

- 150 mg per 1.14 mL
- 200 mg per 1.14 mL

REFERENCE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for SECUKINUMAB (Cosentyx) requires a diagnosis of moderate to severe plaque psoriasis, psoriatic arthritis, or ankylosing spondylitis. Additional guideline requirements apply.

For patients with moderate to severe plaque psoriasis (PsO), approval requires all of the following:
- Therapy prescribed by or in consultation with a dermatologist
- Psoriatic lesions involving greater than or equal to 10% of body surface area (BSA) OR psoriatic lesions affecting the face, hands, feet, or genital area
- Previous trial of at least ONE of the following preferred therapies: PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- 18 years of age or older

For patients with psoriatic arthritis (PsA), approval requires all of the following:
- Therapy prescribed by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least ONE of the following DMARDS (disease-modifying anti-rheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older

For patients with ankylosing spondylitis (AS), approval requires BOTH of the following:
- Therapy prescribed by or in consultation with a rheumatologist
- 18 years of age or older

RENEWAL CRITERIA

Our guideline for SECUKINUMAB (Cosentyx) renewal requires a diagnosis of moderate to severe plaque psoriasis, psoriatic arthritis, or ankylosing spondylitis. Additional guideline requirements apply.

For the diagnosis of moderate to severe plaque psoriasis (PsO), approval requires documentation confirming that the patient has achieved clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50%.

For the diagnosis of psoriatic arthritis (PsA), approval requires documentation confirming that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy.

For the diagnosis of ankylosing spondylitis (AS), approval requires documentation confirming that the patient has experienced or maintained an improvement of at least 50% or 2 units (scale of 1 - 10) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

CONTINUED ON NEXT PAGE
SEUKINUMAB

RATIONALE
Ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for Cosentyx.

FDA APPROVED INDICATIONS
Cosentyx is a human interleukin-17A antagonist indicated for the treatment of:
- Moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
- Adult patients with active psoriatic arthritis
- Adult patients with active ankylosing spondylitis

DOSAGE AND ADMINISTRATION
Cosentyx is administered by subcutaneous injection

Plaque Psoriasis
The recommended dose is 300 mg subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300mg every 4 weeks; for some patients 150mg may be acceptable.

Psoriatic Arthritis
For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing and administration recommendations for plaque psoriasis.

For other psoriatic arthritis patients, administer Cosentyx with or without a loading dose by subcutaneous injection. The recommended dosage:
- With a loading dose is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
- Without a loading dose is 150 mg every 4 weeks.
- If the patient continues to have active psoriatic arthritis, consider a dosage of 300 mg.

Ankylosing Spondylitis
Administer Cosentyx with or without a loading dose by subcutaneous injection. The recommended dosage:
- With a loading dose is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
- Without a loading dose is 150 mg every 4 weeks.

DOSAGE FORMS AND STRENGTHS
Cosentyx Sensoready pen:
- NDC 0078-0639-41: Carton of two 150mg/ml (300mg) Sensoready pens (injection)
- NDC 0078-0639-68: Carton of one 150mg/ml (300mg) Sensoready pens (injection)
Cosentyx prefilled syringe:
- NDC 0078-0639-98: Carton of two 150mg/ml (300mg) single-use prefilled syringes (injection)
- NDC 0078-0639-97: Carton of one 150mg/ml (300mg) single-use prefilled syringes (injection)
For injection: 150mg, lyophilized powder in a single-use vial for reconstitution for healthcare professional use

CONTINUED ON NEXT PAGE
REFERENCES


Created: 06/15
Effective: 06/18/18
Client Approval: 05/31/18
P&T Approval: N/A
## SEDATIVE HYPNOTICS/BENZODIAZEPINES

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SEDATIVE HYPNOTICS/BENZODIAZEPINES

GUIDELINES FOR USE

Our guideline for SEDATIVE HYPNOTICS/BENZODIAZEPINES does not allow the use of sedative hypnotics or benzodiazepines above the standard quantity limits detailed in APPENDIX 1 (located in the rationale of this guideline).

Our guideline for SEDATIVE HYPNOTICS/BENZODIAZEPINES for patients with claims suggesting therapeutic duplication requires that the medications are being cross-tapered or that the medication in history is being discontinued.

Our guideline for BENZODIAZEPINES does not allow use of carisoprodol-containing products at the same time with the requested medication.

Our guideline for BENZODIAZEPINES for patients with claims in history for opioid analgesics requires that the prescriber submit the required fax form documenting ALL of the following:

• The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  o For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or pregabalin
  o For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA)
  o For social anxiety disorder (SAD), a trial of an SSRI is required
  o For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  o For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  o For insomnia, one of the following is required: ramelteon or a sedating antidepressant (i.e., trazodone, amitriptyline, doxepin, mirtazapine)

• The diagnosis contributing to the need for opioid analgesic therapy and previous therapy attempted, including dates and doses of prior therapies
  o For short-acting opioid therapy requested for post-surgical pain or pain related to an acute injury, the date of surgery or injury is required AND the prescriber must provide documentation of a clear plan for opioid dose tapering and discontinuation
  o For short-acting opioid therapy requested for chronic moderate to severe pain, a trial of one non-drug treatment for pain (e.g., thermotherapy, cryotherapy, massage therapy, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), physical therapy) unless contraindicated AND two non-opioid drug treatments prescribed for pain from different drug classes (e.g., non-steroidal anti-inflammatory drugs, acetaminophen, anticonvulsants, antidepressants) at maximum therapeutic doses unless contraindicated or not tolerated is required. Chart notes indicating doses and dates of therapy are required in the absence of electronic prescription claims history

(Guideline continued on next page)

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE (CONTINUED)

- For long-acting opioid therapy requested for chronic moderate to severe pain, **ALL** of the following are required:
  - The patient meets the definition of opioid tolerance (defined as those who are taking, for one week or longer, at least 60mg oral morphine/day, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid)
  - For any long-acting opioid other than MS Contin, the patient has had a trial of at least 30 days generic MS Contin in the previous 120 days
- The prescriber’s signed attestation as to **ALL** of the following:
  - The prescriber will regularly review the patient’s controlled substance utilization contained within INSPPECT
  - The patient has been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both the prescriber and the patient accept the risk of using benzodiazepines and opioid analgesics together at the same time

**RATIONALE**

To promote prudent prescribing of sedative-hypnotics and benzodiazepines and to promote patient safety when benzodiazepines are used in combination with other agents.

A look back period of 60 days will be utilized to identify potential therapeutic duplication of sedative hypnotics/benzodiazepines.

Prior authorization is not required for rectal benzodiazepine preparations.

**Long-Term Benzodiazepine Utilization and Guideline Recommendations**

According to the National Institute for Health and Clinical Excellence (NICE) and the World Federation of Societies of Biological Psychiatry (WFSBP) treatment guidelines, benzodiazepines are not recommended, or are recommended in short-term situations or treatment-refractory patients only for the following disease states: generalized anxiety disorder (GAD), panic disorder, social anxiety disorder (SAD), obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). The American Academy of Sleep Medicine does not recommend long-term hypnotic (including benzodiazepine) use, except for those patients with severe, refractory insomnia. Because of the high risk of side effects and accidental death associated with benzodiazepine use, practice guidelines are decreasingly utilizing benzodiazepines as appropriate options for treatment of mental health disorders. Per the Centers of Disease Control and Prevention, overdose deaths had increased by 23% between 2010 and 2014. Two of the top 10 drugs involved in these overdoses were alprazolam and diazepam, often in combination with other substances. Benzodiazepine agents were involved in around 30% of prescription-drug overdose deaths in 2013; the death rate related to benzodiazepine overdose quadrupled between 1999 and 2013.

**CONTINUED ON NEXT PAGE**
SEDATIVE HYPNOTICS/BENZODIAZEPINES

RATIONALE (CONTINUED)

Benzodiazepine use has both long-term and short-term consequences. Short-term effects include sleepiness, risk of motor vehicle accidents, risk of falls (and potentially consequential fractures), and propensity for abuse or misuse. Long-term consequences include tolerance and physical dependence, as well as cognitive and memory impairment. Treatment discontinuation after long-term use can precipitate withdrawal symptoms, including anxiety, depression, hypersensitivity to sensory stimuli, perceptual distortions, and depersonalizations. In addition, psychiatric symptoms may return in greater severity than pre-treatment levels and may persist for extended periods. Because of the many risks associated with discontinuation of long-term treatment, it is important to have a discontinuation protocol to minimize adverse events of withdrawal. Discontinuation protocols should include a plan for step-wise reduction in benzodiazepine use and methods for managing withdrawal symptoms during tapering.

When discontinuing benzodiazepine therapy, gradual dose tapering with the support of psychotherapy, follow-up visits, and written instructions to manage withdrawal symptoms is an effective discontinuation intervention. Discussing the risk of long-term benzodiazepine use as well as the advantages to discontinuation has been shown to be more effective in achieving benzodiazepine discontinuation when used concurrently with gradual dose tapering. Gradual dose tapering is patient-specific: evaluating current therapies, type of benzodiazepine, current dosing, and other patient factors when designing the taper.

When beginning a gradual taper, many guidelines recommend converting the total daily dose to a diazepam-equivalent dosing and slowly converting the benzodiazepine to a diazepam dose three times a day. Converting to diazepam may prevent sharp plasma fluctuations due to its long half-life, and it is available in multiple strengths that aid in dose reduction. Other studies state that converting to a long-acting benzodiazepine for tapering has not shown additional benefit in preventing withdrawal symptoms. However, if choosing to convert to diazepam, it is recommended to change the evening dose to diazepam first to help limit daytime sleepiness. The conversion table below reflects the approximate equivalent doses and half-life for available benzodiazepines.

CONTINUED ON NEXT PAGE
### RATIONALE (CONTINUED)

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Half-life (hours) [active metabolite]</th>
<th>Approximately Equivalent Oral Dosages (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam (Xanax)</td>
<td>6-12</td>
<td>0.5</td>
</tr>
<tr>
<td>chlordiazepoxide (Librium)</td>
<td>5-30 [36-200]</td>
<td>25</td>
</tr>
<tr>
<td>clobazam (Onfi)</td>
<td>12-60</td>
<td>20</td>
</tr>
<tr>
<td>clonazepam (Klonopin)</td>
<td>18-50</td>
<td>0.5</td>
</tr>
<tr>
<td>clorazepate (Tranxene)</td>
<td>[36-200]</td>
<td>15</td>
</tr>
<tr>
<td>diazepam (Valium)</td>
<td>20-100 [36-200]</td>
<td>10</td>
</tr>
<tr>
<td>estazolam</td>
<td>10-24</td>
<td>1-2</td>
</tr>
<tr>
<td>flurazepam</td>
<td>[40-250]</td>
<td>15-30</td>
</tr>
<tr>
<td>lorazepam (Ativan)</td>
<td>10-20</td>
<td>1</td>
</tr>
<tr>
<td>oxazepam</td>
<td>4-15</td>
<td>20</td>
</tr>
<tr>
<td>quazepam (Doral)</td>
<td>25-100</td>
<td>20</td>
</tr>
<tr>
<td>temazepam (Restoril)</td>
<td>8-22</td>
<td>20</td>
</tr>
<tr>
<td>triazolam (Halcion)</td>
<td>2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Benzodiazepine with Similar Effects</th>
<th>Half-life (hours) [active metabolite]</th>
<th>Approximately Equivalent Oral Dosages (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>zaleplon (Sonata)</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>zolpidem (Ambien)</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>zopiclone</td>
<td>5-6</td>
<td>15</td>
</tr>
<tr>
<td>eszopiclone (Lunesta)</td>
<td>6 (9 in elderly)</td>
<td>3</td>
</tr>
</tbody>
</table>

When beginning the discontinuation phase, it is recommended that the dose be tapered with a 5-10% reduction every 1-2 weeks, with a slower dose reduction when achieving lower doses. Gradual benzodiazepine tapers can often take from 3-4 months to a year (or longer). Benzodiazepine tapers are patient-specific and should be tailored based upon patient factors and responses to the taper. An example dose reduction from diazepam 40mg per day is as follows:

- decrease the dose by 2-4mg every 1-2 weeks until reaching 20mg per day, then
- decrease by 1-2mg every 1-2 weeks until reaching 10mg per day, then
- decrease by 1mg every 1-2 weeks until reaching 5mg per day, then
- decrease dose by 0.5-1mg every 1-2 weeks until complete.

For additional examples on benzodiazepine tapers and information on when and how to convert benzodiazepine dosing to diazepam, please access the Ashton Guidelines at https://benzo.org.uk/manual/bzsched.htm.

CONTINUED ON NEXT PAGE
RATIONAL (CONTINUED)
In addition to planning a discontinuation protocol, it is important to engage a member in their discontinuation or dose reduction of benzodiazepine use. Empowering patients and providing educational interventions can catalyze a shared decision-making relationship, which can improve concordance and clinical outcomes when de-prescribing benzodiazepines. Education can include information regarding risks of benzodiazepine use, evidence for benzodiazepine-induced harms, drug interaction potential, and suggestions for equally or more effective therapeutic substitutes. Conversations regarding benzodiazepine discontinuation can be initiated in both prescriber office and pharmacy settings.

Guideline-centered treatment should be considered as a substitute for short- and long-term benzodiazepine use. The NICE guidelines provide a stepped approach for the disease states below:

- Generalized Anxiety Disorder (GAD) - Those that have found no improvement with low-intensity psychological interventions (individual non-facilitated self-help, individual guided self-help, or psychoeducational group therapy) should be considered for individual high-intensity psychological intervention (cognitive behavioral therapy (CBT) or applied relaxation) and/or drug treatment. Selective serotonin reuptake inhibitors (SSRIs) should be offered as first-line drug therapy. Serotonin-noradrenaline reuptake inhibitors and pregabalin can be considered upon failure of or intolerance to a SSRI. Benzodiazepines are not recommended for the treatment of GAD in primary or secondary care except as a short-term measure during a crisis. Antipsychotics are also discouraged for the treatment of GAD.

- Panic Disorder - For patients with mild to moderate panic disorder, low-intensity interventions may be sufficient. Those with moderate to severe panic disorder should be considered for CBT or pharmacologic intervention. The evidence base suggests SSRI or tricyclic antidepressant (TCA) therapy for longer-term management of panic disorder. Benzodiazepines are associated with a less positive outcome with long-term use and should not be prescribed for the treatment of panic disorder. NICE guidelines also discourage the use of sedating antihistamines or antipsychotics for treatment.

- Social Anxiety Disorder (SAD) - CBT is recommended as the initial treatment option for adults with SAD. For those wishing to consider pharmacological intervention, SSRIs are the recommended therapeutic choice. Anticonvulsants, TCAs, benzodiazepines, and antipsychotics should not be routinely offered for the treatment of SAD.

- Obsessive Compulsive Disorder (OCD) - Initial approach should be low-intensity or high-intensity psychological intervention, depending on severity of the OCD. A SSRI should also be considered for those with moderate to severe functional impairment in coordination with psychological intervention. Benzodiazepine use for the treatment of OCD is not recommended within this guideline.

- Post-Traumatic Stress Disorder (PTSD) - All PTSD sufferers should be offered a course of trauma-focused psychological treatment. For those requiring pharmacological intervention, mirtazapine, paroxetine, amitriptyline, and phenelzine have evidence of clinically or statistically significant benefits. For those with sleep interruption due to PTSD, sedative-hypnotics may be appropriate for short-term use only. Benzodiazepine use for the treatment of PTSD is not recommended within this guideline.

CONTINUED ON NEXT PAGE
**SEDATIVE HYPNOTICS/BENZODIAZEPINES**

**RATIONALE (CONTINUED)**

- Insomnia - Initial approaches to treatment include behavioral interventions and sleep hygiene education. If pharmacological treatment is warranted, the American Academy of Sleep Medicine recommends short-term use of one of the following: sedative-hypnotics (zolpidem, eszopiclone, zaleplon, temazepam), ramelteon, or sedating antidepressants (trazodone, amitriptyline, doxepin, mirtazapine). Use of anti-epilepsy medications (gabapentin, tiagabine) or atypical antipsychotics (quetiapine, olanzapine) should only be considered when comorbidities may benefit from the primary action of the medications. Over-the-counter sleep remedies, barbiturates, and chloral hydrate are not recommended for the treatment of insomnia. Pharmacological therapy should be prescribed initially for 2 to 4 weeks only, followed by re-evaluation of the continued need for treatment. Chronic use of hypnotic medications may be indicated for those with severe or refractory insomnia or chronic comorbid illnesses.

For all of the above disease states, comorbidities (depression, substance abuse, etc.) should be considered and addressed for best clinical outcomes.

**APPENDIX 1: Sedative Hypnotics/Benzodiazepines Standard Quantity Limits**

<table>
<thead>
<tr>
<th>GPID</th>
<th>Generic Drug Name</th>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Route</th>
<th>Strength</th>
<th>Utilization Edit</th>
</tr>
</thead>
<tbody>
<tr>
<td>14260</td>
<td>ALPRAZOLAM</td>
<td>XANAX</td>
<td>TABS</td>
<td>OR</td>
<td>0.25 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14261</td>
<td>ALPRAZOLAM</td>
<td>XANAX</td>
<td>TABS</td>
<td>OR</td>
<td>0.5 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14262</td>
<td>ALPRAZOLAM</td>
<td>XANAX</td>
<td>TABS</td>
<td>OR</td>
<td>1 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14263</td>
<td>ALPRAZOLAM</td>
<td>XANAX</td>
<td>TABS</td>
<td>OR</td>
<td>2 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14264</td>
<td>ALPRAZOLAM</td>
<td>ALPRAZOLAM INTENSOL</td>
<td>CONC</td>
<td>OR</td>
<td>1 MG/ML</td>
<td>4 ML/DAY</td>
</tr>
<tr>
<td>24368</td>
<td>ALPRAZOLAM</td>
<td>ALPRAZOLAM ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>0.25 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>24369</td>
<td>ALPRAZOLAM</td>
<td>ALPRAZOLAM ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>0.5 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>24373</td>
<td>ALPRAZOLAM</td>
<td>ALPRAZOLAM ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>1 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>24374</td>
<td>ALPRAZOLAM</td>
<td>ALPRAZOLAM ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>2 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>17423</td>
<td>ALPRAZOLAM</td>
<td>XANAX XR</td>
<td>TB24</td>
<td>OR</td>
<td>0.5 MG</td>
<td>1/DAY</td>
</tr>
<tr>
<td>17424</td>
<td>ALPRAZOLAM</td>
<td>XANAX XR</td>
<td>TB24</td>
<td>OR</td>
<td>1 MG</td>
<td>1/DAY</td>
</tr>
<tr>
<td>17425</td>
<td>ALPRAZOLAM</td>
<td>XANAX XR</td>
<td>TB24</td>
<td>OR</td>
<td>2 MG</td>
<td>1/DAY</td>
</tr>
<tr>
<td>19681</td>
<td>ALPRAZOLAM</td>
<td>XANAX XR</td>
<td>TB24</td>
<td>OR</td>
<td>3 MG</td>
<td>1/DAY</td>
</tr>
<tr>
<td>14033</td>
<td>CHLORDIAZEPoxide HCL</td>
<td>CHLORDIAZEPoxide HCL</td>
<td>CAPS</td>
<td>OR</td>
<td>5 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14031</td>
<td>CHLORDIAZEPoxide HCL</td>
<td>CHLORDIAZEPoxide HCL</td>
<td>CAPS</td>
<td>OR</td>
<td>10 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14032</td>
<td>CHLORDIAZEPoxide HCL</td>
<td>CHLORDIAZEPoxide HCL</td>
<td>CAPS</td>
<td>OR</td>
<td>25 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14092</td>
<td>CLORAZEPATE DIPOTASSIUM</td>
<td>TRANXENE T</td>
<td>TABS</td>
<td>OR</td>
<td>3.75 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>14093</td>
<td>CLORAZEPATE DIPOTASSIUM</td>
<td>TRANXENE T</td>
<td>TABS</td>
<td>OR</td>
<td>7.5 MG</td>
<td>4/DAY</td>
</tr>
<tr>
<td>Code</td>
<td>Drug Name</td>
<td>Formulation</td>
<td>Route</td>
<td>Dosage</td>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------</td>
<td>-------------</td>
<td>-------</td>
<td>--------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>14090</td>
<td>Clorazepate DIPOTASSIUM</td>
<td>TABS</td>
<td>OR</td>
<td>15 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14221</td>
<td>Diazepam Valium</td>
<td>TABS</td>
<td>OR</td>
<td>2 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14222</td>
<td>Diazepam Valium</td>
<td>TABS</td>
<td>OR</td>
<td>5 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14220</td>
<td>Diazepam Valium</td>
<td>TABS</td>
<td>OR</td>
<td>10 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>45550</td>
<td>Diazepam Intensol</td>
<td>CONC</td>
<td>OR</td>
<td>5 MG/ML</td>
<td>8 ML/DAY</td>
<td></td>
</tr>
<tr>
<td>14160</td>
<td>Lorazepam Ativan</td>
<td>TABS</td>
<td>OR</td>
<td>0.5 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14161</td>
<td>Lorazepam Ativan</td>
<td>TABS</td>
<td>OR</td>
<td>1 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14162</td>
<td>Lorazepam Ativan</td>
<td>TABS</td>
<td>OR</td>
<td>2 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14230</td>
<td>Oxazepam Oxazepam</td>
<td>CAPS</td>
<td>OR</td>
<td>10 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14231</td>
<td>Oxazepam Oxazepam</td>
<td>CAPS</td>
<td>OR</td>
<td>15 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>14232</td>
<td>Oxazepam Oxazepam</td>
<td>CAPS</td>
<td>OR</td>
<td>30 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>13801</td>
<td>Meprobamate Meprobamate</td>
<td>TABS</td>
<td>OR</td>
<td>200 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>13802</td>
<td>Meprobamate Meprobamate</td>
<td>TABS</td>
<td>OR</td>
<td>400 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>9071</td>
<td>Clobazam ONFI</td>
<td>TABS</td>
<td>OR</td>
<td>10 MG</td>
<td>8/DAY</td>
<td></td>
</tr>
<tr>
<td>9070</td>
<td>Clobazam ONFI</td>
<td>TABS</td>
<td>OR</td>
<td>20 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>35026</td>
<td>Clobazam Onfi Suspension</td>
<td>SUSP</td>
<td>OR</td>
<td>2.5 MG/ML</td>
<td>32 ML/DAY</td>
<td></td>
</tr>
<tr>
<td>45264</td>
<td>Clobazam Sympazan</td>
<td>FILM</td>
<td>OR</td>
<td>5 MG</td>
<td>8/DAY</td>
<td></td>
</tr>
<tr>
<td>45265</td>
<td>Clobazam Sympazan</td>
<td>FILM</td>
<td>OR</td>
<td>10 MG</td>
<td>8/DAY</td>
<td></td>
</tr>
<tr>
<td>45266</td>
<td>Clobazam Sympazan</td>
<td>FILM</td>
<td>OR</td>
<td>20 MG</td>
<td>4/DAY</td>
<td></td>
</tr>
<tr>
<td>17470</td>
<td>Clonazepam Klonopin</td>
<td>TABS</td>
<td>OR</td>
<td>0.5 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>17471</td>
<td>Clonazepam Klonopin</td>
<td>TABS</td>
<td>OR</td>
<td>1 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>17472</td>
<td>Clonazepam Klonopin</td>
<td>TABS</td>
<td>OR</td>
<td>2 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>19467</td>
<td>Clonazepam ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>0.125 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>19468</td>
<td>Clonazepam ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>0.25 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>19469</td>
<td>Clonazepam ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>0.5 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>19470</td>
<td>Clonazepam ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>1 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>19472</td>
<td>Clonazepam ODT</td>
<td>TBDP</td>
<td>OR</td>
<td>2 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>13102</td>
<td>Butabarbital Sodium</td>
<td>TABS</td>
<td>OR</td>
<td>30 MG</td>
<td>3/DAY</td>
<td></td>
</tr>
<tr>
<td>19181</td>
<td>Estazolam Estazolam</td>
<td>TABS</td>
<td>OR</td>
<td>1 MG</td>
<td>1/DAY</td>
<td></td>
</tr>
<tr>
<td>19182</td>
<td>Estazolam Estazolam</td>
<td>TABS</td>
<td>OR</td>
<td>2 MG</td>
<td>1/DAY</td>
<td></td>
</tr>
<tr>
<td>14250</td>
<td>Flurazepam HCL</td>
<td>CAPS</td>
<td>OR</td>
<td>15 MG</td>
<td>1/DAY</td>
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</tr>
<tr>
<td>14251</td>
<td>Flurazepam HCL</td>
<td>CAPS</td>
<td>OR</td>
<td>30 MG</td>
<td>1/DAY</td>
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<tr>
<td>40870</td>
<td>Quazepam Doral</td>
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<td>1/DAY</td>
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<tr>
<td>13845</td>
<td>Temazepam Restoril</td>
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<td>OR</td>
<td>7.5 MG</td>
<td>1/DAY</td>
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<td>OR</td>
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<td>OR</td>
<td>22.5 MG</td>
<td>1/DAY</td>
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<td>30 MG</td>
<td>1/DAY</td>
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<tr>
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### APPENDIX 2: Specific Quantity Limits for Initial Benzodiazepine Use with Opioid Analgesics

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<tr>
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</tr>
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<td>1/DAY</td>
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<td>1/DAY</td>
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<td>13841</td>
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<td>RESTORIL</td>
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<td></td>
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<tr>
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<td>TRIAZOLAM</td>
<td>TRIAZOLAM</td>
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<td>2 TABS/10 DAYS</td>
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<td>HALCION</td>
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<td>2 TABS/10 DAYS</td>
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</table>

CONTINUED ON NEXT PAGE
APPENDIX 3: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM

INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY
PRIOR AUTHORIZATION REQUEST FORM

<table>
<thead>
<tr>
<th>Benzodiazepine Agents(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
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<th>Prescriber Name*</th>
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<tbody>
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*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:
- Are you requesting PA for:  Benzodiazepine Agent(s) □  Opioid Agent(s) □  Both □
- Is/are the other prescriber(s) aware of the request for concurrent therapy? □ Yes □ No

PA is required for the following:
- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).
• Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? □ Yes □ No

PA Requirements:

Patient diagnosis/diagnoses for use of benzodiazepine therapy:

Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you plan to continue benzodiazepine therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Patient diagnosis/diagnoses for use of opioid therapy:

Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, ____________________________________________, hereby attest to the following:

(Prescriber Name)

• The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
• I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
• If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
• I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber Signature: ____________________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**
REFERENCES


- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).


This drug requires a written request for prior authorization.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)
Our guideline for SELEXIPAG (Uptravi) requires diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1) and ALL of the following criteria are met:

- Prescribed by or in consultation with a cardiologist or pulmonologist
- Documented confirmatory PAH diagnosis based on right heart catheterization
- NYHA-WHO functional class II-IV symptoms

RENEWAL CRITERIA
The guideline for SELEXIPAG (Uptravi) renewal requires a diagnosis of pulmonary arterial hypertension. The following criteria must also be met:

- The patient has shown improvement from baseline in the 6-minute walk distance test OR
- The patient has a stable 6-minute walk distance test with a stable or improved WHO functional class

RATIONALE
Promote appropriate utilization of SELEXIPAG based on FDA approved indication.

Pulmonary arterial hypertension (PAH) is a chronic, progressive, and debilitating rare lung disease that can lead to death or the need for lung transplantation. The currently available therapeutic options to treat patients with PAH include: endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE-5i), soluble guanylate cyclase stimulators, and prostacyclin receptor agonists. Uptravi will be the second oral prostacyclin agent for PAH, joining Orenitram (treprostinil), although unlike the other prostacyclin agents it is selective for the IP receptor. Inhaled, subcutaneous and intravenously administered forms of prostacyclins are often reserved for more severe/progressive PAH patients.

CONTINUED ON NEXT PAGE
RATIONAL OFF (CONTINUED)

Guidelines recommend a confirmatory diagnosis of PAH based on right heart catheterization. Optimal therapy for a PAH patient is a highly individualized clinical decision considering several factors such as severity of illness, route of administration, side effects, comorbidities, treatment goals. Baseline severity should be determined prior to initiation of therapy and this is done using the World Health Organization functional classifications (WHO-FC), which categorizes patients into four classes (I-IV) based on symptoms and tolerance of physical activity. The overall treatment goals are to address underlying etiology, improve symptoms/exercise capacity (achieve a low risk status [FC I or II]), prevent progression of disease, and improve survival and quality of life. The currently available oral therapeutic options to treat patients with PAH include: endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE-5i), soluble guanylate cyclase stimulators, and prostacyclin receptor agonists (Orenitram). Monotherapy with an oral drug is recommended for initial treatment of PAH and this can include an ERA or PDE-5i, which are typically first line, or a soluble guanylate cyclase stimulator. For those patients with advanced disease (WHO-FC III-IV), an inhaled, subcutaneous or intravenous prostacyclin may also be considered. Current US guidelines recommend treatment with two or more classes of PAH drugs only when the response is inadequate or the patient deteriorates on monotherapy, but recently published European guidelines include recommendations for initial combination therapy. Although there is limited data available on the effectiveness of combination therapy for initial treatment of PAH, the combination therapy of agents with different mechanisms of action may become preferred over monotherapy due to recent data demonstrating a benefit in morbidity/mortality.

DOSAGE
The starting dose of Uptravi is 200mcg by mouth twice daily and increased in increments of 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600mcg twice daily. The target dose will be individualized based on patient tolerability and tolerability may be improved with food. In addition, a dose reduction should be made in patients that reach a dose that can't be tolerated.

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of Uptravi is 200 mcg once daily. Increase in increments of 200 mcg once daily at weekly intervals, as tolerated.

FDA APPROVED INDICATIONS
Uptravi is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

AVAILABLE STRENGTHS
- 200 microgram tablet
- 400 microgram tablet
- 600 microgram tablet
- 800 microgram tablet
- 1000 microgram tablet
- 1200 microgram tablet
- 1400 microgram tablet
- 1600 microgram tablet
- Titration pack: 140 count bottle of 200 microgram tablets and a 60 count bottle of 800 microgram tablets

CONTINUED ON NEXT PAGE
REFERENCES


Created: 01/16
Effective: 11/01/18
Client Approval: 09/24/18
P&T Approval: N/A
# SHORT-ACTING OPIOID ANALGESICS

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<th>Brand</th>
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<th>GCN</th>
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MDwise MANAGED MEDICAID
PRIOR AUTHORIZATION GUIDELINES

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<th>TRAMADOL HCL</th>
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<tr>
<td>TRAMADOL HCL WITH ACETAMINOPHEN</td>
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</table>

**GUIDELINES FOR USE**

RENEWAL CRITERIA will apply in the following scenarios only:

- For patients active with MDwise for 90 days or longer AND previous prior authorization approval for the same medication with the same strength AND recent paid pharmacy claims for the requested medication. Chart notes and/or cash pay for opioid use is not accepted.
- For patients new to MDwise within the past 90 days AND chart notes are provided that document the patient is stable on the requested medication.

All other requests will be reviewed against the INITIAL CRITERIA.

**INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)**

Our guideline for SHORT-ACTING OPIOID ANALGESICS for patients with past use of opioid dependency agents (such as, buprenorphine/naloxone SL tablets/films or buprenorphine SL tablets) requires the buprenorphine/naloxone or buprenorphine prescribing physician be notified about prescribed opiate therapy and must approve the use before the opioid analgesic will be authorized.

Our guideline for SHORT-ACTING OPIOID ANALGESICS does not permit concurrent use with carisoprodol-containing products.

Our guideline for SHORT-ACTING OPIOID ANALGESIC (DEMEROL) requires ALL of the following criteria to be met:

- You have a diagnosis of chronic moderate to severe pain
- Documentation of one non-pharmacological ancillary treatment for pain [such as thermotherapy, cryotherapy, massage therapy, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), physical therapy] of 6 weeks duration within the previous 2 years unless contraindicated. Documentation must include dates of therapy
- You have tried and failed TWO non-opioid pharmacological ancillary treatments prescribed for pain from different drug classes (e.g., NSAIDs, acetaminophen, anticonvulsants, antidepressants) at maximum therapeutic doses within the previous 365 days unless contraindicated or not tolerated. Submission of chart notes documenting trial dates and dosage is required in the absence of electronic prescription claims history
- You have tried and failed TWO oral short-acting opioid analgesics (e.g., codeine/APAP, hydrocodone/APAP, hydromorphone, morphine sulfate IR, oxycodone/APAP, oxycodone IR)

Our guideline for SHORT-ACTING OPIOID ANALGESICS for patients with post-surgical pain (pain after surgery) or pain related to an acute (sudden and severe) injury requires your prescriber has provided BOTH of the following:

- The date of surgery/injury
- Documentation of a clear plan for opioid dose tapering (slow decrease in dose) and discontinuation

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for SHORT-ACTING OPIOID ANALGESICS for patients with moderate to severe chronic pain requires that BOTH of the following rules are met:

- Your provider documented the trial of one non-drug treatment (for example, thermotherapy, cryotherapy, massage therapy, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), physical therapy) of 6 weeks duration within the previous 2 years unless contraindicated AND
- You have tried TWO non-opioid drug treatments prescribed for pain from different drug classes (for example, non-steroidal anti-inflammatory drugs, acetaminophen, anticonvulsants, antidepressants) at maximum therapeutic doses within the previous 365 days unless contraindicated or not tolerated. Chart notes indicating dates of trial and dosage is required in the absence of electronic prescription claims history.

Exceptions may be granted for patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan.

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

Our guideline named SHORT-ACTING OPIOID ANALGESICS for concurrent use of more than one short-acting opioid requires that you meet ALL of the following criteria:

- You have a diagnosis of moderate to severe pain
- You have a pain that is not responding to treatment despite concurrent (used at the same time) therapy with one short-acting opioid and one long-acting opioid
- Your prescriber has consulted with you regarding the risks of opioid therapy and developed a pain management plan with clear treatment goals

Exceptions to these criteria may be authorized in patients with moderate to severe pain from cancer or sickle cell disease or those receiving opioids as part of a palliative care (medical care for symptoms related to illness) plan.

Please note that additional criteria apply for concurrent use of opioid analgesics and benzodiazepines, including submission of signed prescriber attestation on a state-mandated fax form.

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

Our guideline for SHORT-ACTING OPIOID ANALGESICS for patients with claims in history for benzodiazepines requires that your doctor submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies, documented in chart notes
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)

- The diagnosis contributing to the need for opioid analgesic therapy and previous therapy attempted, including dates and doses of prior therapies
  - For short term opioid therapy (up to 30 days) requested for post-surgical pain (pain after surgery) or pain related to an acute (sudden and severe) injury, the date of surgery or injury is required AND your provider must provide documentation of a clear plan for opioid dose tapering (slowly lowering the dosage) and discontinuation
  - For chronic opioid therapy (greater than 30 days), a trial of one non-drug treatment (for example, thermotherapy, cryotherapy, massage therapy, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), physical therapy) for 6 weeks duration within the previous 2 years unless there is a medical reason why you cannot (contraindication) AND TWO non-opioid drug treatments prescribed for pain from different drug classes (for example, non-steroidal anti-inflammatory drugs, acetaminophen, anticonvulsants, antidepressants) at maximum therapeutic doses unless contraindicated or not tolerated is required. Chart notes indicating doses and dates of therapy are required in the absence of electronic prescription claims history
  - For a diagnosis of moderate to severe cancer-related pain, pain related to sickle cell disease, or pain in patients receiving palliative care, no additional criteria applies

Our guideline for SHORT-ACTING OPIOID ANALGESICS for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA

Our guideline for SHORT-ACTING OPIOID ANALGESICS does not permit concurrent use with carisoprodol-containing products.

Our renewal guideline for SHORT-ACTING OPIOID ANALGESICS requires you to meet ALL of the following criteria:

- Opioid therapy has resulted in a meaningful improvement in your pain and/or function
- Your prescriber has developed an updated pain management plan with clear treatment goals
- Risk assessment has been performed including review of the state prescription drug monitoring program (PDMP) data (such as, INSPECT)
- Adherence to prescribed opioid regimen has been periodically assessed (for example, urine drug screen, pill counts)

Our renewal guideline for SHORT-ACTING OPIOID ANALGESICS for patients with claims in history for benzodiazepines requires that the prescriber submit the required fax form documenting ALL of the following:

- The diagnosis contributing to the need for benzodiazepine therapy and previous therapy attempted, including dates and doses of prior therapies
  - For generalized anxiety disorder, one of the following is required: Selective serotonin reuptake inhibitor (SSRI, such as sertraline or citalopram), serotonin-noradrenaline reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), or pregabalin (generic for Lyrica)
  - For panic disorder, one of the following is required: SSRI or tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline)
  - For social anxiety disorder (SAD), a trial of an SSRI is required
  - For obsessive compulsive disorder (OCD), a trial of an SSRI is required
  - For post-traumatic stress disorder (PTSD), one of the following is required: mirtazapine, paroxetine, amitriptyline, or phenelzine
  - For insomnia, one of the following is required: ramelteon or a sedating antidepressant (for example, trazodone, amitriptyline, doxepin, mirtazapine)
- The diagnosis contributing to the need for renewal of the requested opioid analgesic therapy
- Your prescriber has signed an attestation as to ALL of the following:
  - Your provider will regularly review your controlled substance utilization contained within INSPECT
  - You have been educated about the risks of using benzodiazepines and opioid analgesics together at the same time
  - Both you and your provider accept the of using benzodiazepines and opioid analgesics together at the same time

CONTINUED ON NEXT PAGE
SHORT-ACTING OPIOID ANALGESICS

RENEWAL CRITERIA (CONTINUED)

Our guideline for SHORT-ACTING OPIOID ANALGESICS for patients with claims in history antipsychotics requires that your prescriber provides information indicating that the concurrent use of an opioid and an antipsychotic medication is intended and clinically appropriate for your condition. Please consult your physician if you have any questions about this prescription pain medication and the requirements needed for you to obtain an approval for this agent.

RATIONALE
To ensure opioid analgesics are used according to FDA approved indications with patient safety in mind, and to encourage the use of more cost-effective analgesics.

From 2000-2014, almost half a million people died due to drug overdose, with 2014 being the highest year for deaths on record. In that time, the number of opioids prescribed, as well as the number of opioid overdoses, has risen exponentially. At least half of all opioid overdose deaths involve a prescription opioid. Indiana was among the states that had a statistically significant increase of overdose deaths from 2013-2014.

According to recent research, the opioid epidemic has a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed opioids at double the rate of non-Medicaid patients, and are subsequently at much higher risk of prescription opioid overdose.

Improving the way that opioids are prescribed can ensure safer and more effective pain treatment, and reduce the addiction, misuse, abuse, and overdose of these drugs. These guidelines are to ensure that the use of opioids is consistent with their FDA approved indications, and to initiate action combating the current opioid epidemic.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 morphine milligram equivalents (MME)/day such as 60mg oral morphine/day, 25mcg transdermal fentanyl/hour, 40mg oral oxycodone/day, 15mg oral hydromorphone/day, 60mg oral hydrocodone/day, 400mg oral codeine/day, or an equianalgesic dose of another opioid for a week or longer.

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### Opioid Conversion Table

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<thead>
<tr>
<th>Drug</th>
<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
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<td>Butorphanol</td>
<td>7</td>
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<td>Codeine</td>
<td>0.15</td>
<td>400mg</td>
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<td>Fentanyl citrate</td>
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<td>Hydrocodone</td>
<td>1</td>
<td>60mg</td>
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<tr>
<td>Hydromorphone HCl</td>
<td>4</td>
<td>15mg</td>
</tr>
<tr>
<td>Meperidine HCl</td>
<td>0.1</td>
<td>600mg</td>
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<tr>
<td>Morphine</td>
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<td>60mg</td>
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### Methadone Conversion Table

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<th>MME Conversion Factor (1mg of drug to mg morphine)</th>
<th>60mg Morphine Equivalent Dose</th>
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<td>&gt;0, &lt;= 20</td>
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<td>&gt;60</td>
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<td>5mg</td>
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*Opioid Usage in Chronic Pain Management*

Per systematic review in the CDC Guideline for Prescribing Opioids for Chronic Pain, long-term (> 1 year) efficacy of opioids in management of chronic pain, function, or quality of life is not established. Most randomized controlled trials present effectiveness within 6 weeks or less. Conversely, significant risks of adverse events are present with chronic opioid therapy, including opioid abuse and dependence, social role withdrawal, and increased risk of CNS depression, and withdrawal emergencies.

CONTINUED ON NEXT PAGE
SHORT-ACTING OPIOID ANALGESICS

RATIONALE (CONTINUED)

The CDC also recommends re-evaluating and re-establishing treatment goals, including realistic expectation for pain and function, as well as discontinuation strategies when benefits do not outweigh risks. The guideline provides the following recommendations for opioid selection, dosage, duration, follow-up and discontinuation:

- Immediate-release (IR) opioids are preferred over extended-release (ER) forms.
- The lowest effective dosage is preferred with initial opioid use. Caution is warranted at any dose and reassessing benefits and risks is recommended for 50 morphine milligram equivalents (MME) daily or more. 90 MME daily or more should be avoided if possible.
- Within 1 to 4 weeks of therapy, clinicians should evaluate benefits and harms of using opioids to treat chronic pain. Therapy continuation should be evaluated every 3 months or sooner. If benefits do not outweigh harms to continue opioid therapy, other therapies should be optimized and opioid tapering/discontinuation should be considered and encouraged.

Assessing Risk and Addressing Harms of Opioid Use

- Prior to and throughout opioid therapy, adverse events should be evaluated periodically. Factors that increase risk for opioid overdose include history of overdose or substance use disorder, 50 MME daily or more, and concurrent benzodiazepine use.
- Prescription drug monitoring program (PDMP) data (e.g., RXINSPECT) are useful to monitor total opioid dosage. PDMP data is helpful for initial and periodic opioid usage evaluations.
- Prescribing opioids and benzodiazepines concurrently should be avoided.
- For patients with substance use disorder, evidence-based treatment (medication-assisted and behavioral therapy) is recommended.

Analysis performed by the US Department of Health and Human Services Center for Disease Control and Prevention (CDC) determined the risk of harm to individuals increases as their opioid dose increases and as their length of opioid therapy increases. For example:

- Individuals taking opioid doses > 50 morphine milligram equivalents (MMEs) per day had twice the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking opioid doses > 90 (MMEs) per day had 10 times the risk of death from an overdose than those taking < 20 MMEs per day.
- Individuals taking an opioid for > 3 months (even at low doses) had 15 times the risk of addiction to those taking opioids for < 3 months.
APPENDIX 1: BENZODIAZEPINE/OPIOID CONCURRENT USE FAX FORM

INFORMATION

INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
BENZODIAZEPINE AND OPIOID CONCURRENT THERAPY
PRIOR AUTHORIZATION REQUEST FORM

**All sections must be completed or the request will be denied.**

Note: This form must be completed by the prescribing provider.

<table>
<thead>
<tr>
<th>Patient’s Medicaid #</th>
<th>Date of Birth</th>
<th>Patient’s Name</th>
<th>Prescriber’s Name</th>
<th>Prescriber’s IN License #</th>
<th>Specialty</th>
<th>Prescriber’s NPI #</th>
<th>Prescriber’s Signature: <strong>Required below within attestation section.</strong></th>
</tr>
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</tbody>
</table>

PA is required for the following:

- Claim(s) for new opioid(s) to be used concurrently with benzodiazepines and exceeding 7 days within a 180-day period.
- Claim(s) for new benzodiazepine(s) to be used concurrently with opioids and exceeding 7 days of therapy within a 180-day period and/or exceeding established benzodiazepine/opioid concurrent therapy quantity limits (see Sedative Hypnotics/Benzodiazepine PA criteria).

<table>
<thead>
<tr>
<th>Benzodiazepine Agent(s)</th>
<th>Prescriber Name*</th>
<th>Quantity</th>
<th>Dosage Regimen/Duration</th>
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</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>
**Opioid Agent(s)** | **Prescriber Name** | **Quantity** | **Dosage Regimen/Duration**
---|---|---|---

*NOTE: If prescribers of the opioid(s) and benzodiazepine(s) are not the same, please answer the following questions:
- Are you requesting PA for: Benzodiazepine Agent(s) ne(s) are not the same, please answer the fol
- Is/are the other prescriber(s) aware of the request for concurrent therapy? □ Yes □ No
- Has/have the other prescriber(s) been consulted about the risks associated with concurrent therapy, and do all prescribers involved believe continuing with concurrent therapy is warranted, given the risks associated with concurrent use? □ Yes □ No

**PA Requirements:**

Patient diagnosis/diagnoses for use of benzodiazepine therapy:

Prior therapies attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
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</tbody>
</table>

Do you plan to continue benzodiazepine therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Patient diagnosis/diagnoses for use of opioid therapy:

Prior therapies (both drug and non-drug) attempted for the above diagnosis/diagnoses (submission of chart notes required in absence of claims history):

<table>
<thead>
<tr>
<th>Drug/Non-Drug Therapy</th>
<th>Dosage Regimen</th>
<th>Dates of Utilization</th>
<th>Reason for Discontinuation or Failure</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
Do you plan to continue opioid therapy for this patient? □ Yes □ No
If no, please provide withdrawal plan:

Attestation:

I, ________________________________________, hereby attest to the following:

(Prescriber Name)

- The patient’s INSPECT report has been evaluated and continues to be evaluated on a regular basis (Per IC 35-48-7-11.1, DO NOT attach a copy of the INSPECT report to this PA request).
- I have educated the patient in regards to the risks of concurrent utilization of benzodiazepine and opioid therapy, and the patient accepts these risks.
- If applicable, I have consulted other prescriber(s) involved in concurrent therapy and all prescribers involved agree to pursue concurrent opioid and benzodiazepine therapy for this patient.
- I acknowledge, as the prescriber initiating or maintaining concurrent benzodiazepine and opioid therapy, the risk of adverse event(s), including respiratory depression, coma, and death, associated with concurrent utilization.

Prescriber Signature: ________________________________________________________________

**Prescriber signature is required for consideration. Electronic or stamped signature will not be accepted.**

CONFIDENTIAL INFORMATION
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SHORT-ACTING OPIOID ANALGESICS

REFERENCES

- Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016; 65(1);1-49. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

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REFERENCES (CONTINUED)

- Tannenbaum, C., MD, Martin, P., BSc, Tamblyn, R., PhD, A. B., PhD, & S. A., PhD. (2014). Reduction of Inappropriate Benzodiazepine Prescriptions. JAMA Internal Medicine, 174(6).
GUIDELINES FOR USE

Our guideline for SILTUXIMAB requires a diagnosis of multicentric Castleman's disease (MCD) and that the patient is negative for both human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8).

RATIONALE

Promote appropriate utilization of Sylvant based on FDA approved indication.

Castleman's disease (CD), also known as angiofollicular lymph node hyperplasia, is comprised of two distinct diseases: unicentric and multicentric. Unicentric CD usually affects a single group of lymph nodes and removal of the mass cures 90-95% of cases. Multicentric CD (MCD) involves more than a single group of lymph nodes and can affect other organs containing lymphoid tissue. Patients with MCD often have serious infections, severe fatigue, night sweats, recurrent fever, and weight loss. Patients may also experience peripheral edema, anemia, hypoalbuminemia, peripheral neuropathy and hepatosplenomegaly. CD is not officially a cancer, but the multicentric disease form is more aggressive than unicentric CD and roughly 20% of patients with MCD develop lymphoma.

Because MCD is a rare disease and most cases are seen in patients who are HIV/HHV-8 positive, the utilization of Sylvant is expected to be relatively minimal given its specific FDA indication for HIV/HHV-8 negative MCD patients.

DOSAGE

Sylvant 11 mg/kg is given over 1 hour as an intravenous infusion administered every 3 weeks until treatment failure (defined as disease progression based on increase in symptoms, radiologic progression or deterioration in performance status) or unacceptable toxicity.

FDA APPROVED INDICATIONS

Sylvant is indicated for the treatment of patients with Multicentric Castleman’s disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.

Limitation of Use: Sylvant was not studied in patients with MCD who are HIV positive or HHV-8 positive because Sylvant did not bind to virally produced IL-6 in a nonclinical study.

REFERENCES

- Sylvant [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc; May 2014

Created: 10/15
Effective: 11/12/15
Client Approval: 10/19/15
P&T Approval: 10/15
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named SIPONIMOD (Mayzent) requires the patient to be 18 years of age or older AND have one of the following relapsing forms of multiple sclerosis:

- Clinically isolated syndrome
- Relapsing-remitting multiple sclerosis
- Active secondary progressive multiple sclerosis

RENEWAL CRITERIA

The guideline named SIPONIMOD (Mayzent) requires a diagnosis of ONE of the following relapsing forms of multiple sclerosis: clinically isolated syndrome, relapsing-remitting multiple sclerosis, or active secondary progressive multiple sclerosis. In addition, the following criteria must be met:

- Physician attestation that the patient has demonstrated a clinical benefit compared to pre-treatment baseline
- The patient does not have lymphopenia

RATIONALE

To ensure safe and appropriate use of siponimod per approved indication and dosing.

FDA APPROVED INDICATIONS

Mayzent (siponimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

CONTINUED ON NEXT PAGE
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

Recommended Dosage in Patients With CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2
Initiate Mayzent with a 5-day titration, as shown in Table 1. After treatment titration, the recommended maintenance dosage of Mayzent is 2 mg taken orally once daily starting on Day 6.

Table 1: Dose Titration Regimen to Reach Mayzent 2 mg Maintenance Dosage

<table>
<thead>
<tr>
<th>Day</th>
<th>Titration Dose</th>
<th>Titration Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.25 mg</td>
<td>1 x 0.25 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.25 mg</td>
<td>1 x 0.25 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.50 mg</td>
<td>2 x 0.25 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.75 mg</td>
<td>3 x 0.25 mg</td>
</tr>
<tr>
<td>Day 5</td>
<td>1.25 mg</td>
<td>5 x 0.25 mg</td>
</tr>
</tbody>
</table>

Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3
Initiate Mayzent with a 4-day titration, as shown in Table 2. After treatment titration, the recommended maintenance dosage of Mayzent is 1 mg taken orally once daily starting on Day 5.

Table 2: Dose Titration Regimen to Reach Mayzent 1 mg Maintenance Dosage

<table>
<thead>
<tr>
<th>Day</th>
<th>Titration Dose</th>
<th>Titration Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.25 mg</td>
<td>1 x 0.25 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.25 mg</td>
<td>1 x 0.25 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.50 mg</td>
<td>2 x 0.25 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.75 mg</td>
<td>3 x 0.25 mg</td>
</tr>
</tbody>
</table>

REFERENCES


Created: 06/19
Effective: 11/29/19
Client Approval: 11/11/19
P&T Approval: N/A
This drug requires a written request for prior authorization.

**GUIDELINES FOR USE**

**INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)**

**SEROSTIM:**

Our guideline for **SOMATROPIN (Serostim)** requires a diagnosis of HIV wasting/cachexia. The following criteria must also be met:

- The requested agent is **NOT** prescribed for athletic enhancement or anti-aging purposes
- Prescribed by or in consultation with one of the following specialists: Gastroenterologist, Nutritional Support Specialist, **OR** Infectious Disease Specialist
- Patient is on HIV anti-retroviral therapy
- Patient has had inadequate response to previous therapy (i.e., exercise training, nutritional supplements, appetite stimulants, or anabolic steroids)
- Patient has had an inadequate response to previous pharmacological therapy including one of the following: cyproheptadine, Marinol (dronabinol), or Megace (megestrol acetate)
- Alternative causes of wasting have been ruled out. Alternative causes include:
  - Altered metabolism (from metabolic and hormonal abnormalities) including testosterone deficiency or peripheral growth hormone resistance
  - Diarrhea
  - Inadequate energy (caloric) intake
  - Malignancies
  - Opportunistic infections
- The patient meets **ONE** of the following criteria for weight loss:
  - 10% unintentional weight loss over 12 months
  - 7.5% unintentional weight loss over 6 months
  - 5% body cell mass (BCM) loss within 6 months
  - BCM less than 35% (men) and a body mass index (BMI) less than 27kg per meter squared
  - BCM less than 23% (women) of total body weight and a body mass index (BMI) less than 27kg per meter squared
  - BMI less than 18.5kg per meter squared

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SOMATROPIN

INITIAL CRITERIA - SEROSTIM (CONTINUED)

Additional guideline requirements apply:
- For patients who are hypogonadal (patients with low testosterone levels), approval requires the following:
  - Patient has tried testosterone therapy (examples include testosterone cypionate, AndroGel, Androderm, Axiron, Delatestryl, Fortesta, Striant, Testim, Testopel, Vogelxo, Natesto)
  - Patient meets one of the following criteria for low testosterone:
    - Total serum testosterone level of less than 300ng/dL (10.4nmol/L)
    - A low total serum testosterone level as indicated by a lab result, with a reference range, obtained within 90 days
    - A free serum testosterone level of less than 5pg/mL (0.17nmol/L)

ZORBTIVE:
Our guideline for Somatropin (Zorbtive) requires a diagnosis of short bowel syndrome. The following criteria must also be met:
- The requested agent is NOT prescribed for athletic enhancement or anti-aging purposes
- Patient currently on specialized nutritional support (such as high carbohydrate, low-fat diet, adjusted for individual requirements and preferences)
- Prescribed by or in consultation with a gastroenterologist

GENOTROPIN:
Our guideline for SOMATROPIN (Genotropin) requires one of the following diagnoses:
- Pediatric growth hormone deficiency (GHD)
- Growth failure associated with Turner Syndrome
- Growth failure due to Prader-Willi Syndrome (PWS)
- Growth failure in children born small for gestational age (SGA)
- Idiopathic short stature
- Adult growth hormone deficiency

This medication will not be approved for athletic enhancement or anti-aging purposes.

The following criteria must also be met:
- For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Patient meets at least ONE of the following criteria for short stature:
    - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
    - Height velocity less than the 25th percentile of age
    - Documented low peak growth hormone (less than 10ng/mL) on two GH stimulation tests or insulin-like growth factor 1 (IGF-1) greater than or equal to 2 SD below the mean for age

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INITIAL CRITERIA - GENOTROPIN (CONTINUED)

- For the diagnosis of growth failure associated with Turner Syndrome, approval requires:
  o Prescribed by or in consultation with an endocrinologist
  o Patient has tried Norditropin (unless contraindicated)
  o Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of growth failure due to Prader-Willi Syndrome (PWS), approval requires:
  o Confirmed diagnosis of Prader-Willi syndrome (PWS)
  o Prescribed by or in consultation with an endocrinologist

- For the diagnosis of growth failure in children born small for gestational age (SGA), approval requires:
  o Prescribed by or in consultation with an endocrinologist
  o Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of idiopathic short stature, approval requires:
  o Prescribed by or in consultation with an endocrinologist
  o Patient has tried Norditropin (unless contraindicated)

- For the diagnosis of adult growth hormone deficiency, approval requires:
  o Prescribed by or in consultation with an endocrinologist
  o Adults with growth hormone deficiency alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary diseases, hypothalamic disease, surgery, radiation therapy, trauma, or continuation of therapy from childhood onset growth hormone deficiency

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

HUMATROPE:
Our guideline for SOMATROPIN (Humatrope) requires one of the following diagnoses:
• Pediatric growth hormone deficiency (GHD)
• Short stature associated with Turner Syndrome
• Short stature or growth failure in children with SHOX deficiency
• Growth failure in children born small for gestational age (SGA)
• Idiopathic Short Stature
• Adult growth hormone deficiency

This medication will not be approved for the treatment of ANY of the following conditions:
• Athletic enhancement
• Anti-aging purposes

The following criteria must also be met:
• For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:
  o Prescribed by or in consultation with an endocrinologist
  o Patient has tried Norditropin (unless contraindicated)
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Patient meets at least ONE of the following criteria for short stature:
    ▪ Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
    ▪ Height velocity less than the 25th percentile for age
    ▪ Documented low peak growth hormone (less than 10ng/mL) on two GH stimulation tests or insulin-like growth factor 1 (IGF-1) greater than or equal to 2 SD below the mean for age

• For the diagnosis of short stature associated with Turner Syndrome, approval requires:
  o Prescribed by or in consultation with an endocrinologist
  o Patient has tried Norditropin (unless contraindicated)
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

• For the diagnosis of growth failure in children with SHOX deficiency, approval requires:
  o Prescribed by or in consultation with an endocrinologist
  o Patient has tried Norditropin (unless contraindicated)
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

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INITIAL CRITERIA (CONTINUED)

HUMATROPE:

- For the diagnosis of growth failure in children born small for gestational age (SGA), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of idiopathic short stature, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of adult growth hormone deficiency, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - Adults with growth hormone deficiency alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary diseases, hypothalamic disease, surgery, radiation therapy, trauma, or continuation of therapy from childhood onset growth hormone deficiency

NORDITROPIN FLEXPRO, NORDITROPIN NORDIFLEX:

Our guideline for SOMATROPIN (Norditropin Flexpro, Norditropin Nordiflex) requires one of the following diagnoses:

- Pediatric growth hormone deficiency (GHD)
- Short stature associated with Turner Syndrome
- Short stature associated with Noonan Syndrome
- Short stature born small for gestational age (SGA) in a pediatric patient
- Idiopathic Short Stature
- Adult growth hormone deficiency

This medication will not be approved for the treatment of **ANY** of the following conditions:

- Athletic enhancement
- Anti-aging purposes

CONTINUED ON NEXT PAGE
The following criteria must also be met:

- **For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient meets at least **ONE** of the following criteria for short stature:
    - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
    - Height velocity less than the 25th percentile for age
    - Documented low peak growth hormone (less than 10ng/mL) on two GH stimulation tests or insulin-like growth factor 1 greater than or equal to 2 SD below the mean for age

- **For the diagnosis of short stature associated with Turner Syndrome, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- **For the diagnosis of short stature associated with Noonan Syndrome, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- **For the diagnosis of short stature born small for gestational age (SGA) in a pediatric patient, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient with no catch-up growth by age 2 to 4 years
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- **For the diagnosis of idiopathic short stature, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- **For the diagnosis of adult growth hormone deficiency, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Adults with growth hormone deficiency alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary diseases, hypothalamic disease, surgery, radiation therapy, trauma, or continuation of therapy from childhood onset growth hormone deficiency
SOMATROPIN

INITIAL CRITERIA - NUTROPIN, NUTROPIN AQ, NUTROPIN AQ NUSPIN

Our guideline for SOMATROPIN (Nutropin, Nutropin AQ, Nutropin AQ Nuspin), requires one of the following diagnoses:

- Pediatric growth hormone deficiency (GHD)
- Growth failure secondary to chronic renal insufficiency
- Short stature associated with Turner Syndrome
- Idiopathic Short Stature
- Adult growth hormone deficiency

This medication will not be approved for the treatment of ANY of the following conditions:

- Athletic enhancement
- Anti-aging purposes

The following criteria must also be met:

- **For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient’s epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient meets at least **ONE** of the following criteria for short stature:
    - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
    - Height velocity less than the 25th percentile for age
    - Documented low peak growth hormone (less than 10ng/mL) on two GH stimulation tests or insulin-like growth factor 1 (IGF01) greater than or equal to 2 SD below the mean for age

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For the diagnosis of growth failure secondary to chronic renal insufficiency, approval requires:
- Patient has not undergone renal transplantation
- Prescribed by or in consultation with a nephrologist
- Patient's height or growth velocity greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
- Patient has tried Norditropin (unless contraindicated)

For the diagnosis of short stature associated with Turner Syndrome, approval requires:
- Prescribed by or in consultation with an endocrinologist
- Patient has tried Norditropin (unless contraindicated)
- The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
- Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

For the diagnosis of idiopathic short stature, approval requires:
- Prescribed by or in consultation with an endocrinologist
- Patient has tried Norditropin (unless contraindicated)
- The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
- Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

For the diagnosis of adult growth hormone deficiency, approval requires:
- Prescribed by or in consultation with an endocrinologist
- Patient has tried Norditropin (unless contraindicated)
- Adults with growth hormone deficiency alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary diseases, hypothalamic disease, surgery, radiation therapy, trauma, or continuation of therapy from childhood onset growth hormone deficiency

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INITIAL CRITERIA - OMNITROPE

Our guideline for SOMATROPIN (Omnitrope) requires one of the following diagnoses:

- Pediatric growth hormone deficiency (GHD)
- Growth failure due to Prader-Willi Syndrome (PWS)
- Growth failure in children born small for gestational age (SGA)
- Growth failure associated with Turner Syndrome
- Idiopathic Short Stature
- Adult growth hormone deficiency

This medication will not be approved for athletic enhancement or anti-aging purposes.

- **For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient meets at least **ONE** of the following criteria for short stature:
    - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
    - Height velocity less than the 25th percentile for age
    - Documented low peak growth hormone (less than 10ng/mL) on two GH stimulation tests or insulin-like growth factor 1 (IGF-1) greater than or equal to 2 SD below the mean for age

- **For the diagnosis of growth failure due to Prader-Willi Syndrome (PWS), approval requires:**
  - Confirmed diagnosis of Prader-Willi Syndrome (PWS)
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)

- **For the diagnosis of growth failure in children born small for gestational age (SGA), approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - Patient with no catch-up growth by age 2 years
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- **For the diagnosis of growth failure associated with Turner Syndrome, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

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MDwise MANAGED MEDICAID
PRIOR AUTHORIZATION GUIDELINES

SOMATROPIN

INITIAL CRITERIA - OMNITROPE (CONTINUED)

- For the diagnosis of idiopathic short stature, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of adult growth hormone deficiency, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - Adults with growth hormone deficiency alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary diseases, hypothalamic disease, surgery, radiation therapy, trauma, or continuation of therapy from childhood onset growth hormone deficiency

SAIZEN:

Our guideline for **SOMATROPIN (Saizen)** requires one of the following diagnoses:
- Pediatric Growth Hormone Deficiency (GHD)
- Adult Growth Hormone Deficiency

This medication will not be approved for athletic enhancement, anti-aging purposes, or Idiopathic Short Stature.

The following criteria must also be met:

- **For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Patient meets at least **ONE** of the following criteria for short stature:
    - Patient's height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
    - Height velocity less than 25th percentile for age
    - Documented low peak growth hormone (less than 10ng/mL) on two GH stimulation tests or insulin-like growth factor (IGF-1) greater than or equal to 2 SD below mean for age

- **For the diagnosis of adult growth hormone deficiency, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Patient has tried Norditropin (unless contraindicated)
  - Adults with growth hormone deficiency alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary diseases, hypothalamic disease, surgery, radiation therapy, trauma, or continuation of therapy from childhood onset growth hormone deficiency

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INITIAL CRITERIA ZOMACTON (formerly called TEV-TROPIN):

The guideline named **SOMATROPIN (Zomacton)** requires **ONE** of the following diagnoses:

- Pediatric Growth Hormone Deficiency (GHD)
- Short stature associated with Turner Syndrome (TS)
- Short stature in children born small for gestational age (SGA)
- Short stature or growth failure in short stature homeobox-containing gene (SHOX) deficiency
- Adult Growth Hormone Deficiency

This medication will not be approved for treatment of **ANY** of the following conditions:

- Athletic enhancement
- Anti-aging purposes
- Idiopathic Short Stature

The following criteria must also be met.

**For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:**

- The medication is prescribed by or in consultation with an endocrinologist
- The patient has tried Norditropin (unless contraindicated)
- The patient’s epiphyses is **NOT** closed (as confirmed by radiograph of the wrist and hand)
- The patient meets at least **ONE** of the following criteria for short stature:
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender
  - Height velocity less than the 25<sup>th</sup> percentile for age
  - Documented low peak growth hormone (less than 10ng/mL) on two GH stimulation tests or insulin-like growth factor 1 (IGF-1) greater than or equal to 2 SD below the mean for age and gender

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SOMATROPIN

INITIAL CRITERIA - ZOMACTON (CONTINUED)

- For the diagnosis of short stature associated with Turner Syndrome (TS), approval requires:
  - The medication is prescribed by or in consultation with an endocrinologist
  - The patient has tried Norditropin (unless contraindicated)
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of short stature in children born small for gestational age (SGA), approval requires:
  - The medication is prescribed by or in consultation with an endocrinologist
  - The patient has tried Norditropin (unless contraindicated)
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Patient with no catch-up growth by age 2 to 4 years
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of short stature or growth failure in children with SHOX deficiency, approval requires:
  - The medication is prescribed by or in consultation with an endocrinologist
  - The patient has tried Norditropin (unless contraindicated)
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Patient’s height greater than or equal to 2 standard deviations (SD) below the mean height for normal children of the same age and gender

- For the diagnosis of adult growth hormone deficiency, approval requires:
  - The medication is prescribed by or in consultation with an endocrinologist
  - The patient has tried Norditropin (unless contraindicated)
  - The patient has growth hormone deficiency alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary diseases, hypothalamic disease, surgery, radiation therapy, trauma, or continuation of therapy from childhood onset growth hormone deficiency.

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RENEWAL CRITERIA

SEROSTIM:  
Our guideline for SOMATROPIN (Serostim) renewal requires a diagnosis of HIV wasting/cachexia. The following criteria must also be met:

- The requested agent is NOT prescribed for athletic enhancement or anti-aging purposes
- The patient has shown clinical benefit in muscle mass and weight as indicated by the following criteria:
  - ≥ 10% increase in weight or BCM from baseline (Note: current and baseline weight must be documented including dates of measurement)
  - Patient must be on anti-retroviral therapy

ZORBTIVE:
Our guideline for SOMATROPIN (Zorbtive) renewal requires a diagnosis of short bowel syndrome. Therapy is limited to 4 weeks of treatment.

GENOTROPIN:
Our guideline for SOMATROPIN (Genotropin) renewal requires a diagnosis of pediatric growth hormone deficiency (GHD), short stature associated with Turner Syndrome, growth failure due to Prader-Willi Syndrome (PWS), growth failure in children born small for gestational age (SGA), idiopathic short stature, or adult growth hormone deficiency.

This medication will not be approved for the treatment of ANY of the following conditions:

- Athletic enhancement
- Anti-aging purposes

The following criteria must also be met:

(Renewal criteria continued on next page)

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SOBATROPIN

RENEWAL CRITERIA - GENOTROPIN (CONTINUED)

- For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    **AND** patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of short stature associated with Turner Syndrome, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    **AND** patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of growth failure due to Prader-Willi Syndrome (PWS), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Improvement in body composition (e.g., increase in total lean body mass, decrease in fat mass)

- For the diagnosis of growth failure in children born small for gestational age (SGA), approval requires:
  - Prescribed by or in consultation with endocrinologist
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
    Growth velocity of 2cm or more compared with what was observed from the previous year
    **AND** patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of idiopathic short stature, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient's epiphyses are **NOT** closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    **AND** patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of adult growth hormone deficiency, approval requires:
  - Prescribed by or in consultation with an endocrinologist

CONTINUED ON NEXT PAGE
RENEWAL CRITERIA - HUMATROPE

Our guideline for SOMATROPIN (Humatrope) renewal requires a diagnosis of pediatric growth hormone deficiency (GHD), short stature associated with Turner Syndrome, short stature or growth failure in children with SHOX deficiency, growth failure in children born small for gestational age, idiopathic short stature, or adult growth hormone deficiency.

This medication will not be approved for the treatment of ANY of the following conditions:

- Athletic enhancement
- Anti-aging purposes

The following criteria must also be met:

- **For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient's predicted adult height

- **For the diagnosis of short stature associated with Turner Syndrome, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient's predicted adult height

- **For the diagnosis of short stature or growth failure in children with SHOX deficiency, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient's predicted adult height

- **For the diagnosis of growth failure in children born small for gestational age (SGA), approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient's predicted adult height

- **For the diagnosis of idiopathic short stature, approval requires:**
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient's predicted adult height

- **For the diagnosis of adult growth hormone deficiency, approval requires:**
  - Prescribed by or in consultation with an endocrinologist

**CONTINUED ON NEXT PAGE**
SOMATROPIN

RENEWAL CRITERIA (CONTINUED)

NORDITROPIN FLEXPRO, NORDITROPIN NORDIFLEX:

Our guideline for SOMATROPIN (Norditropin Flexpro, Norditropin Nordiflex) renewal requires a diagnosis of growth hormone deficiency (GHD), short stature associated with Noonan Syndrome, short stature associated with Turner Syndrome, short stature born small for gestational age (SGA) in a pediatric patient, childhood onset growth hormone deficiency, idiopathic short stature, or adult onset growth hormone deficiency.

This medication will not be approved for the treatment of ANY of the following conditions:
- Athletic enhancement
- Anti-aging purposes

The following criteria must also be met:
- For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year
  - Patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of short stature associated with Noonan Syndrome, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year
  - Patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of short stature associated with Turner Syndrome, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year
  - Patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of short stature born small for gestational age (SGA) in a pediatric patient, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Growth velocity of 2cm or more compared with what was observed from the previous year
  - Patient has not reached 50th percentile for patient's predicted adult height

(Renewal criteria continued on next page)

CONTINUED ON NEXT PAGE
SOMATROPIN

RENEWAL CRITERIA - NORDITROPIN FLEXPRO, NORDITROPIN NORDIFLEX (CONTINUED)

- For the diagnosis of idiopathic short stature, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    AND patient has not reached 50th percentile for patient’s predicted adult height

- For the diagnosis of adult onset growth hormone deficiency, approval requires:
  - Prescribed by or in consultation with an endocrinologist

NUTROPIN, NUTROPIN AQ, NUTROPIN AQ NUSPIN:

Our guideline for SOMATROPIN (Nutropin, Nutropin AQ, Nutropin AQ Nuspin) renewal requires
one of the following diagnoses:
- Pediatric growth hormone deficiency (GHD)
- Growth failure secondary to chronic renal insufficiency
- Short stature associated with Turner Syndrome
- Idiopathic Short Stature
- Adult growth hormone deficiency

This medication will not be approved for the treatment of ANY of the following conditions:
- Athletic enhancement
- Anti-aging purposes

The following criteria must also be met:
- For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    AND patient has not reached 50th percentile for patient’s predicted adult height

- For the diagnosis of growth failure secondary to chronic renal insufficiency, approval requires:
  - Patient has not undergone a renal transplantation
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    AND patient has not reached 50th percentile for patient’s predicted adult height

(Renewal criteria continued on next page)

CONTINUED ON NEXT PAGE
SOMATROPIN

RENEWAL CRITERIA - NUTROPIN, NUTROPIN AQ, NUTROPIN AQ NUSPIN (CONTINUED)

- For the diagnosis of short stature associated with Turner Syndrome, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    AND patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of idiopathic short stature, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year
    AND patient has not reached 50th percentile for patient's predicted adult height

- For the diagnosis of adult growth hormone deficiency, approval requires:
  - Prescribed by or in consultation with an endocrinologist

OMNITROPE:

Our guideline for SOMATROPIN (Omnitrope) renewal requires one of the following diagnoses:
- Pediatric growth hormone deficiency (GHD)
- Growth failure due to Prader-Willi Syndrome (PWS)
- Growth failure in children born small for gestational age (SGA)
- Growth failure associated with Turner Syndrome
- Idiopathic short stature
- Adult growth hormone deficiency

(Renewal criteria continued on next page)
SOMATROPIN

RENEWAL CRITERIA - OMNITROPE (CONTINUED)

This medication will not be approved for the treatment of ANY of the following conditions:

- Athletic enhancement
- Anti-aging purposes

The following criteria must also be met:

- For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient’s predicted adult height

- For the diagnosis of growth failure due to Prader-Willi Syndrome (PWS), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - Improvement in body composition (e.g., increase in total lean body mass, decrease in fat mass)

- For the diagnosis of growth failure in children born small for gestational age (SGA), approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient’s predicted adult height

- For the diagnosis of growth failure associated with Turner Syndrome, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient’s predicted adult height

- For the diagnosis of idiopathic short stature, approval requires:
  - Prescribed by or in consultation with an endocrinologist
  - The patient’s epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  - Growth velocity of 2cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient’s predicted adult height

- For the diagnosis of adult onset growth hormone deficiency, approval requires:
  - Prescribed by or in consultation with an endocrinologist

CONTINUED ON NEXT PAGE
RENTERAL CRITERIA (CONTINUED)

SAIZEN:

Our guideline for SOMATROPIN (Saizen) renewal requires a diagnosis of pediatric growth hormone deficiency (GHD) or adult growth hormone deficiency.

This medication will not be approved for the treatment of ANY of the following conditions:

- Athletic enhancement
- Anti-aging purposes
- Idiopathic Short Stature

The following criteria must also be met:

- **For the diagnosis of pediatric growth hormone deficiency (GHD), approval requires:**
  o Prescribed by or in consultation with an endocrinologist
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Growth velocity of 2 cm or more compared with what was observed from the previous year AND patient has not reached 50th percentile for patient's predicted adult height

- **For the diagnosis of adult growth hormone deficiency, approval requires:**
  o Prescribed by or in consultation with an endocrinologist

ZOMACTON (formerly called TEV-TROPIN):

The guideline named SOMATROPIN (Zomacton) renewal requires a diagnosis of pediatric growth hormone deficiency (GHD), short stature associated with Turner Syndrome (TS), short stature for children born small for gestational age (SGA), short stature or growth failure in short stature homeobox-containing gene (SHOX) deficiency, or adult growth hormone deficiency.

This medication will not be approved for treatment of ANY of the following conditions:

- Athletic enhancement
- Anti-aging purposes
- Idiopathic Short Stature

The following criteria must also be met:

- **For the diagnosis of pediatric growth hormone deficiency (GHD), renewal requires:**
  o The medication is prescribed by or in consultation with an endocrinologist
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Growth velocity of 2 cm or more compared with what was observed from the previous year or patient has not reached 50th percentile for patient’s predicted adult height

CONTINUED ON NEXT PAGE
SOMATROPIN

RENEWAL CRITERIA (CONTINUED)

ZOMACTON

- For the diagnosis of short stature associated with Turner Syndrome (TS), renewal
  requires:
  o The medication is prescribed by or in consultation with an endocrinologist
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Growth velocity of 2 cm or more compared with what was observed from the previous year
    and/or patient has not reached 50th percentile for patient's predicted adult height
- For the diagnosis of short stature or growth failure in children with SHOX deficiency,
  renewal requires:
  o The medication is prescribed by or in consultation with an endocrinologist
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Growth velocity of 2 cm or more compared with what was observed from the previous year
    and/or patient has not reached 50th percentile for patient's predicted adult height
- For the diagnosis of growth failure in children born small for gestational age (SGA),
  renewal requires:
  o The medication is prescribed by or in consultation with an endocrinologist
  o The patient's epiphyses are NOT closed (as confirmed by radiograph of the wrist and hand)
  o Growth velocity of 2 cm or more compared with what was observed from the previous year
    and/or patient has not reached 50th percentile for patient's predicted adult height
- For the diagnosis of adult growth hormone deficiency, renewal requires:
  o The medication is prescribed by or in consultation with an endocrinologist

CONTINUED ON NEXT PAGE
SOMATROPIN

RATIONALE
Ensure appropriate use of growth hormone with respect to evidence based guidelines.

Growth hormone (GH) is secreted from the anterior pituitary, and is considered a trophic hormone – that is, its release stimulates other body glands and tissues to release additional hormonally active substances. Release of GH from the pituitary is controlled by the hypothalamic release of growth hormone-releasing hormone (GHRH). The secretion and circulating levels of GH vary with age.

Many safety concerns have been raised with recombinant human growth hormone (rhGH) treatment. In 2016, the Growth Hormone Research Society, in conjunction with other endocrinology societies, released a position paper stating that there was insufficient evidence to attribute rhGH treatment with increased risk of all-cause mortality, new or recurrent cancers, or stroke. Treatment with rhGH appears to be safe when used within recommended doses.

FDA APPROVED INDICATIONS
Currently, there are nine rhGH products being marketed. With the exception of Serostim and Zortive, all of the products are indicated for the treatment of pediatric GH deficiency, and additional indications are product specific. Recombinant GH products are used off-label for anti-aging effects and enhancing athletic performance. Use of rhGH in patients with Idiopathic Short Stature (ISS) is controversial as these patients are not growth hormone deficient.

CONTINUED ON NEXT PAGE
SOMATROPIN

FDA APPROVED INDICATIONS (CONTINUED)

DOsing
Dosing of rhGH products varies amongst the products and their indications. Treatment guidelines recommend that treatment be individualized. For pediatric patients, weight based-dosing is utilized whereas in adult patients, either weight based dosing or fixed-doses may be used.

REFERENCES

- Humatrope [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC; December 2016.
GUIDELINES FOR USE

Our guideline for SONIDEGIB requires a diagnosis of locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or that the patient is not a candidate for surgery or radiation therapy. In addition, the patient must have obtained baseline serum creatine kinase (CK) and serum creatinine levels.

RATIONALE
Promote appropriate utilization of SONIDEGIB based on FDA approved indication.

Skin cancer is the most common cancer and basal cell carcinoma accounts for approximately 80 percent of non-melanoma skin cancers. The vast majority of patients can be successfully managed with a variety of simple procedures, such as cryotherapy, curettage and electrodesiccation, topical treatments (5-fluorouracil, imiquimod), or simple surgical excision. When lesions are more advanced, Mohs micrographic surgery, more extensive surgical resection, or radiation therapy generally are generally sufficient to control locoregional disease. The use of systemic therapy is limited to patients with distant metastases or locally advanced disease that cannot be adequately managed with surgical or radiotherapeutic techniques.

The Hedgehog (Hh) signaling pathway plays a key role in directing growth and patterning during embryonic development and is required in vertebrates for the normal development of many structures, including the skin. Signaling in this pathway is initiated by the cell surface receptor smoothened homolog (SMO). In adults, this pathway normally is inhibited by another cell surface receptor, the patched homolog 1 (PTCH1). In the pathogenesis of basal cell carcinoma, either SMO or PTCH1 could have a mutation resulting in aberrant cell proliferation.

Odomzo works by binding to and inhibiting SMO protein, thereby blocking activation of the Hh pathway and the proliferation of tumor cells. It offers an alternative to Erivedge (vismodegib) with a similar safety profile for patients who have a recurrence of BCC following surgery or radiation therapy, or for those patients who are not candidates for surgery or radiation.

CONTINUED ON NEXT PAGE
SONIDEGIB

RATIONALE (CONTINUED)

The safety and effectiveness of Odomzo was evaluated in a single clinical trial conducted in patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma who received Odomzo 200 mg orally, once daily, until disease progression or intolerable toxicity. A total of 66 patients randomized to Odomzo 200 mg daily had laBCC and were followed for at least 12 months unless discontinued earlier. Seventy-six percent of patients had prior therapy for treatment of BCC; this included surgery (73%), radiotherapy (18%), and topical/photodynamic therapies (21%). Approximately half of these patients (56%) had aggressive histology. The ORR was 58% (95% confidence interval: 45, 70), consisting of 3 (5%) complete responses and 35 (53%) partial responses. Among the 38 patients with an objective response, 7 (18%) patients experienced subsequent disease progression with 4 of these 7 patients having maintained a response of 6 months or longer. The remaining 31 patients (82%) have ongoing responses ranging from to 1.9+ to 18.6+ months and the median duration of response has not been reached.

The most common adverse effects seen while using Odomzo were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

There is a black box warning for embryo-fetal death and severe birth defects. Pregnancy Category D.

DOSAGE

Odomzo is taken as a single 200 mg capsule, once daily, on an empty stomach, at least 1 hour before or 2 hours after a meal. Odomzo therapy should be continued until disease progression or unacceptable toxicity.

FDA APPROVED INDICATIONS

Treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

CONTINUED ON NEXT PAGE
REFERENCES


Created: 10/15
Effective: 12/17/15
Client Approval: 10/28/15
P&T Approval: 11/15
SORAFENIB

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GUIDELINES FOR USE

Approval requires a diagnosis of advanced renal cell carcinoma (RCC), unresectable hepatocellular carcinoma, or locally recurrent/metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.

RATIONALE

Ensure appropriate utilization of sorafenib based on FDA approved indication and NCCN guidelines.

FDA APPROVED INDICATION

Sorafenib is indicated for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.

REFERENCES


Created: 06/15
Effective: 07/22/15                Client Approval: 06/15                P&T Approval: 02/14
## SSRI/SNRI Antidepressants

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### Guidelines for Use

**Initial Criteria (Note: For renewal criteria see below)**

Our guideline named **SSRI/SNRI Antidepressants** does not allow the use of the requested medication under the age limit listed in the appendix below. Please consider another SSRI/SNRI antidepressant without an age restriction.

Our guideline named **SSRI/SNRI Antidepressants** does not allow the use of the requested medication above the quantity limit listed in the appendix below. Please consider an alternate dose or dosing schedule.

Our guideline for **SSRI/SNRI Antidepressants** for patients with claims suggesting therapeutic duplication requires that the medications are being cross-tapered or that the historical medication is being discontinued.

**Continued on next page**
GUIDELINES FOR USE (CONTINUED)
RENEWAL CRITERIA

Our guideline for **SSRI/SNRI ANTIDEPRESSANTS** renewal requires that there is history of paid claims for **BOTH** medications identified in the therapeutic duplication for 90 of the past 120 days and that the patient has previous authorizations on file for **BOTH** medications identified in the therapeutic duplication.

RATIONALE
To promote prudent prescribing of SSRI and SNRI antidepressants.
A lookback period of 60 days will be utilized to identify potential therapeutic duplication.

**APPENDIX: SSRI/SNRI Age Edits and Quantity Limits**

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Created: 07/16
Effective: 01/01/20
Client Approval: 12/09/19
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Our guideline for SUNITINIB requires a diagnosis of advanced renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST), unresectable locally advanced or metastatic pancreatic neuroendocrine carcinoma (pNET), or for adjuvant treatment of renal cell carcinoma. In addition, the following must be met:

For diagnosis of gastrointestinal stromal tumor (GIST), approval requires:
- The patient has had a previous trial of or contraindication to imatinib mesylate (Gleevec)

For diagnosis of unresectable locally advanced or metastatic pancreatic neuroendocrine carcinoma (pNET), approval requires:
- The patient's tumor is progressive and well-differentiated

For adjuvant treatment of renal cell carcinoma, approval requires:
- Patient is at least 18 years old
- Patient is at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy

RATIONALE

Ensure appropriate utilization of sunitinib based on FDA approved indication.

FDA APPROVED INDICATIONS

Sutent is a kinase inhibitor indicated for the treatment of:
- Gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate
- Advanced renal cell carcinoma (RCC)
- Progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease
- Adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE AND ADMINISTRATION

GIST and Advanced RCC:
- 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off.

Adjuvant RCC:
- 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off for nine 6-week cycles

pNET:
- 37.5 mg orally once daily, with or without food, continuously without a scheduled off-treatment period.

Dose Modification:
- Dose interruptions and/or dose adjustments of 12.5 mg recommended based on individual safety and tolerability.

REFERENCES

Created: 06/15
Effective: 11/01/18    Client Approval: 09/24/18    P&T Approval: N/A
GUIDELINES FOR USE

Our guidelines for TADALAFIL requires a diagnosis of Benign Prostatic Hyperplasia (BPH) and a trial of a formulary alpha blocker (for example, doxazosin, terazosin, or tamsulosin) AND finasteride.

RATIONALE

To limit the coverage of Cialis to the Medicaid covered indication of benign prostatic hyperplasia (BPH) and exclude coverage for erectile dysfunction (ED). The recommended dose for the treatment of BPH is 5mg daily. A starting dose of 2.5mg daily is recommended for patients with a creatinine clearance of 30 to 50mL/min.

FDA APPROVED INDICATIONS

Cialis is indicated for the treatment of ED, the signs and symptoms of BPH, and ED and the signs and symptoms of BPH. Cialis may be administered once daily or on an as needed basis for the treatment of ED. For the treatment of BPH, Cialis is recommended to be administered on a daily basis.

REFERENCES


Created: 06/15
Effective: 07/01/17
Client Approval: 05/01/17
P&T Approval: 11/14
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named TAFAMIDIS (Vyndaqel, Vyndamax) requires a documented diagnosis of cardiomyopathy associated with wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM). In addition, the following criteria must be met:

- Diagnosis confirmed by ONE of the following:
  - Bone scan (scintigraphy) strongly positive for myocardial uptake of 99mTcPYP/DPD *(Note: Strongly positive defined as heart to contralateral lung [H/CL] ratio of at least 1.5 or Grade 2 or greater localization to the heart using the Perugini Grade 1-3 scoring system)*
  - Biopsy of tissue of affected organ(s) (cardiac and possibly non-cardiac sites) to confirm amyloid presence AND chemical typing to confirm presence of transthyretin (TTR) protein

- The patient is 18 years of age or older

- Therapy is prescribed by or given in consultation with a cardiologist, transthyretin amyloidosis (ATTR) specialist, or medical geneticist

- The patient has New York Heart Association (NYHA) class I, II or III heart failure

RENEWAL CRITERIA

The guideline named TAFAMIDIS (Vyndaqel, Vyndamax) requires a diagnosis of cardiomyopathy associated with wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM). In addition, the following must be met:

- Physician attestation that the patient has not progressed to New York Heart Association (NYHA) Class IV heart failure

RATIONALE

For further information, please refer to the Prescribing Information for Vyndaqel and Vyndamax.

REFERENCES

GUIDELINES FOR USE

The guideline named TALAZOPARIB TOSYLATE (Talzenna) requires a diagnosis of human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. In addition, the following criteria must be met:

- The patient is 18 years of age or older
- The patient has a deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutation (gBRCAm) as confirmed by an FDA-approved test
- The patient has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting
- Patients with hormone receptor (HR)-positive breast cancer must have additional prior treatment with endocrine therapy or be considered inappropriate for endocrine therapy

RATIONALE
For further information, please refer to the Prescribing Information for Talzenna.

REFERENCES

Created: 12/18
Effective: 11/01/19
Client Approval: 10/16/19
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

Our guideline for **TASIMELTEON** requires a diagnosis of Non-24-Hour Sleep-Wake Disorder (Non-24).

RATIONALE

To ensure the appropriate use of Hetlioz.

DOSAGE

The recommended dosage of Hetlioz is 20 mg orally per day taken before bedtime, at the same time every night.

FDA APPROVED INDICATIONS

TASIMELTEON is a melatonin receptor agonist indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24).

AVAILABLE STRENGTHS

- 20 mg capsules

REFERENCES


Created: 03/19
Effective: 05/01/19
Client Approval: 03/20/19
P&T Approval: N/A
GUIDELINES FOR USE

Our guideline for TAVABOROLE requires the following: a diagnosis of onychomycosis of the toenails; presence of complicating factors such as diabetes, peripheral vascular disease, a suppressed immune system, or pain surrounding the nail or soft tissue; and previous trial or contraindication to oral terbinafine or oral itraconazole and ciclopirox topical solution.

RATIONALE

to promote clinically appropriate utilization of Kerydin (tavaborole) based on its FDA approved indication and dosing.

Kerydin is an oxaborole antifungal. Onychomycosis refers to nail infections caused by any fungus, including yeasts and non-dermatophyte molds. Although onychomycosis is usually a cosmetic concern to patients, it also causes physical discomfort for some, particularly with more severe or advanced disease. Patients may experience chronic pain or acute pain exacerbated by nail cutting, footprint, or pressure from bedclothes. Additionally, in patients with diabetes or other immunocompromised states, onychomycosis may increase the risk of bacterial infections such as cellulitis.

Kerydin may not be as efficacious as oral antifungals (e.g. terbinafine and itraconazole) in the treatment of onychomycosis, but its safety profile is improved. The most common adverse reactions associated with Kerydin are ingrown toenails, application site reactions (i.e. dermatitis, exfoliation, erythema). Additionally, Kerydin neither interacts with cytochrome P450 enzymes nor is associated with hepatotoxicity, as seen with oral antifungals.

DOSAGE AND ADMINISTRATION

Apply enough medication to cover the entire toenail surface and under the tip of each affected toenail once daily for 48 weeks. Use the dropper tip to gently spread Kerydin to the entire toenail up to the edges of the toenail as well as under the tip of the toenail.

For topical use only and not for oral, ophthalmic, or intravaginal use.

FDA APPROVED INDICATIONS

For the topical treatment of onychomycosis of the toenails due to Trichophyton rubrum or Trichophyton mentagrophytes.

REFERENCES


Created: 06/15
Effective: 04/15/19
Client Approval: 03/28/19
P&T Approval: 11/14
GUIDELINES FOR USE

Approval requires the patient to be at least 18 years of age with a diagnosis of Short Bowel Syndrome (SBS) that is dependent on intravenous parenteral nutrition, defined as requiring parenteral nutrition at least three times per week.

RATIONALE
To ensure appropriate use of Gattex based on FDA approved indication.

The recommended daily dose of Gattex is 0.05mg/kg body weight administered by subcutaneous injection once daily. Gattex should not be administered intravenously or intramuscularly. Patients should be advised to alternate sites of injection. Recommended sites of administration include: thighs, arms and quadrants of the abdomen. Missed doses should be taken as soon as possible that day but patients should not take 2 doses on the same day.

A 50% dose reduction is recommended in patient with moderate and severe renal impairment (creatinine clearance < 50ml/min) and ESRD. There is potential for increased absorption of concomitant oral medications, which should be considered if these drugs require titration or have a narrow therapeutic index.

Gattex is the first GLP-2 analog indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. SBS is a condition that results from the partial or complete surgical removal of the small and/or large intestine. A normal human small intestine ranges between 3 and 8 m in length. SBS is defined in adults as < 200cm of small intestine. Extensive loss of the small intestine can lead to poor absorption of fluids and nutrients from food needed to sustain life. As a result, patients with SBS often receive parenteral nutrition. The number of patients with SBS in the United States is unknown but extrapolating from European data the estimated incidence is 2 per million individuals.

Teduglutide is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. GLP-2 is known to increase intestinal and portal blood flow, and inhibit gastric acid secretion. Teduglutide binds to the glucagon-like peptide-2 receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of multiple mediators including insulin-like growth factor (IGF)-1, nitric oxide and keratinocyte growth factor (KGF).
RATIONALE (CONTINUED)

Gattex joins two other agents that are FDA approved for SBS. Zorbtive [somatropin (rDNA origin)] was approved in 2003 and is a human growth hormone (hGH) produced by recombinant DNA technology. Intestinal mucosa contains receptors for growth hormone and for insulin-like growth factor-1 (IGF-I), which is known to mediate many of the cellular actions of growth hormone. Thus, the actions of growth hormone on the gut may be direct or mediated via the local or systemic production of IGF. In human clinical studies the administration of growth hormone has been shown to enhance the transmucosal transport of water, electrolytes, and nutrients. NutreStore (glutamine) was approved in 2004 and is an amino acid indicated for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication. Another differentiating factor besides mechanism of action of these agents is duration of use. Administration over 4 weeks has not been studied for Zorbtive whereas Gattex has been studied out to 1 ½ years.

Gattex was approved based on the evaluation of two clinical trials and two extension studies.

Study 1 was a randomized, double-blind, placebo-controlled, parallel-group, multi-national, multi-center clinical trial in n=86 adults with SBS who were dependent on parenteral nutrition/intravenous (PN/I.V.) support for at least 12 months and required PN at least 3 times per week. Optimization and stabilization of PN/IV fluid volumes were achieved before randomization to treatment (Gattex 0.05mg/kg/day) or placebo. Gattex was administered subcutaneously once daily for 24 weeks. The primary endpoint was defined as a subject achieving at least 20% reduction in weekly PN/I.V. volume from baseline (prior to randomization) to both 20 and 24 weeks. At week 24 the mean reduction in weekly PN/I.V. volume was 4.4 Liters for Gattex-treated subjects (from pre-treatment baseline of 12.9 Liters) versus 2.3 Liters for placebo-treated subjects (from pre-treatment baseline of 13.2 Liters/week) (p<0.001). Twenty-one subjects on Gattex (53.8%) versus 9 on placebo (23.1%) achieved at least a one-day reduction in PN/I.V. support. Study 2 was the ongoing two-year open-label extension of Study 1. The extension study demonstrated continuous response after one year, further reductions in parenteral support as well as the ability for a small number of patients to discontinue PN/I.V. support.

Study 3 was similar to Study 1 in terms of design and the patient inclusion criteria. After similar optimization and stabilization as in Study 1, subjects were randomized for 24 weeks to either Gattex 0.05mg/kg/day (n=35), Gattex 0.10 mg/kg/day (n=32), or placebo (n=16). The high dose of Gattex 0.10mg/kg/day did not reach statistical significance. Further evaluation of PN/I.V. volume reduction using the endpoint of response (defined as at least 20% reduction in PN/I.V. fluid from Baseline to Weeks 20 and 24) showed that 46% of subjects on Gattex 0.05 mg/kg/day responded versus 6% on placebo. Subjects on Gattex at both dose levels experienced a 2.5 L/week reduction in parenteral support requirements versus 0.9 L/week for placebo at 24 weeks. Two subjects in the Gattex 0.05 mg/kg/day dose group were weaned off parenteral support by Week 24. Study 4 was a blinded, uncontrolled extension of Study 3 with n=65 subjects. Subjects were treated for an additional 28 weeks. Of responders in Study 3 who entered Study 4, 75% sustained response on Gattex after one year of treatment. The mean reduction of weekly PN/I.V. volume was 4.9 L/week (52% reduction from baseline) after one year of continuous Gattex treatment.

CONTINUED ON NEXT PAGE
TEDUGLUTIDE

RATIONALE (CONTINUED)

Gattex has warnings and precautions that include neoplastic growth, colorectal polyps, intestinal obstruction, biliary and pancreatic disease and fluid overload. Patients may also experience an increase of absorption of concomitant oral medications.

The most commonly reported adverse drug reactions (≥10%) are abdominal pain, injection site reactions, nausea, headaches, abdominal distension and upper respiratory tract infection. A 50% dose reduction is recommended in patient with moderate and severe renal impairment (creatinine clearance < 50ml/min) and ESRD. Gattex is pregnancy category B; no well-controlled studies have been conducted in pregnant women.

Immunogenicity was seen in patients on Gattex and increased in incidence over time. Anti-Gattex antibodies did not appear to have an impact on efficacy or safety in patients who were treated up to 1.5 years, but long-term impact is unknown.

The FDA is requiring a REMS program for Gattex consisting of a communication plan and training for prescribers, and a post marketing study of SBS patients treated with the drug to evaluate future risk of colorectal cancer and other conditions.

FDA APPROVED INDICATIONS

Gattex (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.

REFERENCES

- Buchman, Alan L. Etiology and Initial Management of Short Bowel Syndrome. Gastroenterology; 2006; 130; S5-S15.
**GUIDELINES FOR USE**

Approval for **TELOTRISTAT (Xermelo)** requires a diagnosis of carcinoid tumors, trial and failure monotherapy with a somatostatin analog (e.g., lanreotide, octreotide acetate), and use of Xermelo in combination with a somatostatin analog (e.g., lanreotide, octreotide acetate).

**RATIONALE**

To ensure appropriate use of Xermelo based on FDA approved indication and dosing.

**FDA APPROVED INDICATIONS**

Xermelo is a tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Dosing:
The recommended dosage of Xermelo in adult patients is 250 mg three times daily for patients whose diarrhea is inadequately controlled by a SSA therapy.

**REFERENCE**


Created: 05/17  
Effective: 07/22/17  
Client Approval: 05/30/17  
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires a diagnosis of metastatic melanoma, anaplastic astrocytoma, glioblastoma multiforme, or small cell lung cancer (SCLC).

RATIONALE

Based on FDA approved indications and NCCN recommendations. Temodar is approved for the treatment of newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment; and refractory anaplastic astrocytoma patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. NCCN recommends Temodar for SCLC patients with relapse <2-3 months, performance status 0-2 or relapse >2-3 up to 6 months (most useful if brain metastases are present); and for the treatment of metastatic melanoma. NCCN considers temozolomide to be a systemic therapy option for advanced or metastatic melanoma. No quantity limit is included within this guideline since there are multiple dosing regimens available, all of which are based on body surface area.

FDA APPROVED INDICATIONS

Temodar is an alkylating drug indicated for the treatment of adult patients with:
- Newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and then as maintenance treatment.
- Refractory anaplastic astrocytoma patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

REFERENCES

GUIDELINES FOR USE

Our guideline for TERIFLUNOMIDE requires a diagnosis of relapsing-remitting, secondary-progressive, or progressive-relapsing multiple sclerosis.

RATIONALE
To ensure appropriate use of Aubagio consistent with FDA approved indication.

The recommended dose of Aubagio is 7 mg or 14 mg orally once daily, with or without food.

Aubagio is the second oral medication approved by the U.S. Food and Drug Administration (FDA) to treat relapsing forms of multiple sclerosis. It is an immunomodulatory agent that inhibits dihydroorotate dehydrogenase, an enzyme involved in pyrimidine synthesis. The drug reduces T- and B- cell activation, proliferation and function in response to auto antigens. Aubagio is the active metabolite of leflunomide, an agent used for rheumatoid arthritis, which has been on the market since 1998.

The relapsing remitting form of multiple sclerosis accounts for roughly 85% of the total multiple sclerosis population. Guidelines and consensus statements from the American Academy of Neurology and National Clinical Advisory Board of the National Multiple Sclerosis Society do not indicate preference of first line agents. Current first line treatments available for relapsing forms of multiple sclerosis include: interferon beta-1a (Avonex, Rebif), interferon beta-1b (Betaseron, Extavia), and glatiramer acetate (Copaxone).

The FDA approval of Aubagio stems from one large phase III study and another smaller phase III imaging study.

Study 1 (TEMSO) was a double-blind, placebo-controlled study that evaluated teriflunomide 7mg and 14mg versus placebo in 1088 patients with relapsing forms of multiple sclerosis over 108 weeks. Inclusion criteria included a definite diagnosis of MS and at least 1 relapse over the year preceding the trial or 2 relapses over the 2 years preceding the trial. MRI was performed at screening and at various time points thereafter. Upon entry to the trial, the patient’s Expanded Disability Status Scale (EDSS) score was ≤ 5.5. The primary endpoint of the study was the annualized relapse rate (ARR).

CONTINUED ON NEXT PAGE
TERIFLUNOMIDE

RATIONALE (CONTINUED)

The ARR was reduced in both the 7mg (ARR= 0.370) and 14mg (ARR=0.369) treatment arms compared with placebo (ARR= 0.539), which was statistically significant (p=0.0005 and p=0.0002, respectively). The disability progression measurement assessed by EDSS at week 108 was only statistically significant in the 14mg arm (20.2%) versus placebo (27.3%). MRI endpoints included median change from baseline in total lesion volume and mean number of Gd-enhancing T1-lesions per scan. Teriflunomide 7mg and 14 mg demonstrated statistically significant decreases in both lesion volume and fewer Gd-enhancing lesions versus placebo.

Study 2 was a randomized, double blind, placebo-controlled study in 179 patients treated for 36 weeks that further demonstrated the effects of teriflunomide on MRI activity. The primary endpoint of average number of unique active lesions per MRI scan was lower in the teriflunomide 7mg and 14mg arms (0.98, 1.06) compared to placebo (2.69; p=0.0052 and p=0.0234, respectively).

Aubagio has a black box warning for hepatotoxicity and risk of teratogenicity, and is contraindicated in patients with severe hepatic impairment and in pregnant women. Aubagio is classified as pregnancy category X. Women of childbearing potential must not be started on Aubagio until pregnancy is excluded and it has been confirmed that they are using reliable contraception.

Warnings and precautions include hepatotoxicity, bone marrow and immunosuppression, risk of infections, malignancy, peripheral neuropathy, acute renal failure, hyperkalemia, dermatological toxicity, increases in blood pressure, and respiratory disease. The most common side effects seen with Aubagio are ALT elevations, alopecia, diarrhea, influenza, nausea and paresthesia. Co-administration with leflunomide is contraindicated. Aubagio may increase levels of CYP2C8 substrates and oral contraceptives, and decrease levels of warfarin and CYP1A2 substrates.

FDA APPROVED INDICATIONS

Aubagio is indicated for the treatment of patients with the relapsing forms of multiple sclerosis.

REFERENCES

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline named TERIPARATIDE (Forteo) requires that the patient has a diagnosis of postmenopausal osteoporosis, primary or hypogonadal osteoporosis in a male patient, or glucocorticoid-induced osteoporosis, AND the patient has not received a total of 24 months or more of parathyroid hormone therapy with Tymlos or Forteo. In addition, one of the following criteria must be met:

- The patient is at high risk for fractures defined as ONE of the following:
  - History of osteoporotic (e.g., fragility, low trauma) fracture(s)
  - 2 or more risk factors for fracture (e.g., history of multiple recent low trauma fractures, BMD T-score less than or equal to -2.5, corticosteroid use, or use of GnRH analogs such as nafarelin, etc.)
  - No prior treatment for osteoporosis AND FRAX score ≥ 20% for any major fracture OR ≥ 3% for hip fracture
- The patient is unable to use oral therapy (e.g., upper gastrointestinal [GI] problems - unable to tolerate oral medication, lower GI problems - unable to absorb oral medications, trouble remembering to take oral medications or coordinating an oral bisphosphonate with other oral medications or their daily routine)
- The patient has an adequate trial of, intolerance to, or a contraindication to bisphosphonates (e.g., alendronate, risedronate, ibandronate)

RATIONALE
To ensure safe use of teriparatide for the treatment of osteoporosis in patients who have failed or are intolerant to anti-resorptive agents.

FDA APPROVED INDICATIONS
- For the treatment of postmenopausal women with osteoporosis at high risk for fracture
- To increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- For the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

REFERENCE
GUIDELINES FOR USE

Approval requires that the patient is infected with HIV (AIDS), and has excess abdominal fat with lipodystrophy.

RATIONALE
Ensure that tesamorelin is used solely for its FDA approved indication.

FDA APPROVED INDICATION
Tesamorelin is indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 02/11
GUIDELINES FOR USE

Our guideline for TETRABENAZINE requires a diagnosis of chorea (involuntary movements) associated with Huntington’s disease and that the medication has been prescribed or recommended by a neurologist. Requests for a tetrabenazine dosage that exceeds 50mg requires that the patient has been genotyped for CYP2D6 and is identified as an extensive (EM) or intermediate metabolizer (IM) of CYP2D6.

RATIONALE

Ensure appropriate diagnostic, utilization and safety criteria are used for tetrabenazine management.

FDA APPROVED INDICATION

Xenazine is indicated for the treatment of chorea associated with Huntington’s disease.

DOSAGE

The dose of Xenazine should be individualized.

*Dosing Recommendations Up to 50 mg per day*

The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given as 12.5 mg twice a day. Xenazine should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. If a dose of 37.5 to 50 mg per day is needed, it should be given in a three times a day regimen. The maximum recommended single dose is 25 mg. If adverse reactions such as akathisia, restlessness, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing Xenazine treatment or initiating other specific treatment.

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**Dosing Recommendations Above 50 mg per day**

Patients who require doses of Xenazine greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of Xenazine should then be individualized accordingly to their status as PMs or EMs.

- **Extensive and Intermediate CYP2D6 Metabolizers**
  Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of Xenazine above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. If adverse reactions such as akathisia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing Xenazine treatment or initiating other specific treatment (e.g., antidepressants).

- **Poor CYP2D6 Metabolizers**
  In PMs, the initial dose and titration is similar to EMs except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg.

**REFERENCES**


Created: 02/16
Effective: 06/01/16
Client Approval: 04/18/16
P&T Approval: N/A
GUIDELINES FOR USE

Approval requires a diagnosis of multiple myeloma and that Thalomid is being used in combination with dexamethasone or prednisone; or a diagnosis of erythema nodosum lepromatous (ENL); or a diagnosis of anemia due to myelodysplastic syndrome that has been previously treated; or a diagnosis of Waldenström’s Macroglobulinemia.

RATIONALE

To ensure appropriate use aligned with FDA approved indications and NCCN guidelines.

The FDA approved dose for multiple myeloma is 200mg once daily along with dexamethasone 40mg daily on days 1-4, 9-12, and 17-20 every 28 days. For cutaneous erythema nodosum lepromatous the dosage is 100 to 300mg daily and up to 400mg daily for severe cases.

NCCN multiple myeloma treatment guidelines consider primary induction therapy for stem cell transplant candidates with lenalidomide in combination with dexamethasone, and thalidomide in combination with bortezomib and dexamethasone to have the strongest evidence. Other combinations involving bortezomib, lenalidomide or thalidomide are also considered effective. For primary induction therapy for non-transplant candidates in patients with newly diagnosed multiple myeloma, NCCN considers thalidomide and melphalan in combination prednisone, melphalan in combination with prednisone and bortezomib, and lenalidomide in combination with low-dose dexamethasone to have the strongest evidence. Other combinations involving melphalan, lenalidomide or thalidomide are also considered effective. For maintenance therapy following disease response in patients with newly diagnosed multiple myeloma who undergo stem cell transplant, NCCN considers thalidomide monotherapy to have the strongest evidence. Lenalidomide monotherapy, thalidomide in combination with prednisone and interferon monotherapy are also considered effective. For salvage therapy in patients who did not respond to or were ineligible for stem cell transplant, re-induction with the same regimen can be considered if the relapse occurs at greater than 6 months after completion of the initial induction therapy. NCCN considers lenalidomide in combination with dexamethasone to have the best evidence. Other therapies involving lenalidomide, thalidomide or bortezomib may be considered.

The NCCN myelodysplastic syndrome guidelines recognize thalidomide as a non-chemotherapy, low-intensity agent that has demonstrated efficacy in a phase II trial.

NCCN guidelines for Waldenström’s Macroglobulinemia state that primary treatment options include oral alkylators, nucleoside analogs, rituximab alone or in combination with cyclophosphamide, bortezomib, nucleoside analogues, thalidomide, or bendamustine.

CONTINUED ON NEXT PAGE
THALIDOMIDE

FDA APPROVED INDICATIONS
Thalomid in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myelomas. Thalomid is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). Thalomid is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. Thalomid is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

REFERENCES
THYROTROPIN ALFA FOR INJECTION

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GUIDELINES FOR USE

The guideline requires that the requested product being used as adjunctive treatment for radioiodine ablation of thyroid tissue remnants for thyroid cancer without evidence of metastatic disease.

RATIONALE

To ensure appropriate use of Thyrogen based on FDA approved indication and dosage. Limit diagnostic use to the medical benefit.

Two-injection regimen of Thyrogen 0.9 mg IM, followed by a second 0.9 mg IM injection 24 hours later.

FDA APPROVED INDICATION

Thyrogen (thyrotropin alfa for injection) is indicated for use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer.

Thyrogen (thyrotropin alfa for injection) is indicated for use as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of metastatic thyroid cancer.

REFERENCES


Created: 09/18
Effective: 04/01/19
Client Approval: 03/13/19
P&T Approval: N/A
**GUIDELINES FOR USE**

**INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)**

Our guideline for TILDRAKIZUMAB-ASMN (Ilumya) requires a diagnosis of moderate to severe plaque psoriasis (PsO). The following criteria must also be met.

- Therapy initiated by or in consultation with a dermatologist
- Plaque psoriasis involves at least 10% of body surface area (BSA) OR psoriatic lesions affect the hands, feet, genital area, or face
- Previous trial with ONE of the following conventional therapies: PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- 18 years of age or older
- Previous trial with any TWO of the following preferred agents: Cosentyx, Enbrel, Cimzia, or Otezla

**RENEWAL CRITERIA**

Our guideline for TILDRAKIZUMAB-ASMN (Ilumya) renewal requires a diagnosis of moderate to severe plaque psoriasis (PsO) and documentation that the patient has achieved or maintained clear or minimal disease or a decrease in PASI (Psoriasis Area and Severity Index) of at least 50%.

**RATIONALE**

Ensure appropriate diagnostic, utilization and safety criteria are used for the management of requests for Ilumya.

**FDA APPROVED INDICATIONS**

Ilumya is an interleukin-23 antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

**DOsing & Administration**

Ilumya is administered by subcutaneous injection. Ilumya should only be administered by a healthcare provider. The recommended dose is 100 mg at Week 0, Week 4, and every 12 weeks thereafter.

**Dosage Forms and Strengths**

Single-dose prefilled syringes are available for subcutaneous administration: 100 mg per mL.

**REFERENCES**


Created: 03/19
Effective: 04/15/19
Client Approval: 03/20/19
P&T Approval: N/A
TOBRAMYCIN INHALED

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GUIDELINES FOR USE

Approval requires a diagnosis of cystic fibrosis and a lung infection with a gram-negative species.

RATIONALE

Promote appropriate utilization of Tobi based on FDA approved indication.

TOBI Dosage: One ampule (300mg/5ml) every 12 hours in repeated cycles of 28 days on drug followed by 28 days off drug.

TOBI Podhaler Dosage: Inhalate four 28mg capsules twice daily for 28 days. After 28 days of therapy, patients should stop TOBI Podhaler therapy for the next 28 days, and then resume therapy for the next 28 day on and 28 day off cycle.

Bethkis Dosage: One ampule (300mg/4ml) twice daily by oral inhalation in repeated cycles of 28 days on drug, followed by 28 days off drug.

Kitabis Pak Dosage: One ampule (300mg/5ml) twice a day by oral inhalation in repeated cycles of 28 days on drug, followed by 28 days off drug.

FDA APPROVED INDICATIONS

TOBI is indicated for the management of cystic fibrosis patients with *P. aeruginosa*. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV₁ <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.

TOBI Podhaler is an antibacterial aminoglycoside indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV₁) <25% or >80% or patients colonized with *Burkholderia cepacia*.

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BETHKIS is an inhaled aminoglycoside antibacterial indicated for the management of cystic fibrosis patients with Pseudomonas aeruginosa. Safety and efficacy have not been demonstrated in patients under the age of six years, patients with a forced expiratory volume in less than one second (FEV1) less than 40% or greater than 80% predicted, or patients colonized with Burkholderia cepacia.

KITABIS PAK is a co-packaging of tobramycin inhalation solution with a PARI LC PLUS Resuable Nebulizer. Tobramycin is an aminoglycoside antibacterial drug indicated for the management of cystic fibrosis in adults and pediatric patients 6 years and older with Pseudomonas aeruginosa. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV1 <25% or >75% predicted, or patients colonized with Burkholderia cepacia.

REFERENCES

NOTE: For requests for the SQ dosage form of Actemra, please see the TOCILIZUMAB SQ PA Guideline.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

The guideline named TOCILIZUMAB - IV (Actemra - IV) requires a diagnosis of moderate to severe rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), systemic juvenile idiopathic arthritis (SJIA), or chimeric antigen receptor (CAR) T cell-induced severe or life-threatening Cytokine Release Syndrome (CRS). In addition, the following criteria must be met:

For patients with moderate to severe rheumatoid arthritis, approval requires all of the following:
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older
- Previous trial of TWO of the following preferred self-administered immunomodulators: Cimzia, Enbrel, Ocrevus, Simponi, or Xeljanz

For patients with polyarticular juvenile idiopathic arthritis, approval requires all of the following:
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 2 years of age or older
- Previous trial of the preferred formulary TNF (tumor necrosis factor) inhibitor: Enbrel

For patients with systemic juvenile idiopathic arthritis, approval requires all of the following:
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial of at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 2 years of age or older

For the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS), approval requires both of the following:
- The patient is 2 years of age or older
- Actemra is ordered for co-administration with Kymriah (tisagenlecleucel) or Yescarta (axicabtagene ciloleucel) if necessary

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TOCILIZUMAB – IV

RENEWAL CRITERIA

The guideline named TOCILIZUMAB - IV (Actemra - IV) requires a diagnosis of moderate to severe rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, or systemic juvenile idiopathic arthritis for renewal. In addition, the following criterion must be met:

- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy.

TOCILIZUMAB – IV

RATIONALE

Ensure appropriate utilization criteria are met for the management of requests for tocilizumab.

FDA APPROVED INDICATIONS

Actemra - IV (tocilizumab - IV) is an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

DOSAGE AND ADMINISTRATION

<table>
<thead>
<tr>
<th>Rheumatoid Arthritis</th>
<th>Recommended Adult Intravenous (IV) Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response. Doses exceeding 800 mg per infusion are not recommended in RA patients.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Intravenous PJIA Dosage Every 4 Weeks</td>
</tr>
<tr>
<td>Patients less than 30 kg weight 10 mg per kg</td>
</tr>
<tr>
<td>Patients at or above 30 kg weight 8 mg per kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Juvenile Idiopathic Arthritis (SJIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Intravenous SJIA Dosage Every 2 Weeks</td>
</tr>
<tr>
<td>Patients less than 30 kg weight 12 mg per kg</td>
</tr>
<tr>
<td>Patients at or above 30 kg weight 8 mg per kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytokine Release Syndrome (CRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Intravenous CRS Dosage</td>
</tr>
<tr>
<td>Patients less than 30 kg weight 12 mg per kg</td>
</tr>
<tr>
<td>Patients at or above 30 kg weight 8 mg per kg</td>
</tr>
</tbody>
</table>

Alone or in combination with corticosteroids.

If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of ACTEMRA may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients.
FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE FORMS AND STRENGTHS
Single-use vials of ACTEMRA (20 mg per mL) are available for intravenous administration:
- 80 mg per 4 mL
- 200 mg per 10 mL
- 400 mg per 20 mL

REFERENCE

Created: 02/18
Effective: 06/01/18
Client Approval: 05/14/18
P&T Approval: N/A
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named TOCILIZUMAB - SQ (Actemra - SQ) requires a diagnosis of moderate to severe rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (PJIA), systemic juvenile idiopathic arthritis (SJIA) or chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome for approval. In addition, the following criteria must be met:

For patients with moderate to severe rheumatoid arthritis (RA), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist
- The patient has had a previous trial of at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 18 years of age or older

For patients with giant cell arteritis (GCA), approval requires:
- The patient is 18 years of age or older

For patients with polyarticular juvenile idiopathic arthritis (PJIA), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist
- The patient has had a previous trial of at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 2 years of age or older

For patients with systemic juvenile idiopathic arthritis (SJIA), approval requires:
- Therapy is prescribed by or given in consultation with a rheumatologist
- The patient has had a previous trial of at least one of the following DMARDs (disease-modifying antirheumatic drugs: methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- The patient is 2 years of age or older

For patients with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome, approval requires:
- The patient is 2 years of age or older

CONTINUED ON NEXT PAGE
TOCILIZUMAB - SQ

GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

The guideline named TOCILIZUMAB - SQ (Actemra - SQ) requires a diagnosis of moderate to severe rheumatoid arthritis (RA), giant cell arteritis (GCA), systemic juvenile idiopathic arthritis (SJIA), polyarticular juvenile idiopathic arthritis (PJIA) or chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome for renewal. In addition, the following criteria must be met:

For patients with moderate to severe rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), or systemic juvenile idiopathic arthritis (SJIA), approval requires:
- The patient has experienced or maintained a 20 percent or greater improvement in tender joint count or swollen joint count while on therapy

For patients with giant cell arteritis (GCA) or chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome, approval requires:
- The patient has experienced symptomatic improvement or maintained stable clinical status

RATIONALE
Ensure appropriate use of Actemra SQ consistent with its FDA approved indications.

REFERENCES

Created: 03/15
Effective: 03/01/19
Client Approval: 02/14/19
P&T Approval: N/A
TOFACITINIB

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
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<th>GCN</th>
<th>Exception/Other</th>
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<tr>
<td>TOFACITINIB CITRATE</td>
<td>XELJANZ</td>
<td></td>
<td>33617</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>44882</td>
<td></td>
</tr>
<tr>
<td>TOFACITINIB CITRATE</td>
<td>XELJANZ XR</td>
<td></td>
<td>38086</td>
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</table>

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for TOFACITINIB requires a diagnosis of moderate to severe rheumatoid arthritis (RA), active or psoriatic arthritis (PsA), or moderately to severely active ulcerative colitis (UC). Additional guideline requirements apply.

For patients with moderate to severe rheumatoid arthritis (RA), approval requires all of the following:
- Therapy prescribed by or in consultation with a rheumatologist
- Previous trial with at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, sulfasalazine
- 18 years of age or older

For patients with active psoriatic arthritis (PsA), approval requires all of the following:
- Therapy prescribed by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, sulfasalazine
- Concurrent use of a non-biologic DMARD such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- 18 years of age or older

For patients with moderately to severely active ulcerative colitis (UC), approval requires all of the following:
- Therapy prescribed by or in consultation with a gastroenterologist
- Previous trial with at least ONE of the following conventional therapies: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
- 18 years of age or older

CONTINUED ON NEXT PAGE
TOFACITINIB

GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

Our guideline for the renewal of TOFACITINIB requires a diagnosis of moderate to severe rheumatoid arthritis (RA), psoriatic arthritis (PsA), or moderately to severely active ulcerative colitis (UC). Additional guideline requirements apply.

Renewal for patients with moderate to severe rheumatoid arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender and swollen joint count while on therapy.

Renewal for patients with active psoriatic arthritis requires:
- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender and swollen joint count while on therapy.
- Concurrent use of a non-biologic DMARD such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine.

Renewal for patients with moderately to severely active ulcerative colitis requires:
- Documentation that the patient has achieved or maintained symptomatic improvement while on therapy

RATIONALE

To ensure appropriate use of Xeljanz/Xeljanz XR consistent with FDA approved indication.

Xeljanz/Xeljanz XR may be used as monotherapy or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs). The recommended dose of Xeljanz is 5 mg orally twice daily, and the recommended dose of Xeljanz XR is 11 mg once daily. Xeljanz/Xeljanz XR is given orally with or without food. Patients treated with Xeljanz 5 mg twice daily may be switched to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg.

Dosage modifications are needed for patients with moderate hepatic impairment, moderate to severe renal impairment, concomitant use of potent inhibitors of CYP2C19, concomitant use of moderate/potent inhibitors/inducers of CYP3A4, lymphopenia, neutropenia and anemia. Use of Xeljanz/Xeljanz XR in patients with severe hepatic impairment is not recommended.

Xeljanz, an oral agent, is the first selective inhibitor of Janus kinase (JAK) 1 and JAK3 available for the treatment of RA, PsA, and ulcerative colitis (UC). JAKs are intracellular kinases, which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence intracellular immune processes. Xeljanz inhibits the signaling of several cytokine members simultaneously. While Xeljanz is FDA approved as first line therapy following failure of a DMARD, initially its utilization is expected to be limited to those patients who have failed or are not candidates for injectable biologic therapy (i.e., TNF inhibitors).

CONTINUED ON NEXT PAGE
RATIONALE (CONTINUED)

The American College of Rheumatology RA treatment guidelines recommend DMARDs (i.e. MTX, hydroxychloroquine, leflunomide, minocycline and sulfasalazine) as first line pharmacological treatment. Failure with a DMARD is followed by a trial of one or more TNF inhibitors (Humira, Cimzia, Enbrel, Simponi, and Remicade) followed by a non-TNF biologic such as abatacept (T-cell costimulation modulator), Rituximab (B-cell CD20 antagonist) and tocilizumab (IL-6 receptor antagonist). The TNF and non-TNF inhibitor biologics currently on the market today are administered via subcutaneous (SC) injection or intravenous (IV) infusion.

The American Academy of Gastroenterology UC treatment guidelines recommend TNF inhibitors or anti-adhesion molecules (i.e., vedolizumab) to induce remission in patients with moderately active UC who are past conventional therapies (e.g., MTX, mercaptopurine, mesalamine, azathioprine, and corticosteroids). In the maintenance phase, patients should use the initial induction medications at the optimal maintenance dose along with thiopurine or MTX.

Xeljanz has black box warnings of serious infections and malignancies. Prior to starting Xeljanz patients should be tested for latent tuberculosis (TB) and all patients should be monitored for active TB during treatment even if the initial TB test was negative. Other warnings and precautions include gastrointestinal perforations, hepatic impairment, concurrent use of live vaccines, and the necessity to monitor specific laboratory parameters including lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. The most common adverse reactions reported in >2% of patients treated with Xeljanz monotherapy or in combination with DMARDs were upper respiratory tract infections, headache, diarrhea and nasopharyngitis.

As Xeljanz undergoes hepatic metabolism via the Cytochrome P450 enzymes CYP3A4 and CYP2C19, drug-drug interactions with inhibitors/inducers of those enzymes can occur. Xeljanz is pregnancy category C.

FDA APPROVED INDICATIONS

Xeljanz/Xeljanz XR is indicated for the treatment of adult patients with:

- Moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).
- Psoriatic arthritis in combination with non-biologic disease-modifying antirheumatic drugs (DMARDs).
- Moderately to severely active ulcerative colitis (UC).

Xeljanz/Xeljanz XR should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

AVAILABLE STRENGTHS

- 5, 10, and 11 mg tablets

CONTINUED ON NEXT PAGE
REFERENCES

- Bernstein CN. Treatment of IBD: Where we are and where we are going. *Am J Gastroenterol* 2015;110:114-126.
GUIDELINES FOR USE

The guideline named TOLVAPTAN (Jynarque) requires a diagnosis of autosomal dominant polycystic kidney disease. In addition, the following criteria must be met:
- The patient is 18 years of age or older
- The patient is at risk of rapidly progressing ADPKD

RATIONALE
To promote appropriate utilization of JYNARQUE based on FDA approved indication and dosing.

FDA APPROVED INDICATION
Jynarque is a selective vasopressin V2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease.

DOSAGE & ADMINISTRATION
The initial dosage for Jynarque is 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later. Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations. Patients may down-titrate based on tolerability.

<table>
<thead>
<tr>
<th>Initial dosage</th>
<th>Titration Step</th>
<th>Target Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Dose</td>
<td>1st Dose</td>
<td>1st Dose</td>
</tr>
<tr>
<td>45 mg</td>
<td>60 mg</td>
<td>90 mg</td>
</tr>
<tr>
<td>2nd dose (8 hours later)</td>
<td>2nd dose (8 hours later)</td>
<td>2nd dose (8 hours later)</td>
</tr>
<tr>
<td>15 mg</td>
<td>30 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Total Daily Dose</td>
<td>Total Daily Dose</td>
<td>Total Daily Dose</td>
</tr>
<tr>
<td>60 mg</td>
<td>90 mg</td>
<td>120 mg</td>
</tr>
</tbody>
</table>

REFERENCES

Created: 05/18
Effective: 07/21/18
Client Approval: 05/29/18
P&T Approval: N/A
TOPICAL ACNE PRODUCTS

<table>
<thead>
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<th>Generic</th>
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</thead>
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<tr>
<td>ADAPALENE</td>
<td>DIFFERIN, PLIXDA</td>
<td>11233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRETINOIN</td>
<td>ALTRENO, ATRALIN, AVITA, RETIN-A, TRETIN-X</td>
<td>02468</td>
<td></td>
<td>ROUTE ≠ ORAL OR MISCELL.</td>
</tr>
<tr>
<td>TRETINOIN MICROSPHERES</td>
<td>RETIN-A MICRO, RETIN-A MICRO PUMP</td>
<td>32888</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIFAROTENE</td>
<td>AKLIEF</td>
<td>46048</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR USE

Approval requires a non-cosmetic diagnosis.

RATIONALE

To prevent use of tretinoin, trifarotene, and adapalene products for the treatment of cosmetic conditions such as melasma, photoaging, or wrinkles.

FDA APPROVED INDICATION

Tretinoin, trifarotene, and adapalene are indicated for the topical treatment of acne vulgaris.

REFERENCES

- Galderma Laboratories. Aklief package insert. Fort Worth, TX, October 2019.

Created: 02/17
Effective: 11/29/19
Client Approval: 11/06/19
P&T Approval: N/A
Approval requires the patient to be a female who is postmenopausal with a diagnosis of estrogen receptor-positive or unknown hormone receptor status metastatic breast cancer.

**RATIONALE**
Coverage of Fareston (toremifene) is based on FDA approved indication and NCCN recommendations.

Fareston is dosed 60mg daily.

NCCN guidelines recognize several hormonal therapies as appropriate options for the treatment of ER-positive metastatic breast cancer including: anastrozole, letrozole, exemestane, fulvestrant, tamoxifen, toremifene, megestrol acetate, fluoxymesterone, and ethinyl estradiol. Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines.

**FDA Approved Indication**
Fareston is an estrogen agonist/antagonist indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors.

**REFERENCES**

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 08/13
GUIDELINES FOR USE

The guideline named TRAMETINIB (Mekinist) requires a diagnosis of unresectable or metastatic melanoma, melanoma with the involvement of lymph node(s), metastatic non-small cell lung cancer (NSCLC), or locally advanced or metastatic anaplastic thyroid cancer (ATC) and that the following criteria are met:

For patients with unresectable or metastatic melanoma for use as a single agent:
- The patient has BRAF V600E or V600K mutations as detected by an FDA-approved test
- The medication will be used as a single agent
- The patient has not received prior BRAF inhibitor therapy (e.g., Zelboraf, Tafinlar)

For patients with unresectable or metastatic melanoma for use in combination with Tafinlar:
- The patient has BRAF V600E or V600K mutations as detected by an FDA-approved test
- The medication will be used in combination with Tafinlar (dabrafenib)
- The patient has not received prior BRAF inhibitor therapy (e.g., Zelboraf, Tafinlar)

For patients with melanoma with the involvement of lymph node(s):
- The patient has BRAF V600E or V600K mutations as detected by an FDA-approved test
- The medication will be used in combination with Tafinlar (dabrafenib) as the adjuvant treatment following complete resection
- The patient has not received prior BRAF inhibitor therapy (e.g., Zelboraf, Tafinlar)

For patients with metastatic non-small cell lung cancer (NSCLC):
- The patient has BRAF V600E mutation as detected by an FDA-approved test
- The medication will be used in combination with Tafinlar (dabrafenib)

For patients with locally advanced or metastatic anaplastic thyroid cancer (ATC):
- The patient has BRAF V600E mutation as detected by an FDA-approved test
- The patient has no satisfactory locoregional treatment options
- The medication will be used in combination with Tafinlar (dabrafenib)

RATIONALE
Ensure appropriate use of Mekinist based on FDA approved indications and dosing.

FDA APPROVED INDICATIONS
MEKINIST is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

CONTINUED ON NEXT PAGE
TRAMETINIB

RATIONALE (CONTINUED)

MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with:

- Unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test
- Melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s) following complete resection
- Metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test
- Locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options

Limitation of use: MEKINIST is not indicated for treatment of patients with melanoma who have progressed on prior BRAF-inhibitor therapy.

DOSAGE AND ADMINISTRATION

Melanoma: Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with MEKINIST.

NSCLC: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST in combination with dabrafenib.

ATC: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib.

The recommended dosage regimen of MEKINIST is 2 mg orally once daily. Take MEKINIST at least 1 hour before or at least 2 hours after a meal.

**Recommended Dose Reductions for MEKINIST for Adverse Reactions**

<table>
<thead>
<tr>
<th>First Dose Reduction</th>
<th>1.5 mg orally once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second Dose Reduction</td>
<td>1 mg orally once daily</td>
</tr>
<tr>
<td>Subsequent Modification</td>
<td>Permanently discontinue if unable to tolerate MEKINIST 1 mg orally once daily</td>
</tr>
</tbody>
</table>

REFERENCES

- Mekinist [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2018
TREPROSTINIL

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
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<td>ORENITRAM</td>
<td>40827</td>
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</table>

GUIDELINES FOR USE

Our guideline for TREPROSTINIL requires a diagnosis of pulmonary arterial hypertension with New York Heart Association (NYHA) Functional Class II - IV symptoms.

RATIONALE

Ensure appropriate use of Remodulin, Tyvaso and Orenitram.

FDA APPROVED INDICATION

REMODULIN is indicated as a continuous subcutaneous infusion or intravenous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise. Although injectable treprostinil is FDA-approved for use in functional class II patients, it would rarely be recommended for these patients due to its complex administration, cost, safety concerns and adverse effects. Thus, a trial of an oral Phosphodiesterase-5 inhibitor or an Endothelin receptor antagonist is required prior to approval for functional class II PAH.

TYVASO is indicated to increase walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms.

ORENITRAM is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).

When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

CONTINUED ON NEXT PAGE
TREPROSTINIL

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 02/11
GUIDELINES FOR USE

Our guideline for TRIFLURIDINE/TIPIRACIL requires a diagnosis of metastatic colorectal cancer. In addition, the following criteria must also be met:

- Previous treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy in combination with an anti-VEGF biological therapy [e.g. Avastin (bevacizumab), Zaltrap (ziv-aflibercept), Cyramza (ramucirumab)]

For patients who are negative for the RAS mutation (i.e., RAS wild-type), an anti-EGFR agent [e.g. Erbitux (cetuximab), Vectibix (panitumumab)] must also be tried.

RATIONALE

To ensure appropriate use of Lonsurf consistent with FDA approved indication.

Lonsurf is an oral cytotoxic agent that combines two drugs (trifluridine and tipiracil) to treat patients with recurrent colorectal cancer despite previous chemotherapy treatments. Lonsurf consists of a thymidine-based nucleoside analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Tipiracil increases trifluridine exposure by preventing rapid degradation of trifluridine through inhibition of thymidine phosphorylase.

About 35-45% of colorectal cancers have a mutated KRAS oncogene, which is strong predictor that the cancer will not respond to EGFR inhibitors (Vectibix and Erbitux). Since Lonsurf has demonstrated anti-tumor activity against KRAS wild-type (no mutation) and KRAS-mutant human colorectal cancer xenografts in mice, it is possible that it may be considered a treatment alternative.

FDA APPROVED INDICATIONS

Lonsurf is approved for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

DOSAGE

The recommended starting dose is 35mg/m²/dose (up to a maximum of 80 mg per dose, which based on trifluridine component and rounded to the nearest 5mg increment) orally twice a day within one hour of consuming the morning and evening meals on Days 1 through 5 and on Days 8 through 12 of each 28-day cycle. Treatment should be continued until unacceptable toxicity or disease progression.

AVAILABLE STRENGTHS:

- 15 mg trifluridine/ 6.14mg tipiracil tablet
- 20 mg trifluridine/ 8.19mg tipiracil tablet

CONTINUED ON NEXT PAGE
REFERENCES


Created: 10/15
Effective: 12/17/15  Client Approval: 10/28/15  P&T Approval: 11/15
GUIDELINES FOR USE

Our guideline named **TRIPTORELIN PAMOATE** requires that administration will occur under physician supervision and that Trelstar is being used for the treatment of prostate cancer, or that Triptodur is being used for the treatment of central precocious puberty (≥2 years old) confirmed by the following tests: measurement of blood concentrations of luteinizing hormone, sex steroids, and assessment of bone age versus chronological age.

**RATIONALE**

Promote appropriate utilization and dosing based on FDA approved indications.

**FDA APPROVED INDICATIONS**

Trelstar is indicated for the palliative treatment of advanced prostate cancer.

Triptodur is indicated for the treatment of pediatric patients 2 years and older with central precocious puberty.

**DOSEAGE AND ADMINISTRATION**

Trelstar is administered by a single intramuscular injection in either buttock. The lyophilized microgranules are to be reconstituted in sterile water. No other diluent should be used. Trelstar is administered intramuscularly as follows: 3.75mg (1 injection every 4 weeks), 11.25mg (1 injection every 12 weeks), or 22.5mg (1 injection every 24 weeks).

Triptodur is administered by a single intramuscular injection of 22.5mg once every 24 weeks in either the buttock or the thigh.

**REFERENCES**

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named UPADACITINIB (Rinvoq) requires a diagnosis of moderate to severe rheumatoid arthritis. In addition, the following criteria must be met:
- The patient is 18 years of age or older
- Therapy is prescribed by or given in consultation with a rheumatologist
- Previous trial with at least one of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine
- Previous trial with TWO of the following preferred agents: Actemra SC, Cimzia, Enbrel, Simponi, Orencia SC, or Xeljanz/Xeljanz XR

RENEWAL CRITERIA

The guideline named UPADACITINIB (Rinvoq) requires a diagnosis of moderate to severe rheumatoid arthritis. In addition, the following must be met:
- The patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy

RATIONALE

For further information, please refer to the Prescribing Information for Rinvoq.

REFERENCES

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

The guideline named USTEKINUMAB (Stelara) requires a diagnosis of psoriatic arthritis, moderate to severe plaque psoriasis, moderately to severely active Crohn's disease, or moderately to severely active ulcerative colitis. In addition, the following criteria must be met:

For patients with psoriatic arthritis (PsA) without co-existent plaque psoriasis (PsO), our guideline requires:

- Therapy prescribed by or in consultation with a rheumatologist or dermatologist
- Previous trial with at least ONE of the following DMARDs (disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, sulfasalazine
- 18 years of age or older
- Previous trial of any TWO of the following preferred agents: Cimzia, Cosentyx, Enbrel, Orenica SC, Otezla, Simponi, or Xeljanz/Xeljanz XR

For patients with moderate to severe plaque psoriasis (PsO) OR moderate to severe PsO with co-existent psoriatic arthritis (PsA), our guideline requires:

- Therapy prescribed by or in consultation with a dermatologist
- Plaque psoriasis involves at least 10% body surface area (BSA) or psoriatic lesions affecting the face, hands, feet, or genital area
- Previous trial with at least ONE of the following preferred conventional therapies: PUVA (Phototherapy Ultraviolet Light A), UVB (Ultraviolet Light B), topical corticosteroids, calcipotriene, acitretin, methotrexate, or cyclosporine
- 12 years of age or older
- Documentation of the patient's current weight
- Previous trial of any TWO of the following preferred agents: Cimzia, Cosentyx, Enbrel, or Otezla

For patients with moderately to severely active Crohn's disease (CD), our guideline requires:

- Therapy prescribed by or in consultation with a gastroenterologist
- Previous trial of ONE or more of the following conventional agents: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
- Previous trial of or contraindication to Cimzia
- 18 years of age or older
- Documentation of the patient's current weight

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE

INITIAL CRITERIA (CONTINUED)

For patients with moderately to severely active ulcerative colitis, our guideline requires:

- Therapy prescribed by or in consultation with a gastroenterologist
- Previous trial of **ONE** or more of the following conventional agents: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
- Previous trial of or contraindication to Simponi
- 18 years of age or older
- Documentation of the patient's current weight

RENEWAL CRITERIA

Our guideline for the renewal of **USTEKINUMAB (Stelara)** requires a diagnosis of psoriatic arthritis, moderate to severe plaque psoriasis, moderately to severely active Crohn’s disease, or moderately to severely active ulcerative colitis. The following criteria must also be met:

**Renewal for the diagnosis of psoriatic arthritis requires:**

- Documentation that the patient has experienced or maintained a 20% or greater improvement in tender joint count or swollen joint count while on therapy

**Renewal for the diagnosis of moderate to severe plaque psoriasis requires:**

- Documentation that the patient has achieved clear or minimal disease (Physician's Global Assessment equal to zero or one) or documentation of the percentage of decrease in PASI (Psoriasis Area and Severity Index) of at least 50% while on therapy
- Documentation of the patient's current weight

**Renewal for the diagnosis of moderately to severely active Crohn's disease, or moderately to severely active ulcerative colitis requires:**

- Documentation that the patient has experienced or maintained symptomatic improvement while on therapy
- Documentation of the patient's current weight

RATIONALE

Ensure that appropriate diagnostic, utilization, and safety criteria are utilized for the management of Stelara.

CONTINUED ON NEXT PAGE
USTEKINUMAB

FDA APPROVED INDICATIONS
Stelara is a human interleukin-12 and -23 antagonist indicated for the treatment of:
Adult patients with:
- Moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy
- Active psoriatic arthritis (PsA), alone or in combination with methotrexate
- Moderately to severely active Crohn’s disease (CD)
- Moderately to severely active ulcerative colitis
Adolescent patients (12 years or older) with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy

DOSEAGE AND ADMINISTRATION
Psoriatic Arthritis
- The recommended dose is 45mg initially and 4 weeks later, followed by 45mg every 12 weeks
- For patients with co-existent moderate-to-severe plaque psoriasis weighing >100kg (220lbs), the recommended dose is 90mg initially and 4 weeks later, followed by 90mg every 12 weeks

Psoriasis Adult Subcutaneous Recommended Dosage:
- For patients weighing <100 kg (220lbs), the recommended dose is 45mg initially and 4 weeks later, followed by 45mg every 12 weeks
- For patients weighing >100 kg (220lbs), the recommended dose is 90mg initially and 4 weeks later, followed by 90mg every 12 weeks

Psoriasis Adolescent (12 years and older) Subcutaneous Recommended Dosage:
Weight based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.
- Less than 60 kg: 0.75 mg/kg
- 60 kg to 100 kg: 45 mg
- Greater than 100 kg: 90 mg

Crohn's Disease and Ulcerative Colitis:
Intravenous Induction Adult Dosage Regimen: A single intravenous infusion dose using the weight-based dosage regimen specified in Table 1

Table 1. Initial Intravenous Dosage of Stelara

<table>
<thead>
<tr>
<th>Body weight of patient at the time of dosing</th>
<th>Dose</th>
<th>Number of 130 mg/26 mL (5 mg/mL) vials</th>
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<tbody>
<tr>
<td>≤ 55 kg</td>
<td>260 mg</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 55 - 85 kg</td>
<td>390 mg</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 85 kg</td>
<td>520 mg</td>
<td>4</td>
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</table>

Subcutaneous Maintenance Adult Dosage Regimen: The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

REFERENCES

Created: 03/15
Effective: 01/01/20
Client Approval: 12/09/19
P&T Approval: N/A
GUIDELINES FOR USE

The guideline named **VALBENAZINE (Ingrezza)** requires a diagnosis of moderate to severe tardive dyskinesia. In addition, the following criteria must be met:

- Moderate to severe tardive dyskinesia has been present for at least 4 weeks
- Patient age of at least 18 years
- Therapy is prescribed by or given in consultation with a psychiatrist, neurologist or movement disorder specialist
- Patient has history of antipsychotic medications or dopamine receptor blocking drugs used in the treatment of nausea and gastroparesis (e.g., metoclopramide, prochlorperazine, promethazine) for at least 3 months (or at least 1 month if patient is 60 years of age or older) as documented in the medical record or in prescription claims history

RATIONALE

Promote appropriate utilization of **VALBENAZINE (Ingrezza)** based on FDA approved indication and dosing. Duration per clinical trial design (Inclusion criteria and DSM-IV indication).

FDA APPROVED INDICATION

Ingrezza is indicated for the treatment of adults with tardive dyskinesia.

DOSEAGE

The initial dose for Ingrezza is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients. Administer Ingrezza orally with or without food.

REFERENCES

- Ingrezza [Prescribing Information]. San Diego, CA. Neurocrine Biosciences, Inc; December 2018.
VANDETANIB

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</table>

GUIDELINES FOR USE

Approval requires a diagnosis of symptomatic or progressive medullary thyroid cancer with unresectable locally advanced or metastatic disease.

RATIONALE

Ensure appropriate utilization of vandetanib based on FDA approved indication and NCCN guidelines. Vandetanib is recommended as an option for the treatment of recurrent or persistent medullary thyroid carcinoma.

FDA APPROVED INDICATIONS

Vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

REFERENCES


Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/13
GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for VEDOLIZUMAB requires a diagnosis of moderate to severe Crohn's disease or moderate to severe ulcerative colitis. Additional guideline requirements apply.

For patients with moderate to severe Crohn's disease requires all of the following:

• Therapy initiated by or in consultation with a gastroenterologist
• Previous trial with at least ONE of the following conventional agents: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
• 18 years of age or older
• Previous trial with the preferred formulary TNF (tumor necrosis factor) inhibitor: Cimzia

For patients with moderate to severe ulcerative colitis requires all of the following:

• Therapy initiated by or in consultation with a gastroenterologist
• Previous trial with at least ONE of the following conventional agents: corticosteroids (e.g., budesonide, methylprednisolone), azathioprine, mercaptopurine, methotrexate, or mesalamine
• 18 years of age or older
• Previous trial with the preferred formulary TNF (tumor necrosis factor) inhibitor: Simponi

RENEWAL CRITERIA

Our guideline for VEDOLIZUMAB renewal requires a diagnosis of moderate to severe Crohn's disease or moderate to severe ulcerative colitis and documentation that the patient has experienced or maintained symptomatic improvement while on therapy.

RATIONALE

Promote clinically appropriate utilization of Entyvio (vedolizumab) based on its FDA approved indication and dosing.

Entyvio is the only integrin receptor antagonist with dual indication for treatment of moderate to severe ulcerative colitis (UC) and Crohn's disease (CD). It is a monoclonal antibody that binds to integrin α4β7, thereby blocking the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and inhibiting the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. The interaction of the α4β7 integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of UC and CD.
VEDOLIZUMAB

DOSE
Ulcerative colitis: 300 mg IV infusion over 30 minutes at week 0, 2, and 6, then every 8 weeks.
Crohn's disease: 300 mg IV infusion over 30 minutes at week 0, 2, and 6, then every 8 weeks.

FDA APPROVED INDICATIONS
Adult Ulcerative Colitis (UC)
- Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids:
  - Inducing and maintaining clinical response
  - Inducing and maintaining clinical remission
  - Improving endoscopic appearance of the mucosa
  - Achieving corticosteroid-free remission

Adult Crohn’s Disease (CD)
- Adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids:
  - Achieving clinical response
  - Achieving clinical remission
  - Achieving corticosteroid-free remission

REFERENCES
- Entyvio [Prescribing Information]. Deerfield, IL: Takeda Pharmaceuticals America, INC. May 2014.
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

The guideline named VEMURAFENIB (ZELBORAF) requires a diagnosis of unresectable or metastatic melanoma with a BRAFV600E mutation as detected by an FDA-approved test or Erdheim-Chester Disease with a BRAF V600 mutation.

RATIONALE

Ensure appropriate use of vemurafenib based on FDA approved indication.

FDA APPROVED INDICATIONS

Zelboraf is a kinase inhibitor indicated for the treatment of patients with
- Unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.
- Erdheim-Chester Disease with BRAFV600 mutation.

Limitation of Use: Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.

DOSAGE AND ADMINISTRATION

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with ZELBORAF.

Recommended dose: 960 mg orally twice daily taken approximately 12 hours apart with or without a meal.

REFERENCES


Created: 06/15
Effective: 11/01/18
Client Approval: 09/24/18
P&T Approval: N/A
VENETOCLAX

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<td>VENCLEXTA</td>
<td>43284</td>
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GUIDELINES FOR USE

The guideline named VENETOCLAX (Venclexta) requires a diagnosis of chronic lymphocytic leukemia, small lymphocytic lymphoma, or newly-diagnosed acute myeloid leukemia (AML). In addition, the following must be met:

For patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), approval requires:
- The patient is 18 years of age or older
- The patient has received at least one prior therapy

For patients with newly-diagnosed acute myeloid leukemia (AML), approval requires:
- The patient is 75 years of age or older, OR the patient is 18 years of age or older with comorbidities that preclude the use of intensive induction chemotherapy
- The requested medication will be used in combination with azacitidine or decitabine or low-dose Cytarabine

RATIONALE
To ensure appropriate use of Venclexta consistent with FDA approved indication and dosing.

FDA APPROVED INDICATIONS
Venclexta is a BCL-2 inhibitor indicated
- For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

CONTINUED ON NEXT PAGE
VENETOCLAX

FDA APPROVED INDICATIONS (CONTINUED)

DOSAGE
All Venclexta dose regimens begin with a 5-week ramp-up. The ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of tumor lysis syndrome (TLS).

Venclexta is initiated at a dose of 20 mg orally daily for 7 days and then titrated up on a weekly schedule (according the table below) to a daily dose of 400 mg.

<table>
<thead>
<tr>
<th>Week</th>
<th>Venclexta Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 mg</td>
</tr>
<tr>
<td>2</td>
<td>50 mg</td>
</tr>
<tr>
<td>3</td>
<td>100 mg</td>
</tr>
<tr>
<td>4</td>
<td>200 mg</td>
</tr>
<tr>
<td>5 and beyond</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

HOW SUPPLIED
The CLL/SLL Starting Pack provides the first 4 weeks of VENCLEXTA according to the ramp-up schedule. Venclexta is also available as 10mg 50mg, and 100mg tablets.

REFERENCES
• Venclexta [Prescribing Information]. Abbvie Inc.: North Chicago, IL; July 2019.

Created: 06/17
Effective: 11/01/19
Client Approval: 10/16/19
P&T Approval: N/A
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of metastatic basal cell carcinoma?
   
   If yes, **approve for 12 months with a quantity limit of #1 capsule per day.**
   
   If no, continue to #2.

2. Does the patient have a diagnosis of locally advanced basal cell carcinoma that has recurred following surgery or is the patient not a candidate for surgery or radiation?
   
   If yes, **approve for 12 months with a quantity limit of #1 capsule per day.**
   
   If no, do not approve.

   **DENIAL TEXT:** Approval requires a diagnosis of metastatic basal cell carcinoma or locally advanced basal cell carcinoma that has recurred following surgery or the patient is not a candidate for surgery or radiation.

RATIONALE

To promote appropriate utilization of Erivedge based on its FDA approved indication.

Vismodegib is an inhibitor of the Hedgehog signaling pathway. This pathway is important in embryonic development and becomes reactivated in cancer. Because this pathway is not required in most adult tissues, inhibitors selectively attack tumor cells. Vismodegib is the first drug approved for advanced BCC. BCC is the most common type of skin cancer and is typically localized, slow-growing and painless. Localized disease is usually curable by surgery and radiation treatment. Advanced disease is more deadly and has no other FDA approved treatment options.

A single-arm, open-label trial was conducted in patients with either mBCC (n=33) or laBCC (n=71) who received 150mg vismodegib daily until disease progression or unacceptable toxicity. Objective response rates were 30.3% for mBCC and 42.9% for laBCC. No mBCC patients achieved complete response, while 20.6% of laBCC patients had a complete response. Median response duration was 7.6 months for both mBCC and laBCC.

The common adverse reactions are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia.

There is a **black box warning** for embryo-fetal death and severe birth defects. Pregnancy Category D.

**Dosage:** One 150mg capsule once daily with or without food.

**CONTINUED ON NEXT PAGE**
FDA APPROVED INDICATION
Erivedge is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

REFERENCES

Created: 06/15
Effective: 07/22/15
Client Approval: 06/15
P&T Approval: 11/13
GUIDELINES FOR USE

Approval requires a diagnosis of metastatic basal cell carcinoma or locally advanced basal cell carcinoma that has recurred following surgery or the patient is not a candidate for surgery or radiation.

RATIONALE
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Vismodegib is an inhibitor of the Hedgehog signaling pathway. This pathway is important in embryonic development and becomes reactivated in cancer. Because this pathway is not required in most adult tissues, inhibitors selectively attack tumor cells. Vismodegib is the first drug approved for advanced BCC. BCC is the most common type of skin cancer and is typically localized, slow-growing and painless. Localized disease is usually curable by surgery and radiation treatment. Advanced disease is more deadly and has no other FDA approved treatment options.

A single-arm, open-label trial was conducted in patients with either mBCC (n=33) or laBCC (n=71) who received 150mg vismodegib daily until disease progression or unacceptable toxicity. Objective response rates were 30.3% for mBCC and 42.9% for laBCC. No mBCC patients achieved complete response, while 20.6% of laBCC patients had a complete response. Median response duration was 7.6 months for both mBCC and laBCC.

The common adverse reactions are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia.

There is a black box warning for embryo-fetal death and severe birth defects. Pregnancy Category D.

**Dosage:** One 150mg capsule once daily with or without food.

**FDA APPROVED INDICATION**
Erivedge is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

**REFERENCES**
This drug requires a written request for prior authorization.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA SEE BELOW)

Our guideline for ZOLEDRONIC ACID (Reclast) requires that the patient has a diagnosis of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, male osteoporosis, or Paget's disease. For all diagnoses, a trial of or contraindication to an oral bisphosphonate is required. Reclast will not be approved for the prevention or treatment of osteoporosis in men. The following criteria must also be met:

- **For the prevention and treatment of glucocorticoid-induced osteoporosis**, patients must be taking a systemic glucocorticoid daily dose equivalent of 7.5mg or more of prednisone and expected to remain on glucocorticoids for at least 12 months.

RENEWAL CRITERIA

Our guideline for renewal of ZOLEDRONIC ACID (Reclast) requires that the patient have a diagnosis of postmenopausal osteoporosis, male osteoporosis, glucocorticoid-induced osteoporosis, or Paget's disease. The following criteria must also be met:

- **For the prevention and treatment of glucocorticoid-induced osteoporosis**, patients must be taking a systemic glucocorticoid daily dose equivalent of 7.5mg or more of prednisone and expected to remain on glucocorticoids for at least 12 months.

RATIONALE

To ensure appropriate use of RECLAST based on FDA approved indications and dosing.

RECLAST Dosing:

- Treatment of Osteoporosis in Postmenopausal Women: Administer 5mg IV infusion over no less than 15 minutes once a year.
- Prevention of Osteoporosis in Postmenopausal Women: Administer 5mg IV infusion over no less than 15 minutes every 2 years.
- Treatment of Osteoporosis in Men: Administer 5mg IV infusion over no less than 15 minutes once a year.
- Treatment and Prevention of Glucocorticoid-Induced Osteoporosis: Administer 5mg IV infusion over no less than 15 minutes once a year.
- Treatment of Paget's Disease: Administer 5mg IV infusion over no less than 15 minutes as a single dose. Patients should receive 1500 mg elemental calcium and 800 international units vitamin D daily. The Endocrine Society guidelines suggest re-treatment is seldom required within 5 years.

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This drug requires a written request for prior authorization.

<table>
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<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOLEDRONIC ACID</td>
<td>RECLAST</td>
<td></td>
<td>25026</td>
<td></td>
</tr>
</tbody>
</table>
FDA APPROVED INDICATIONS
RECLAST is an infused bisphosphonate indicated for:
• Treatment and Prevention of Osteoporosis in Postmenopausal Women
• Treatment of Osteoporosis in Men
• Treatment and Prevention of Glucocorticoid-Induced Osteoporosis.
• Treatment of Paget’s Disease

Limitations of use: Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use.

REFERENCES
• Reclast (zoledronic acid) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2017.

Created: 09/18
Effective: 10/01/18
Client Approval: 08/22/18
P&T Approval: 3QTR
GUIDELINES FOR USE

Our guideline for ZOLEDRONIC ACID (Zometa) requires that the patient have a diagnosis of: (1) hypercalcemia of malignancy; (2) multiple myeloma; (3) documented bone metastases from solid tumors; or (4) prostate cancer that has progressed after treatment with at least one hormonal therapy. Zometa will not be approved for use in hyperparathyroidism or non-tumor-related hypercalcemia.

RATIONALE

To ensure appropriate use of ZOMETA based on FDA approved indications and dosing.

ZOMETA Dosing:

- Hypercalcemia of malignancy: Administer 4mg as a single-use IV infusion over no less than 15 minutes. Patients may receive 4mg as retreatment after a minimum of 7 days if needed.
- Multiple myeloma and bone metastasis from solid tumors: Administer 4mg as a single-use IV infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of greater than 60mL/min.
  - CrCl >60 mL/minute: 4 mg (no dosage adjustment is necessary)
  - CrCl 50 to 60 mL/minute: Reduce dose to 3.5 mg
  - CrCl 40 to 49 mL/minute: Reduce dose to 3.3 mg
  - CrCl 30 to 39 mL/minute: Reduce dose to 3 mg
  - CrCl <30 mL/minute: Use is not recommended.
- Coadminister oral calcium supplements of 500 mg and a multiple vitamin containing 400 international units of vitamin D daily.

FDA APPROVED INDICATIONS

- Hypercalcemia of malignancy
- Multiple myeloma and bone metastasis from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Limitation of use: The safety and efficacy of Zometa has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia.

CONTINUED ON NEXT PAGE
REFERENCES

- Zometa (zoledronic acid) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2016.

Created: 09/18
Effective: 10/01/18 Client Approval: 08/22/18 P&T Approval: 3QTR
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