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This document addresses the use of intravenous or subcutaneous administration of dihydroergotamine (DHE) mesylate injection for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes in adults.

**Clinical Indications**

**Medically Necessary:**

I. Intravenous or subcutaneous dihydroergotamine therapy is considered **medically necessary** for the acute treatment of *migraine attacks with aura* in an adult meeting the following International Headache Society (IHS) diagnostic criteria:
   
   A. Individual has **2 or more** headache attacks; **and**
   
   B. Individual has **1 or more** of the following fully reversible aura symptoms:
      
      1. Visual (for example, flickering lights, spots or lines); **or**
      2. Sensory (for example, pins and needles, numbness); **or**
      3. Speech and/or language (for example, aphasia); **or**
      4. Motor (for example, weakness); **or**
      5. Brainstem (for example, ataxia or vertigo); **or**
      6. Retinal (for example, blindness); **and**

   C. Individual has **2 or more** of the following characteristics:
      
      1. At least 1 aura symptom develops gradually over 5 or more minutes, and/or 2 or more aura symptoms occur in succession; **or**
      2. Each individual aura symptom lasts 5 to 60 minutes; **or**
      3. At least 1 aura symptom is unilateral; **or**
      4. The aura is accompanied, or followed within 60 minutes, by headache; **and**

   D. Individual’s headache is not attributed to another disorder (for example, ischemia stroke or transient ischemic attack).

II. Intravenous or subcutaneous dihydroergotamine therapy is considered **medically necessary** for the acute treatment of *migraine attacks without aura* in an adult meeting the following IHS diagnostic criteria:

   A. Individual has **5 or more** headache attacks; **and**

   B. Individual’s headaches last 4 to 72 hours (untreated or unsuccessfully treated); **and**

   C. Individual's headache has **2 or more** of the following characteristics:
      
      1. Unilateral location; **or**
      2. Pulsating quality; **or**
3. Moderate or severe pain intensity; or
4. Aggravation by or causing avoidance of routine physical activity (for example, walking or climbing stairs); and
D. Individual's headache is accompanied by 1 or more of the following:
   1. Nausea, vomiting or both; or
   2. Photophobia or phonophobia; and
E. Individual's headache is not attributed to another headache disorder.

III. Intravenous or subcutaneous dihydroergotamine therapy is considered medically necessary for the acute treatment of cluster headache episodes in an adult meeting the following IHS diagnostic criteria:

A. Individual has 5 or more headache attacks; and
B. Individual has severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15 to 180 minutes if untreated; and
C. Individual's headache is accompanied by 1 or both of the following:
   1. 1 or more of the following symptoms or signs, ipsilateral to the headache:
      a. Conjunctival injection and/or lacrimation; or
      b. Nasal congestion and/or rhinorrhea; or
      c. Eyelid edema; or
      d. Forehead and facial sweating; or
      e. Forehead and facial flushing; or
      f. Sensation of fullness in the ear; or
      g. Miosis and/or ptosis; or
   2. A sense of restlessness or agitation; and
D. Attacks have a frequency from 1 every other day to 8 per day for more than half of the time the disorder is active; and
E. Individual's headache is not attributed to another headache disorder.

IV. Intravenous or subcutaneous dihydroergotamine therapy is considered medically necessary in an adult for any of the following conditions:

A. Individual has status migrainosis or rebound withdrawal type of headaches; or
B. As an alternative to narcotic therapy for severe migraine or cluster headaches; or
C. Individual is unresponsive to prior use of triptans for severe migraine or cluster headache.

Not Medically Necessary:

Intravenous or subcutaneous dihydroergotamine therapy is considered not medically necessary when the criteria are not met and for all other indications.

<table>
<thead>
<tr>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.</td>
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<table>
<thead>
<tr>
<th>HCPCS</th>
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<tr>
<td>J1110</td>
<td>G43.001-G43.919</td>
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<td>G44.001-G44.029</td>
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<td>G44.40-G44.41</td>
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</table>

Discussion/General Information

Migraine is a common disabling primary headache disorder with two major subtypes:
1. **Migraine without aura** is a clinical syndrome characterized by headaches with specific features and associated symptoms.

2. **Migraine with aura** is primarily characterized by focal neurological symptoms that usually precede or sometimes accompany the headache. Some individuals also experience a premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain (IHS, 2013).

Aura is an early symptom of an attack of migraine with aura, defined by the IHS (2013) as “...the complex of neurological symptoms that occurs usually before the headache...but it may begin after the pain phase has commenced, or continue into the headache phase.” Most aura symptoms typically last for 1 hour unless the aura includes motor symptoms, which may last for a longer time.

**Acute Migraine Treatment**

Effective migraine treatment begins with an accurate diagnosis and a thorough understanding of the impact a primary headache has on the individual’s daily life. Clinicians should be aware of the use and the effectiveness of previous and current treatments, keeping in mind that both prescription and over-the-counter (OTC) products have the potential for exacerbating underlying headache patterns. Once a diagnosis is established, it is essential to explain the condition to the individual. Reassuring an individual that their headaches are not caused by something life-threatening, such as a brain tumor or an aneurysm, is an important part of the treatment process.

Kelley and Tepper (2012) analyzed published reports on the acute treatment of migraine headache with triptans, DHE, and magnesium in emergency department, urgent care, and headache clinic settings. Effectiveness varied widely, even when the pain-free and pain-relief statistics were evaluated separately. When paired comparisons were performed, DHE was equivalent to sumatriptan. Although there are relatively few studies involving health-care provider-administered triptans or DHE for acute rescue, they appear to be equivalent to the dopamine antagonists for migraine pain relief. The relatively rare inclusion of a placebo arm and the frequent use of combination medications in active treatment arms complicate the comparison of single agents with each other.

The American Headache Society (AHS) (Marmura, 2015) performed an updated assessment of the evidence for use of medications in the acute treatment of adult migraine headache. The review, conducted by members of the AHS Guidelines Section, identified no new Class I or II studies evaluating the use of DHE (including nasal spray, intramuscular, or intravenous) for acute migraine headache since the American Academy of Neurology (AAN) published guidelines (Silberstein, 2000); therefore, the AHS assigned a level of evidence B for use of DHE (“Level B: Probably effective [or ineffective] for acute migraine, supported by 1 Class I study or 2 Class II studies”).

**Cluster Headache Treatment**

The IHS (2013) has published criteria for diagnosing cluster headache. Diagnostic criteria specify an individual must have had at least five attacks occurring from one every other day to eight per day, attributable to no other disorder. In addition, headaches must cause severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes if untreated, and be accompanied by a sense of restlessness or agitation and/or one or more of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, forehead and facial flushing, sensation of fullness in the ear, or miosis and/or ptosis.

Episodic cluster headache is defined as at least two cluster periods lasting 7 to 365 days (when untreated) and separated by pain-free remission periods of 1 month or longer. Chronic attacks recur over more than 1 year without remission or with remission lasting less than 1 month (IHS, 2013).

The absence of aura, nausea, or vomiting has helped distinguish cluster from migraine headaches, but studies indicate that 14% of individuals with cluster headache experience aura, 51% have a personal or family history of migraine, 56% report photophobia, 43% report phonophobia, and 23% report osmophobia (Van Vliet, 2003). Therefore, the presence of aura, nausea, vomiting, or photophobia should not rule out a diagnosis of cluster headache. A characteristic feature of cluster headache, noted by 93% of individuals in one study, is restlessness, with behaviors such as pacing and rocking the head and trunk with head in hands (Bahra, 2002). Most of these headaches last 15 minutes to 3 hours and recur at the same time of day, often at night. Many attacks begin during
the first rapid-eye-movement sleep phase. Individuals may report a seasonal pattern of cluster headache with spring and autumn peaks.

**U.S. Headache Consortium**

The U.S. Headache Consortium (Matchar, 2003) identified the following goals for successful treatment of acute attacks of migraine:

- Treat attacks rapidly and consistently and prevent recurrence
- Restore the patient's ability to function
- Minimize the use of backup and rescue medications
- Optimize self-care and reduce subsequent use of resources
- Be cost-effective in overall management
- Have minimal or no adverse events.

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**References**

**Peer Reviewed Publications:**


**Government Agency, Medical Society, and Other Authoritative Publications:**


Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member’s card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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White blood cell growth factors, also known as colony stimulating factors (CSF), are administered to enhance recovery of blood related functions in neutropenia (low white blood count) including febrile neutropenia (FN). CSFs are also utilized to decrease the incidence and severity of infection associated with select disease-related and drug-related myelosuppression (inhibition of bone marrow function).

Granulocyte colony stimulating factors (G-CSF) are glycoproteins which exert major control over the reproduction and maturation of certain white blood cells, which include the following U.S. Food & Drug Administration (FDA) approved products:

- Filgrastim (Neupogen®, Amgen, Thousand Oaks, CA)
- Pegfilgrastim (Neulasta®, Amgen, Thousand Oaks, CA)
- Tbo-filgrastim (Granix®, Sicor Biotech UAB/Teva Pharmaceuticals North Wales, PA)

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells.

- Sargramostim (Leukine®, Sanofi-aventis U.S. LLC, Bridgewater, NJ)

Note: Please refer to CG-DRUG-64 FDA-Approved Biosimilar Products for additional information on clinical criteria for review of a biosimilar product to an already FDA-approved white blood cell growth factor (addressed in CG-DRUG-16).

Note: For additional information please see the following document:

- MED.00117 Autologous Cell Therapy for the Treatment of Damaged Myocardium

Medically Necessary:

Note: See Definition section for definition of febrile neutropenia.
I. **Filgrastim (Neupogen)** is considered **medically necessary** when used for any of the following:

A. **Primary prophylaxis** of febrile neutropenia (FN) in individuals with a risk of FN of 20% or greater based on chemotherapy regimen; or

B. **Primary prophylaxis** of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individuals have one or more of the following risk factors for FN:
   1. Age greater than 65 years; or
   2. Poor performance status (Eastern Cooperative Oncology Group [ECOG] 3 or 4); or
   3. Previous episodes of FN; or
   4. Bone marrow involvement by tumor producing cytopenias; or
   5. Preexisting neutropenia (absolute neutrophil count [ANC] less than 1500mm$^3$); or
   6. Poor nutritional status (baseline albumin less than or equal to 3.5g/dL or body mass index [BMI] less than 20); or
   7. Poor renal function (glomerular filtration rate [GFR] less than 60mL/min); or
   8. Liver dysfunction (liver function tests at least 2X upper limit of normal); or
   9. The presence of open wounds; or
   10. Advanced cancer; or
   11. Other serious comorbidities; or

C. **Secondary prophylaxis** of FN in individuals who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome; or

D. **Adjunctive treatment** of individuals with FN and high risk for infection-associated complications as demonstrated by any of the following:

   1. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10$^9$/L) neutropenia; or
   2. Age greater than 65 years; or
   3. Uncontrolled primary disease; or
   4. Pneumonia; or
   5. Hypotension and multi organ dysfunction (sepsis syndrome); or
   6. Invasive fungal infection; or
   7. Hospitalized at the time of the development of fever; or

E. In an individual with acute lymphocytic leukemia (ALL) after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy; or

F. Use in adult individuals with acute myeloid leukemia (AML) shortly after the completion of induction or repeat induction chemotherapy, or after the completion of consolidation chemotherapy for AML; or

G. Treatment of moderate to severe aplastic anemia; or

H. Treatment of severe neutropenia in individuals with hairy cell leukemia; or

I. In an individual with myelodysplastic syndromes (MDS) with severe neutropenia (ANC less than or equal to 500 mm$^3$) or experiencing recurrent infection; or

J. In an individual receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer; or

K. Chronic administration to reduce the incidence and duration of sequelae of neutropenia (for example, fever, infections, oropharyngeal ulcers) in symptomatic individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; or

L. Treatment of (non-chemotherapy) drug-induced neutropenia; or

M. Treatment of low neutrophil counts in individuals with glycogen storage disease type 1b; or

N. Treatment for neutropenia associated with human immunodeficiency virus (HIV) infection and antiretroviral therapy; or

O. In individuals receiving radiation therapy in the absence of chemotherapy if prolonged delays secondary to neutropenia are expected; or

P. After accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome); or

Q. After a hematopoietic progenitor stem cell transplant (HPCT/HSCT) for the following indications:

   1. To promote myeloid reconstitution; or
   2. When engraftment is delayed or has failed; or

R. To mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT); or
S. Use as an alternate or adjunct to donor leukocyte infusions (DLI) in individuals with leukemic relapse after an allogeneic hematopoietic stem cell transplant.

II. Pegfilgrastim (Neulasta) is considered medically necessary when used for any of the following:

A. Primary prophylaxis of FN in individuals with a risk of FN of 20% or greater based on chemotherapy regimen; or

B. Primary prophylaxis of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individuals have one or more of the following risk factors for FN:
   1. Age greater than 65 years; or
   2. Poor performance status (ECOG 3 or 4); or
   3. Previous episodes of FN; or
   4. Bone marrow involvement by tumor producing cytopenias; or
   5. Preexisting neutropenia (ANC less than 1500/mm^3); or
   6. Poor nutritional status (baseline albumin less than or equal to 3.5 g/dL or BMI less than 20); or
   7. Poor renal function (GFR less than 60 mL/min); or
   8. Liver dysfunction (liver function tests at least 2X upper limit of normal); or
   9. The presence of open wounds; or
   10. Advanced cancer; or
   11. Other serious comorbidities; or

C. Secondary prophylaxis of FN in individuals who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome; or

D. Adjunctive treatment of individuals with FN and high risk for infection-associated complications as demonstrated by any of the following:
   1. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia; or
   2. Age greater than 65 years; or
   3. Uncontrolled primary disease; or
   4. Pneumonia; or
   5. Hypotension and multi organ dysfunction (sepsis syndrome); or
   6. Invasive fungal infection; or
   7. Hospitalized at the time of the development of fever; or

E. In an individual with acute lymphocytic leukemia (ALL) after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy; or

F. In an individual with myelodysplastic syndromes (MDS) with severe neutropenia (ANC less than or equal to 500/mm^3) or experiencing recurrent infection; or

G. In an individual receiving dose dense therapy (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer; or

H. After accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome); or

I. After a hematopoietic progenitor stem cell transplant (HPCT/HSCT) for the following indications:
   1. To promote myeloid reconstitution; or
   2. When engraftment is delayed or has failed.

III. Sargramostim (GM-CSF, Leukine) is considered medically necessary for individuals when any of the following are met:

A. Primary prophylaxis of FN in individuals with a risk of FN of 20% or greater based on chemotherapy regimen; or

B. Primary prophylaxis of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individuals have one or more of the following risk factors for FN:
   1. Age greater than 65 years; or
   2. Poor performance status (ECOG 3 or 4); or
   3. Previous episodes of FN; or
4. Bone marrow involvement by tumor producing cytopenias; or
5. Preexisting neutropenia (ANC less than 1500mm$^3$); or
6. Poor nutritional status (baseline albumin less than or equal to 3.5g/dL or BMI less than 20); or
7. Poor renal function (GFR less than 60mL/min); or
8. Liver dysfunction (liver function tests at least 2X upper limit of normal); or
9. The presence of open wounds; or
10. Advanced cancer; or
11. Other serious comorbidities; or

C. **Secondary prophylaxis** of FN in individuals who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome; or

D. **Adjunctive treatment** of individuals with FN and high risk for infection-associated complications as demonstrated by any of the following:

1. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10$^9$/L) neutropenia; or
2. Age greater than 65 years; or
3. Uncontrolled primary disease; or
4. Pneumonia; or
5. Hypotension and multi organ dysfunction (sepsis syndrome); or
6. Invasive fungal infection; or
7. Hospitalized at the time of the development of fever; or

E. In an individual receiving **dose dense therapy** (treatment given more frequently, such as every 2 weeks instead of every 3 weeks) for adjuvant treatment of breast cancer; or

F. In an individual with **acute lymphocytic leukemia (ALL)** after completion of the first few days of initial induction chemotherapy or first post-remission course of chemotherapy; or

G. For administration shortly after the completion of induction or repeat induction chemotherapy of **acute myeloid leukemia (AML)** for individuals over 55 years of age; or

H. In an individual with **myelodysplastic syndromes (MDS)** with severe neutropenia (ANC less than or equal to 500 mm$^3$) or experiencing recurrent infection; or

I. In individuals receiving radiation therapy in the absence of chemotherapy if prolonged delays secondary to neutropenia are expected; or

J. After accidental or intentional total body radiation of myelosuppressive doses (greater than 2 Grays [Gy]) (such as Hematopoietic Syndrome of Acute Radiation Syndrome); or

K. After a hematopoietic progenitor stem cell transplant (HPCT/HSCT) for the following indications:

1. To promote myeloid reconstitution; or
2. When engraftment is delayed or has failed; or

L. To mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT).

IV. **Tbo-Filgrastim (Granix)** is considered **medically necessary** when used for any of the following:

A. **Primary prophylaxis** of FN in individuals with a risk of FN of 20% or greater based on chemotherapy regimen; or

B. **Primary prophylaxis** of developing FN is greater than or equal to 10% and less than 20% based on chemotherapy regimen and individuals have one or more of the following risk factors for FN:

1. Age greater than 65 years; or
2. Poor performance status (ECOG 3 or 4); or
3. Previous episodes of FN; or
4. Bone marrow involvement by tumor producing cytopenias; or
5. Preexisting neutropenia (ANC less than 1500mm$^3$); or
6. Poor nutritional status (baseline albumin less than or equal to 3.5g/dL or BMI less than 20); or
7. Poor renal function (GFR less than 60mL/min); or
8. Liver dysfunction (liver function tests at least 2X upper limit of normal); or
9. The presence of open wounds; or
10. Advanced cancer; or
11. Other serious comorbidities; or
C. Secondary prophylaxis of FN in individuals who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome; or

D. Adjunctive treatment of individuals with FN and high risk for infection-associated complications as demonstrated by any of the following:

1. Expected prolonged (greater than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia; or
2. Age greater than 65 years; or
3. Uncontrolled primary disease; or
4. Pneumonia; or
5. Hypotension and multi organ dysfunction (sepsis syndrome); or
6. Invasive fungal infection; or
7. Hospitalized at the time of the development of fever; or

E. After a hematopoietic progenitor stem cell transplant (HPCT/HSCT) for the following indications:

1. To promote myeloid reconstitution; or
2. When engraftment is delayed or has failed; or
3. To mobilize progenitor cells into peripheral blood for collection by leukapheresis, as an adjunct to peripheral blood/hematopoietic stem cell transplantation (PBSCT/PHSCT).

Not Medically Necessary:

The use of CSFs (filgrastim, pegfilgrastim, sargramostim and tbo-filgrastim) is considered not medically necessary for any of the following:

1. As prophylaxis for FN, except when criteria above are met; or
2. As treatment of neutropenia in individuals who are febrile, except when criteria above are met; or
3. As adjunctive therapy in individuals with uncomplicated febrile neutropenia, defined as: fever less than 10 days duration, no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multi-organ dysfunction, or invasive fungal infection; and no uncontrolled malignancies; or
4. Chemo sensitization of myeloid leukemias; or
5. As prophylaxis for FN during concomitant chemotherapy and radiation therapy; or
6. Continued use if no response is seen within 28-42 days (individuals who have failed to respond within this time frame are considered non-responders); or
7. For uses not meeting the criteria above.

### Clinically Equivalent Cost Effective Agents

**Note:** When a white blood cell growth factor, also known as a colony stimulating factor (CSF) is determined to be medically necessary based on the clinical criteria above, the benefit plan may have in addition a medically necessary criterion that the treatment be cost effective.

A benefit plan may select any one or more of the following as a clinically equivalent cost effective white blood cell growth factors: Filgrastim (Neupogen), pegfilgrastim (Neulasta), and Tbo-filgrastim (Granix). A list of the cost effective white blood cell growth factors is available [here](#).

**Note:** Pegfilgrastim (Neulasta) must be selected as one of the clinically equivalent cost effective white blood cell growth factor agents

In benefit plans where there is a requirement to use a cost effective white blood cell growth factor, requests for a white blood cell growth factor that is not cost effective may be approved when the following criteria are met:

1. The individual has had a trial and inadequate response or is intolerant to one cost effective agent; or
2. For the prescribed indication, the cost effective agent is not FDA-approved or does not meet the off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use (see below).
### FDA-approved Indications or Indications Meeting off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use

<table>
<thead>
<tr>
<th>Indication</th>
<th>Filgrastim (Neupogen)</th>
<th>Pegfilgrastim (Neulasta)</th>
<th>Tbo-filgrastim (Granix)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To decrease incidence of FN in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of FN</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>To reduce time to neutrophil recovery and duration of fever following induction and consolidation chemotherapy in AML</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Use in mobilization and following transplantation of autologous peripheral blood progenitor cells</td>
<td>X</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>To reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For the mobilization of hematopoietic progenitor cells into the peripheral blood for stem cell collection</td>
<td>X</td>
<td>Y</td>
<td></td>
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<tr>
<td>To increase survival in patients acutely exposed to myelosuppressive doses of radiation</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>For chronic administration to reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital, cyclic, or idiopathic neutropenia</td>
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<tr>
<td>For treatment of lower risk disease associated with symptomatic anemia</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>For treatment of chemotherapy-induced FN in individuals who have been receiving prophylactic white blood cell growth factors</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>For treatment of chemotherapy-induced FN in individuals who have not received prophylactic G-CSF but have risk factors for an infection-associated complication</td>
<td>Y</td>
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<tr>
<td>For prophylaxis of chemotherapy-induced neutropenia or other dose-limiting neutropenic events in high-risk individuals with solid tumors and nonmyeloid malignancies receiving treatment in the curative/adjuvant or palliative setting</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>For prophylaxis of chemotherapy-induced neutropenia or other dose-limiting neutropenic event in intermediate-risk individuals who with solid tumors and nonmyeloid malignancies receiving treatment in the curative/adjuvant or palliative setting who have one or more risk factors</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Used for mobilization of donor hematopoietic progenitor cells or for granulocyte transfusion in the allogeneic setting</td>
<td>Y</td>
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<tr>
<td>Used in supportive care in the posttransplant setting</td>
<td>Y</td>
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<tr>
<td>For individuals with ALL after completion of initial induction chemotherapy or first post-remission course of chemotherapy</td>
<td>Y</td>
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<tr>
<td>For treatment of moderate to severe aplastic anemia</td>
<td>Y</td>
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<tr>
<td>For treatment of severe neutropenia in hairy cell leukemia</td>
<td>Y</td>
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<tr>
<td>For treatment of individuals with MDS with severe neutropenia or experiencing recurrent infection</td>
<td>Y</td>
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<tr>
<td>For treatment of low neutrophil counts in individuals with glycogen storage disease type 1b</td>
<td>Y</td>
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<tr>
<td>For treatment of neutropenia associated with HIV infection</td>
<td>Y</td>
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</table>
FN = Febrile Neutropenia, AML = Acute Myeloid Leukemia, BMT = Bone Marrow Transplantation, NHL = non-Hodgkin’s Lymphoma, ALL = Acute Lymphoblastic Leukemia, HD = Hodgkin’s Disease, HLA = Human Leukocyte Antigen

X = FDA-approved Indications (excluding cosmetic indications)
Y = Indications Meeting off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT
96377 Application of on-body injector (includes cannula insertion) for timed subcutaneous injection [Neulasta OnPro injector]

HCPCS
J1442 Injection, filgrastim (G-CSF), excludes biosimilars, 1 microgram [Neupogen]
J1447 Injection, tbo-filgrastim, 1 microgram [Granix]
J2505 Injection, pegfilgrastim, 6 mg [Neulasta]
J2820 Injection, sargramostim (GM-CSF), 50 mcg [Leukine, Prokine]
Q5101 Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5108 Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg
Q5110 Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram
Q5111 Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg [Note: code effective 01/01/2019; NOC code J3490 until 12/31/2018]
S9537 Home therapy; hematopoietic hormone injection therapy (e.g., erythropoietin, G-CSF, GM-CSF); per diem [when specified as G-CSF, GM-CSF]

ICD-10 Diagnosis All diagnoses

Discussion/General Information

**Filgrastim, Pegfilgrastim, Sargramostim:**

Filgrastim, pegfilgrastim and sargramostim are recombinant colony-stimulating factors (CSFs) approved by the U.S. Food and Drug Administration (FDA) for stimulation, proliferation, differentiation of neutrophils, and end cell functional activation of hematopoietic cells.

- **Filgrastim** – a recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production of hematopoietic cell types other than the neutrophil lineage (Product Information Label, 2016).
- **Pegfilgrastim** – a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol (Product Information Label, 2017).
- **Sargramostim** – a recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) that stimulates proliferation and differentiation of hematopoietic progenitor cells. GM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways which include neutrophils, monocytes/macrophages and myeloid-derived dendritic cells. GM-CSF is also capable of activating mature granulocytes and macrophages (Product Information Label, 2017).

The American Society of Clinical Oncology (ASCO) (Smith, 2015) *Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline* was adapted for the oncologic indications in this document. Additional non-FDA approved indications are based on expert consensus guidelines (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines (CPG) in Oncology and European...
Neutropenia, a decreased number of neutrophils (white blood cells which fight infection) in the blood is commonly caused by chemotherapy, and often results in hospitalization. Neutropenia occurs when myelosuppressive chemotherapeutic treatments reduce the neutrophil counts. The risk of infection increases as the absolute neutrophil count (ANC) drops below 1000/microL (Crawford, 2004; Dale, 2002). Febrile neutropenia can occur as a result of severe neutropenia. Febrile neutropenia is defined as the occurrence of fever (greater than 38.3°C for more than 1 hour) in association with an ANC less than 0.5 x 10⁹/L, but some studies have used an ANC less than 1.0 x 10⁹/L as the threshold (Dale, 2002; NCCN, 2018). The severity of neutropenia is related to the intensity and type of the chemotherapy regimen, individual-risk factors, and disease-related factors (NCCN, 2018; Ozer, 2000; Smith, 2015). Colony stimulating factors (CSFs) are used to prevent severe neutropenia, reduce the duration of neutropenia, prevent febrile neutropenia, and infection-related complications in individuals with cancer. The routine use of CSFs in neutropenic individuals who are febrile is not recommended (Smith, 2015).

According to ASCO, no guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents, G-CSF (filgrastim) and GM-CSF (sargramostim). There is currently no data available to support preferential use of filgrastim or pegfilgrastim in the treatment of febrile neutropenia. Similarly, there is no currently available data to support preferential use of filgrastim or sargramostim in the treatment of AML or myelodysplastic syndrome (Smith, 2015). Further trials are recommended to study the comparative clinical activity, toxicity, and cost effectiveness of G-CSF and GM-CSF.

The currently available agents differ in their pharmacokinetic properties. Both sargramostim and filgrastim can be administered intravenously (IV) or subcutaneously (SC), whereas pegfilgrastim is administered only SC. The use of sargramostim (GM-CSF) as an inhaled therapy is currently being studied; for example, as experimental therapy in treating pulmonary alveolar proteinosis, where diminished GM-CSF protein or function is hypothesized to play an etiologic role in the disease. Pegfilgrastim is a pegylated form of filgrastim developed to allow for less frequent dosing. Although the two agents have the same mechanism of action, pegfilgrastim has reduced renal clearance and prolonged persistence in vivo compared to filgrastim (Product Information Labels, 2016, 2016, 2017).

Pegfilgrastim (Neulasta) is not labeled for use in myeloid malignancies as it has not been studied for this indication. According to the product information label (2016), the possibility pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, cannot be excluded.

Standard practice in protecting against chemotherapy-associated infection has been chemotherapy dose modification or dose delay, administration of progenitor-cell support, or selective use of prophylactic antibiotics. Chemotherapy associated neutropenic fever or infection has customarily involved treatment with intravenous antibiotics, usually accompanied by hospitalization. The hematopoietic CSFs have been introduced into clinical practice as additional supportive measures to reduce the likelihood of neutropenic complications due to chemotherapy in individuals who are at high risk.

The NCCN CPG in Oncology for Myeloid Growth Factors (2018), ASCO (Smith, 2006) and EORTC (Aapro, 2011) recommend the assessment of risk for chemotherapy induced FN prior to initiating the first cycle of chemotherapy. Factors in the evaluation include disease type, individual risk factors, the intent of treatment and the type of chemotherapy regimen. The risk stratification includes high risk (greater than 20% risk of FN), intermediate risk (10-20% risk) and the low risk (less than 10% risk) groups. NCCN recommends routine CSFs for primary prophylaxis of FN for individuals in the high risk group. For individuals in the intermediate risk (10-20%), NCCN notes CSFs may be considered for primary prophylaxis when additional risk factors are present that would increase the individual’s risk of FN (for example, age greater than 65). Routine use of CSF is not recommended as primary prophylaxis of FN when an individual is considered a low risk. However, NCCN notes for low-risk individuals, “CSF may be considered if the individual is receiving curative or adjuvant therapy and is at significant risk for serious medical consequences of FN, including death.” Schnipper (2012) and colleagues reaffirmed the ASCO guidelines recommend “using white cell stimulating factors when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen is approximately 20% and equally effective treatment programs that do not require white cell stimulating factors are unavailable.” Independent clinical judgment based on the individual’s clinical situation facilitates identifying the appropriate risk group. After the initial treatment cycle and prior to each subsequent cycle, a risk categorization should be evaluated. If FN or a dose-limiting neutropenic event occurred with the previous cycle of treatment with the same dose and schedule planned for the current cycle, the individual is now in the high risk group. The use of white blood cell growth factors as prophylaxis is recommended for individuals considered at high-risk for febrile neutropenia, regardless if the treatment is intended to be curative, to prolong survival or to manage
symptoms. In all risk categories, low, intermediate- and high-risk for chemotherapy-induced neutropenia or other neutropenic-related events that may compromise or delay treatment, careful discussion to determine the risks and benefits of CSF use is recommended (NCCN, 2018).

The EORTC guidelines (Aapro, 2011) note for dose dense (increased frequency) or dose-intense (increased dose) chemotherapy “multiple studies have confirmed that, because the time to neutrophil recovery is around 12 days, pegfilgrastim can be conveniently administered together with chemotherapy in patients receiving treatment at 14 days intervals.” The NCCN Clinical Guidelines for Myeloid Growth Factors (2018) note dose-dense regimens with CSF support “improved disease-free and/or overall survival compared to conventional chemotherapy.” In addition, specialty consensus opinion suggests white blood cell growth factors are used with dose dense chemotherapy regimens in the adjuvant setting to treat individuals with breast cancer.

Neutropenia also commonly occurs in individuals with human immunodeficiency virus (HIV) with 10% to 20% of individuals with early disease experiencing cytopenias and in 35% to 75% of individuals with advanced HIV (Kuritzkes, 2000). Neutropenia, defined as an absolute neutrophil count (ANC) less than 1000 x 10^{6}/L, may be resulting from multiple factors in individuals with HIV. Additionally, neutropenia may be compounded by frontline treatment that may have myelosuppressive effects. Granulocyte colony stimulating factors have been used in individuals with HIV to stimulate granulopoiesis and increase circulating lymphocyte counts (Kuritzkes, 2000).

The American Hospital Formulary Service® (AHFS®, 2016) notes filgrastim has been used effectively to treat neutropenia in a small number of individuals receiving myelosuppressive drugs for nonmalignant conditions. Additionally, the AHFS notes filgrastim has been used to increase neutrophil counts for severe neutropenia in individuals with hairy cell leukemia.

**Radiation**

In 2015, filgrastim and pegfilgrastim received Supplemental Biologics License Application (sBLA) approval for use to increase survival in individuals acutely exposed to myelosuppressive doses of radiation (that is greater than 2 Gy). The condition is also known as Hematopoietic Syndrome of Acute Radiation Syndrome. The label includes a warning to avoid use of filgrastim with concurrent radiation therapy. Available human data is based on information reported in anecdotal reports of accidental irradiation and the subsequent use of growth factors. The specific dosing and timing of G-CSF infusions after exposure continue to be investigated in animal models. Data from a randomized controlled non-human primate study were extrapolated to humans as this type of study in humans is not feasible. Farese and colleagues (2013) reported a significant increase in survival by 38.3% over the 60-day in-life study for subjects treated with G-CSF compared to controls.

ASCO recommendations for the management of individuals exposed to lethal doses of total body radiotherapy or accidental total body radiation include the administration of CSFs or pegylated G-CSF. The recommendation is based on observation of cases in the Radiation Emergency Assistance Center Training Site in the Radiation Accident Registry Center (REAC/TS registry). Twenty-five of 28 individuals experienced enhanced neutrophil recovery with the use of hematopoietic growth factors after accidental radiation exposures (Smith, 2015).

The use of CSFs in conjunction with concomitant use of radiation and chemotherapy is not recommended by ASCO (Smith, 2015) and the NCCN clinical practice guideline for myeloid growth factors in cancer treatment (2018). Smith and colleagues (2015) stated, “in the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.”

In March 2018, the FDA expanded approved sargramostim (Leukine), the third countermeasure to increase survival in children and adults exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome [H-ARDS])). The FDA approval was approval was supported by efficacy studies in animals that could not be ethically conducted in humans. Total body irradiation exposure up to 48 hours, increased survival in 50 % of exposed individuals at doses expected to be fatal, who were under minimal supportive care.

**TBO-filgrastim:**

In August 2012, the FDA approved tbo-filgrastim to reduce the severe neutropenia in individuals with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Tbo-filgrastim is a recombinant methionyl human granulocyte colony-stimulating growth factor (r-metHuG-CSF) that binds to GCSF receptors and stimulates the growth of neutrophils. Tbo-filgrastim is a biosimilar...
product to filgrastim (Neupogen) and is administered subcutaneously (del Giglio, 2008; Product Information Label, 2017).

A randomized, controlled, multinational phase III study involved 348 individuals with high-risk stage II, stage III or stage IV breast cancer who had not previously received treatment with chemotherapy. Participants were randomized to tbo-filgrastim or placebo. Treatment began 1 day after chemotherapy for at least 5 days and continued to achieve an ANC of greater than or equal to $10,000 \times 10^6$ /L after nadir was reached, or until a maximum of 14 days of treatment. The primary endpoint was duration of severe neutropenia (DSN) in cycle 1. Tbo-filgrastim had a superior DSN compared to placebo with a significant reduction in DSN (1.1 days compared to 3.8 days, $p<0.0001$). The mean DSN in cycle 1 was 1.1 days (range 0-5 days) for both tbo-filgrastim and filgrastim (Neupogen). The median time to ANC recovery in cycle 1 was 8.0 days for both tbo-filgrastim and filgrastim (Neupogen) compared to 15 days in the placebo group. The safety and effectiveness of tbo-filgrastim have not been established in individuals under 18 years of age. The FDA has required post-approval studies of tbo-filgrastim to determine the safety and efficacy in the pediatric population (del Giglio, 2008; Product Information Label, 2017).

**Warnings and Precautions:**

Product information labels for filgrastim (Neupogen, 2016) and pegfilgrastim (Neulasta, 2017) include the following warnings and precautions:

- **Allergic Reactions**
  Serious allergic reactions, including anaphylaxis, have been reported. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, in individuals receiving filgrastim can recur within days after the discontinuation of initial anti-allergic treatment.

- **Splenic Rupture**
  Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Evaluate for an enlarged spleen or splenic rupture in individuals who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

- **Acute Respiratory Distress Syndrome**
  Adult respiratory distress syndrome (ARDS) has been reported in individuals receiving filgrastim or pegfilgrastim. Evaluate individuals who develop fever and lung infiltrates or respiratory distress for ARDS.

- **Sickle Cell Disorders**
  Severe sickle cell crises can occur in individuals with sickle cell disorders receiving filgrastim or pegfilgrastim.

  Pegfilgrastim includes an additional warning:
  The On-body Injector for Neulasta uses acrylic adhesive. For individuals who have reactions to acrylic adhesives, use of this product may result in a significant reaction.

General information for filgrastim (Neupogen, 2016) and pegfilgrastim (Neulasta, 2015) include the following:

The safety and efficacy of growth factors given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy:

- Do not use filgrastim in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy
- Do not use pegfilgrastim between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

The safety and efficacy of filgrastim have not been evaluated in individuals receiving concurrent radiation therapy. Simultaneous use of filgrastim with chemotherapy and radiation therapy should be avoided.

Additional information from product labels for filgrastim (Neupogen, 2016) includes:

- **Pediatric Use**
  In a phase 3 study to assess the safety and efficacy of Neupogen in the treatment of severe chronic
neutropenia (SCN), 120 individuals with a median age of 12 years were studied. Of the 120 participants, 12 were infants (1 month to 2 years of age), 47 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of individuals in the clinical studies and information from additional participants who entered directly into the postmarketing surveillance study. Of the 531 participants in the surveillance study as of 31 December 1997, 32 were infants, 200 were children, and 68 were adolescents.

Children with congenital types of neutropenia (Kostmann’s syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown. Limited data from children who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Additional product information for pegfilgrastim (Neulasta, 2017) includes:

**Pediatric Use**
Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean (± standard deviation [SD]) systemic exposure (AUC$_{0-t}$) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 (± 13.1) mcg·hr/mL in the 6 to 11 years age group (n = 10), 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13), and 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 (± 11.3) hours, 21.2 (± 16.0) hours, and 30.1 (± 38.2) hours, respectively. The most common adverse reaction was bone pain.

The product information label for sargramostim (Leukine, 2018) includes the following warnings and precautions:

**Pediatric Use**
Benzyl alcohol is a constituent of liquid sargramostim and bacteriostatic water for injection diluents. Benzyl alcohol has been reported to be associated with a fatal “Gasping Syndrome” in premature infants. Liquid solutions containing benzyl alcohol (including liquid leukine) or lyophilized leukine reconstituted with bacteriostatic water for injection, USP (0.9% benzyl alcohol) should not be administered to neonates.

**Fluid Retention**
Edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported in individuals after sargramostim administration. Use with caution in individuals with preexisting fluid retention, pulmonary infiltrates or congestive heart failure.

**Respiratory Symptoms**
Sequestration of granulocytes in the pulmonary circulation has been documented following sargramostim infusion and dyspnea has been reported occasionally in individuals treated with sargramostim. Use with caution in individuals with hypoxia or preexisting lung disease.

**Cardiovascular Symptoms**
Occasional transient supraventricular arrhythmia has been reported in uncontrolled studies during sargramostim administration, particularly with individuals with a previous history of cardiac arrhythmia. Arrhythmias have been reversible after discontinuation of sargramostim. Use with caution in individuals with preexisting cardiac disease.

**Renal and Hepatic Dysfunction**
In some individuals with preexisting renal or hepatic dysfunction enrolled in uncontrolled clinical trials, administration of sargramostim has induced elevation of serum creatinine or bilirubin and hepatic enzymes. Dose reduction or interruption of sargramostim has resulted in a decrease to pretreatment levels. Monitoring of renal and hepatic function in individuals displaying renal or hepatic dysfunction prior to initiation of treatment is recommended at least every other week during sargramostim administration.

**General Precautions**
Serious allergic or anaphylactic reactions have been reported. If serious allergic or anaphylactic reaction occurs, sargramostim therapy should immediately be discontinued and appropriate therapy initiated.
A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia has been reported following the first administration of sargramostim in a particular cycle. These signs have resolved with symptomatic treatment and usually do not recur with subsequent doses in the same cycle of treatment.

Safety and effectiveness of sargramostim use in pediatric individuals have not been established; however, available safety data indicate that sargramostim does not exhibit any greater toxicity in pediatric cases than in adults.

The product information label for tbo-filgrastim (Granix, 2017) includes the following warnings and precautions:

**Splenic Rupture**
Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In individuals who report upper abdominal or shoulder pain after receiving tbo-filgrastim, discontinue tbo-filgrastim and evaluate for an enlarged spleen or splenic rupture.

**Acute Respiratory Distress Syndrome (ARDS)**
Acute respiratory distress syndrome (ARDS) can occur in individuals receiving human granulocyte colony-stimulating factors. Evaluate individuals who develop fever and lung infiltrates or respiratory distress after receiving tbo-filgrastim, for ARDS. Discontinue tbo-filgrastim in individuals with ARDS.

**Allergic Reactions**
Serious allergic reactions including anaphylaxis can occur in individuals receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue tbo-filgrastim in individuals with serious allergic reactions. Do not administer tbo-filgrastim to individuals with a history of serious allergic reactions to filgrastim or pegfilgrastim.

**Use in Individuals with Sickle Cell Disease**
Severe and sometimes fatal sickle cell crises can occur in individuals with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in individuals with sickle cell disease. Discontinue tbo-filgrastim in individuals undergoing a sickle cell crisis.

**Glomerulonephritis**
Evaluate and consider dose-reduction or interruption of Granix if causality is likely.

**Capillary Leak Syndrome**
Capillary leak syndrome (CLS) can occur in individuals receiving human granulocyte colony-stimulating factors and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Individuals who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Additional product information for tbo-filgrastim (Granix, 2017) includes:

**Pediatric Use**
The safety and effectiveness of tbo-filgrastim in children under 18 years of age have not been established.

**Other Proposed Uses:**
The use of sargramostim to induce remission in Crohn's disease has been proposed. In a Cochrane review (Roth, 2011), data from three studies did not show any difference between sargramostim and placebo drug to induce remission or clinical improvement for individuals with active Crohn's disease. The investigators recommended randomized controlled trials to research the effects of sargramostim on Crohn's disease.

Multiple phase I and phase II clinical trials are studying the safety and efficacy of sargramostim to treat malignant melanoma. However, the published data have been primarily from smaller series that included a variety of additional
immunomodulatory agents and outcomes were mixed. Investigators have noted the outcomes from larger randomized phase III trials with longer follow-up are needed. NCCN CPG (2018) for melanoma do not include treatment regimens which include sargramostim or filgrastim.

There is moderate evidence from three separate systematic reviews which showed CSFs should not be used routinely for the prevention or treatment of non-chemotherapy induced infection, specifically, neonatal infection, and diabetic foot infections or as an adjunct to antibiotics in treating non-neutropenic adults with pneumonia (Carr, 2003; Cheng, 2007).

Based on encouraging data from phase II trials, a large randomized multicenter, placebo-controlled double-blind trial (AX200), investigated the use of G-CSF initiated ≤ 9 hours since onset of stroke symptoms. The primary and secondary endpoints of the trial were not met as G-CSF did not improve the outcomes of stroke over those treated with placebo (Ringelstein, 2013). The use of G-CSF continues to be investigated for off-label indications to evaluate efficacy and safety.

### Definitions

Absolute neutrophil count (ANC): A measure of the number of neutrophils (a type of white blood cell) in the blood.

Acute Radiation Syndrome (ARS): Also known as Radiation Sickness.

Adjuvant or adjunctive treatment: Treatment given after the primary treatment to increase the chances of a cure and may include chemotherapy, radiation, hormone, or biological therapy.

Advanced cancer: Cancer in which the disease has spread from where it started (the primary site) to other parts of the body.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

ECOG Performance Status: A scale used to determine the individual’s level of functioning.

- 0= Fully active, able to carry on all pre-disease performance without restriction
- 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2= Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3= Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4= Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5= Dead

Febrile neutropenia: Febrile neutropenia can occur as a result of severe neutropenia; defined as the occurrence of fever (greater than or equal to 38.3°C for more than 1 hour) in association with an ANC less than 0.5 x 10⁹/L or ANC less than 1.0 x 10⁹/L and a predicted decline to less than or equal to 0.5 x 10⁹/L over the subsequent 48 hours.

Karnofsky Score: A measure of the individual’s overall physical health, judged by their level of activity. The score is based on the following scale:

- 100% Normal, no complaints, no signs of disease
- 90% Capable of normal activity, few symptoms or signs of disease
- 80% Normal activity with some difficulty, some symptoms or signs
- 70% Caring for self, not capable of normal activity or work
- 60% Requiring some help; can take care of most personal requirements
- 50% Requires help often, requires frequent medical care
- 40% Disabled, requires special care and help
- 30% Severely disabled, hospital admission indicated but no risk of death
- 20% Very ill, urgently requiring admission, requires supportive measures or treatment
10% Moribund, rapidly progressive fatal disease processes
0% Death

Neutropenia: A decrease in the number of neutrophils (white blood cells that respond quickly to infection) in the blood. Neutrophils less than 1,500/mm³ is considered to be neutropenic and at risk for infection. Neutrophils fewer than 500 cells/mm³ is considered at high risk of infection.

Neutrophil: A type of white blood cell that helps fight infection.

Primary prophylaxis: Prevention of febrile neutropenia with the first cycle of a specified chemotherapy regimen.

Secondary prophylaxis: Prevention of febrile neutropenia given with the second and/or subsequent cycle of a given regimen of chemotherapy for individuals who had a neutropenic complication from the preceding cycle of chemotherapy and there is no plan to reduce the dose intensity.

References

Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:


### Websites for Additional Information


### Index

Colony Stimulating Factors (CSF)
Granix
Hematopoietic Stimulating Growth Factors
Leukine
Neulasta
Neupogen
Tbo-filgrastim

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

### History

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<td>Updated Coding section with 01/01/2019 HCPCS changes; added Q5111.</td>
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<td>Updated Coding section with 10/01/2018 HCPCS changes; added Q5108 replacing J3590 NOC, and Q5110.</td>
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Reviewed 05/15/2008 MPTAC review.

Hematology/Oncology Subcommittee review. Format changed to align indications with specific agents. Updated the off-label indications for filgrastim and sargramostim. Clarified the FDA labeled indications for sargramostim.

Revised 05/17/2007 MPTAC review.


Revised 05/16/2007 MPTAC. New Guideline including 2006 American Society of Clinical Oncology (ASCO) Updated recommendations.


Pre-Merger Organizations Last Review Date Document Number Title
Anthem, Inc. No document

Anthem BCBS No document

WellPoint Health Networks, Inc. 10/03/2005 Pharmacology Toolkit Filgrastim (Neupogen®, G-CSF)
01/03/2005 Pharmacology Toolkit Neulasta® (Pegfilgrastim)
10/03/2005 Pharmacology Toolkit Sargramostim (Leukine®, Prokine®)

Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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This document addresses the use of repository corticotropin injection (H.P. Acthar Gel), a highly purified sterile preparation of the adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances.

**Clinical Indications**

**Medically Necessary:**

I. Repository corticotropin injection is considered **medically necessary** as monotherapy for the treatment of infantile spasms (West syndrome) in infants and children less than 2 years of age.

II. Repository corticotropin injection is considered **medically necessary** when all of the following criteria are met:
   A. The individual is an adult with a corticosteroid-responsive condition, including but not limited to acute exacerbations of multiple sclerosis; and
   B. The individual has no contraindications to or is not limited by contraindication to or intolerance of glucocorticoid effects; and
   C. There is clear documentation of why all other well-established routes for corticosteroid therapy (for example, oral prednisone and intravenous methylprednisolone) cannot be used.

**Not Medically Necessary:**

Repository corticotropin injection is considered **not medically necessary** when the above criteria are not met and for all other indications.

**Coding**

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**HCPCS**

J0800 Injection, corticotropin, up to 40 units [H.P. Acthar]
Infantile Spasms

In October 2010, repository corticotropin (H.P. Acthar Gel) was approved by the United States Food and Drug Administration (FDA) as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age. Prior to this approval, repository corticotropin injection had been used as an off-label treatment in thousands of infants since its introduction in 1952. Infantile spasms are a very rare and potentially life-threatening form of epilepsy that typically begins in the first year of life. It is characterized by a peculiar type of seizure and electroencephalogram (EEG) findings of hypsarrhythmia and mental retardation, although not all three components are required. Often the term infantile spasm is used synonymously with West syndrome. Infantile spasms are characterized by an initial contraction phase followed by a more sustained tonic phase.

The current FDA approved product label describes a study by Baram and colleagues (1996) supporting the effectiveness of repository corticotropin injection for infantile spasms. In a single blinded clinical trial, infants under 2 years of age (median age of 6 months) with clinical spasms were randomized to receive either a 2-week course of treatment with repository corticotropin (intramuscular injection twice daily) or prednisone (by mouth twice daily). The primary outcome was a comparison of the number of infants in each group who were treatment responders (defined as having complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video electroencephalogram [EEG] performed 2 weeks following initiation of treatment, rated by an investigator blinded to the treatment). Of 15 infants randomized to repository corticotropin injection, 13 (86.7%) responded as compared to 4 of 14 subjects (28.6%) given prednisone.

In a retrospective, multi-center study, Ito and colleagues (2002) reviewed the medical records of 138 infants or children (age at onset of spasms, 1.5 to 60 months; mean age 7.8 months) given low dose synthetic ACTH for the treatment of cryptogenic or symptomatic West syndrome between 1989 and 1998. The authors concluded that at the end of ACTH therapy, excellent effect on seizures was noted in 106 of 138 (76%) subjects, good effect in 23 (17%), and poor effect in 9 (7%).

According to Riikonen (2004), ACTH should be the first choice for treatment of infantile spasms because it is a safe drug when used at the minimal effective dose and duration. The side effects of ACTH are well known, treatable, and reversible (Riikonen, 2004).

Verrotti and colleagues (2007) report that in the United States, the majority of child neurologists use ACTH as the drug of choice for the treatment of infantile spasms. There are variations in the dosage and treatment duration reported. The literature also suggests that ACTH is more effective than oral corticosteroids in causing the cessation of seizures.

Cohen-Sadan and colleagues (2009) reported on a long-term follow-up of children with West syndrome treated with ACTH or vigabatrin. The medical records of 28 normal MRI West syndrome cases were reviewed for seizure development and cognitive outcome in relation to treatment type and timing. The authors concluded that for West syndrome:

ACTH and vigabatrin appear to be equally effective in the short term if treatment is administered within one month of symptom onset. On long-term follow-up, early ACTH treatment appeared to yield a better outcome than early vigabatrin or late ACTH treatment in terms of both cognition and seizure development.

Pellock and colleagues (2010), in an industry-sponsored Infantile Spasms Working Group, published a consensus report on diagnosis and treatment of infantile spasms. Regarding treatment, the report concluded: “At this time, ACTH and VGB (vigabatrin) are the only drugs with proven efficacy to suppress clinical spasms and abolish the hyparrhythmic EEG in a randomized clinical trial setting (Mackay, 2004) and thus remain first-line treatment.”

Hussain and colleagues (2014) evaluated the short-term response of infantile spasms to very high dose prednisolone administered before high dose ACTH. A total of 27 children with infantile spasms confirmed by video EEG received
high dose oral prednisolone (maximum of 60 mg/day) for 2 weeks. Responders were tapered over 2 weeks and non-responders were immediately transitioned to high dose intramuscular ACTH. Response was determined by repeat video EEG. The majority of the participants, 63% (17/27) responded completely to prednisolone. A total of 40% (4/10) of prednisolone non-responders demonstrated a complete response following the additional 2-week course of ACTH. Of 27 subjects with a median follow-up of 13.5 months, 12% (2/17) of prednisolone responders and 50% (2/4) of ACTH responders experienced a relapse between 2 and 9 months after initial response. The authors reported study limitations consisting of a small study population, lack of a control group, lack of standardized and blinded developmental assessments and limited follow-up time.

The American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012) analyzed pre-2002 and more recent evidence on infantile spasms, and subsequently revised their corresponding practice parameters. Recommendations include the following:

- Low-dose ACTH should be considered for treatment of infantile spasms.
- ACTH or vigabatrin (VGB) may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over VGB.
- Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
- A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB may be considered to improve long-term cognitive outcomes.

A Cochrane review (Hancock, 2013) compared the effects of single drugs used to treat infantile spasms in terms of long-term psychomotor development, spasm control, subsequent epilepsy, and adverse effects. Eleven randomized controlled trials (n=514) were included and eight different drugs were tested. Overall methodology of the studies appeared to be poor. No study assessed long-term psychomotor development or onset of other seizure types. The authors concluded:

We found no single treatment to be proven to be more efficacious in treating infantile spasms than any of the others (other than vigabatrin in the treatment of infantile spasms in tuberous sclerosis in one underpowered study). Few studies considered psychomotor development or subsequent seizure rates as outcomes and none had long-term follow-up. Further trials with larger numbers of participants, and longer follow-up are required.

Other conclusions of the Cochrane review include:

- The strongest evidence suggests that hormonal treatment (prednisone, tretocosactide [synthetic ACTH (cosyntropin)] and ACTH) leads to resolution of spasms faster and in more infants that does vigabatrin.
- Responses without subsequent relapse may be no different; that is, the percent of cases that remain seizure-free may be similar when recurrence of seizures is considered.
- There is a suggestion that prednisolone or tetracosactide (cosyntropin) might improve the long-term developmental outcomes compared to vigabatrin in infants not found to have an underlying cause of their infantile spasms.
- Vigabatrin may be the treatment of choice in infantile spasms related to tuberous sclerosis.
- The authors also noted that naturally occurring ACTH is not available in the U.K.

Wanigasinghe and colleagues (2014) published a randomized controlled trial that blindly assigned children with previously untreated West syndrome to treatment with 40 to 60 IU synthetic ACTH every other day or 40 to 60 mg/day of oral prednisolone. The primary outcome was change in a hypsarrhythmia severity scale (possible score range, 0-16). A total of 92 children (age 2 months-2 years) were randomized, and follow-up data were available on 80 (82%) of them. Mean improvement in the hypsarrhythmia score was 7.95 in the prednisolone arm and 6.00 in the ACTH arm. The difference between the two groups was significantly different (p<0.01), favoring treatment with prednisolone. Both forms of therapy were well tolerated; however, irritability, frequent crying, weight gain, increased appetite, and abdominal distension were more common, but not statistically significant with prednisolone. This study suggests that prednisolone may at least as effective as synthetic ACTH for treatment of infantile spasms. Multiple limitations of the study were noted including a dropout rate of over 20%, lack of intention-to-treat analysis, short-term follow-up only, and use of intermediate outcomes.

Multiple Sclerosis
The product label (2015) states repository corticotropin injection is indicated for the treatment of exacerbations of multiple sclerosis in adults. Acute exacerbations of multiple sclerosis or relapses are typically steroid responsive and as such are treated with corticosteroids such as methylprednisolone (MP). The term “acute exacerbation” in multiple sclerosis is synonymous with “relapse” or “attack”. Repository corticotropin injection augments circulating steroids via adrenal gland stimulation and therefore produces the same types of effects and side effects which occur when steroids are used. Unlike steroids, repository corticotropin acts indirectly since the adrenal glands are activated. Exogenous corticosteroids act directly, are available in multiple formulations and delivery methods (oral, intravenous, intramuscular, subcutaneous), and are widely accepted as the appropriate therapy for steroid responsive conditions. Accordingly, there is no clinical basis for selecting a repository corticotropin when an individual is able to receive exogenous corticosteroids.

Available peer reviewed literature describing the use of repository corticotropin injection for the treatment of multiple sclerosis relapses or exacerbations consists mainly of old studies which are not of high quality (Miller, 1961; Rose, 1970; Thompson, 1989). In addition, Abbruzzese (1983) indicated there was equal efficacy for IV MP and ACTH for the treatment of multiple sclerosis. In a systematic review, Filippini and colleagues (2000) attempted to determine the safety and efficacy of corticosteroids (MP) or ACTH in reducing the short- and long-term morbidity from multiple sclerosis. The authors noted that overall, MP or ACTH showed a protective effect against the disease getting worse or stable within the first 5 weeks of treatment (odds ratio 0.37, 95% confidence interval, 0.24 to 0.57) with some but nonsignificant greater effect for MP or intravenous administration. More recently, Sismarian and colleagues (2011) in a prospective, randomized, open-label pilot trial examined the safety and efficacy of a 5-day self-administered ACTH dosing protocol for multiple sclerosis exacerbations, and also compared intramuscular and subcutaneous routes of administration. Of the 20 subjects enrolled, 19 completed the study and results suggested that a 5-day course of “patient-administered” ACTH gel therapy may relieve symptoms of acute exacerbations of multiple sclerosis when administered either as intramuscular or subcutaneous injections. The authors concluded that larger, placebo-controlled studies are needed to determine the optimal dose of ACTH gel, duration of treatment, and route of administration, as well as its role compared with steroid therapy.

In 2016, Murray and colleagues reported on a small case series of 6 individuals with multiple sclerosis and a history of neuropsychiatric side effects after treatment with intravenous MP. All 6 individuals were subsequently treated with repository corticotropin injection for MS exacerbations and each appeared to tolerate treatment without mood changes and showed improvement in MS symptoms. Limitations included the inherent observational nature of a cases series and the very small number of individuals involved.

Other Uses

Repository corticotropin injection has been used as an aid in the diagnosis of adrenocortical insufficiency; however, this indication was removed from the product label in October 2010. There is a lack of peer reviewed published literature to support this use.

In addition to infantile spasms and multiple sclerosis, the product label (2015) states repository corticotropin injection may be used for treatment of the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state. The published evidence in support of these conditions is limited; however, repository corticotropin injection may potentially be a treatment option for an individual with one of these corticosteroid responsive conditions under very specific circumstances.

A systematic review and meta-analysis of 36 clinical trials by Chen (2013) evaluated immunosuppression for treatment of the most common form of primary nephrotic syndrome in adults, membranous nephropathy. Of all the studies, two (n=62 subjects) evaluated adrenocorticotropic hormone (versus no treatment or corticosteroids and alkylating agents). Adrenocorticotropic hormone significantly decreased proteinuria at the end of 22 months of follow-up. However, multiple study limitations were present including small sample sizes and a high risk of bias. The authors concluded: “More methodologically sound and sufficiently powered studies with adequate follow-up are still urgently needed for clinical decision making, especially for adrenocorticotropic hormone and rituximab.”

There have been additional small studies and case series published evaluating repository corticotropin for a variety of conditions, including rheumatoid arthritis (Gillis, 2017; Fischer, 2018), myositis (Aggarwal, 2018), chronic pulmonary sarcoidosis (Baughman, 2017), systemic lupus erythematosus (Fiechtner, 2014); nephrotic syndrome (Bomback, 2011; Hladunewich, 2014; Madan, 2016); and membranous glomerulopathy (Watson, 2014). All authors concluded that repository corticotropin may be an effective therapy for their respective conditions. However, limitations included small numbers of participants.
The following are contraindications included in the Product Information Label (2015):

- Administration of live or live attenuated vaccines is contraindicated in individuals receiving immunosuppressive doses of repository corticotropin injection.
- Intravenous administration of this drug is contraindicated.
- Repository corticotropin injection is contraindicated in individuals with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin.
- Repository corticotropin injection is contraindicated in children under 2 years of age with suspected congenital infections.
- Treatment is contraindicated when conditions are accompanied by primary adrenocortical insufficiency or adrenocortical hyperfunction.

**Definitions**

Hypsarrhythmia: Chaotic abnormal brain wave patterns.

**References**

**Peer Reviewed Publications:**


Government Agency, Medical Society, and Other Authoritative Publications:


Index

Acthar
Adrenocorticotropic Hormone (ACTH)
Corticotropin
H.P. Acthar Gel
Repository Corticotropin Injection
The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

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<td>07/26/2018</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. The document header wording updated from “Current Effective Date” to “Publish Date.” Discussion and References sections updated.</td>
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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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This document addresses palonosetron, an intravenous (IV) antiemetic that is a selective type 3 serotonin receptor antagonist. The drug blocks two pathways of serotonin release to help prevent nausea and vomiting in certain individuals. Not addressed in this document is the oral combination of netupitant-palonosetron (Akynzeo®).

### Clinical Indications

#### Medically Necessary:

Palonosetron is considered **medically necessary** for adults as prevention of any of the following:

- A. Acute or delayed nausea and vomiting associated with initial and repeat courses of moderately or highly emetogenic cancer chemotherapy; or
- B. Postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.

Palonosetron is considered **medically necessary** for an infant, child, or adolescent (age 1 month to less than 17 years) as prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.

#### Not Medically Necessary:

Palonosetron is considered **not medically necessary** for all other uses.

### Coding

*The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

**HCPCS**

- J2469  
  Injection, palonosetron HCl, 25 mcg
Palonosetron is an intravenous serotonin 3 (5-HT3) receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. The drug responds to high levels of serotonin released after chemotherapy and also binds to the serotonin receptors in the gastrointestinal tract, to keep the vomiting center in the brain from being stimulated. Palonosetron is available as a generic and also under the brand name of Aloxi® (Eisai, Woodcliff Lake, NJ).

Palonosetron was initially approved by the FDA in 2003 for adult use, and subsequently in May 2014, pediatric indications were added for the branded Aloxi.

FDA approved indications for palonosetron (Aloxi) in adults are:

- Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses.
- Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses.
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

FDA approved indications for palonosetron (Aloxi) in infants and children age 1 month to less than 17 years are:

- Prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.

Currently available published literature demonstrates the safety and efficacy of palonosetron for adults and the pediatric population age 1 month to 17 years of age for the specific FDA approved indications. The safety and efficacy of palonosetron have not been established in the infants and children for prevention of postoperative nausea and vomiting.

**Adults**

**Moderately Emetogenic Cancer Chemotherapy**

In 2 randomized clinical trials (n=1132) (Eisenberg, 2003; Gralla, 2003), complete response (CR) rates defined as no emetic episodes and no rescue medication over 0 to 24 hours (acute phase) were 81% and 63% for palonosetron 0.25 mg IV compared with 69% for ondansetron 32 mg IV and 53% for dolasetron 100 mg IV. For prevention of delayed emesis (24 to 120 hours), complete response (CR) rates were 74% and 54% compared with 55% and 39%, respectively. Overall CR rates were 69% and 46% compared with 50% and 34%, respectively. About half of participants were chemotherapy-naive and only a few received concomitant prophylactic corticosteroids.

**Highly Emetogenic Cancer Chemotherapy**

In a phase III clinical trial, Aapro and colleagues (2006) evaluated the safety and efficacy of palonosetron in preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV) following highly emetogenic chemotherapy (HEC). Subjects were randomized to a single intravenous dose of palonosetron 0.25 mg or 0.75 mg, or ondansetron 32 mg prior to HEC. Dexamethasone pre-treatment (with stratification) was used at investigator discretion. The primary efficacy endpoint was the proportion of subjects with CR during the first 24 hours post-
chemotherapy (acute phase). In the intent-to-treat analysis (n=667), palonosetron 0.25 mg and 0.75 mg were at least as effective as ondansetron in preventing acute CINV (59.2%, 65.5%, and 57.0% CR rates, respectively); CR rates were slightly higher with palonosetron than ondansetron during the delayed (24–120 h) and overall (0–120 h) phases. Two thirds of subjects (n=447) received concomitant dexamethasone. Subjects pre-treated with palonosetron 0.25 mg and dexamethasone had significantly higher CR rates than those treated with ondansetron plus dexamethasone during the delayed (42.0% versus 28.6%) and overall (40.7% versus 25.2%) phases. The authors concluded that single-dose palonosetron was as effective as ondansetron in preventing acute CINV following HEC. In addition, when dexamethasone was given as a pre-treatment, the effectiveness of palonosetron was significantly increased over ondansetron throughout the 5-day period after chemotherapy.

Prevention of Post-operative Nausea and Vomiting

Kovac and colleagues (2008) performed a multicenter, randomized, double-blind study to assess the efficacy and safety of different doses of palonosetron versus placebo on the incidence and severity of PONV for up to 72 hours postoperatively. A total of 544 female subjects undergoing either elective gynecological or breast surgery were stratified according to risk factors of non-smoking status and history of motion sickness or PONV. Subjects were randomized to receive palonosetron 0.025 mg (n=136), palonosetron 0.050 mg (n=137), palonosetron 0.075 mg (n=135) or placebo (n=136) immediately prior to the start of anesthesia. The primary efficacy end-point was CR (CR: no emesis and no use of rescue medications) evaluated at the 0–24 and 24–72 hour time intervals after surgery. CR rates for placebo and palonosetron 0.075 mg were 36% and 56% for 0–24 hours and 36% and 52% for the 0–72 hour postoperative period. Palonosetron 0.075 mg was associated with less intense nausea versus placebo during the 0–24 hour time interval and significantly delayed median time to emesis and treatment failure. In the safety population, most adverse events were either mild or moderate in intensity and no subject was withdrawn from the study due to adverse events. The proportion of subjects with treatment-related adverse events was similar among all treatments groups, including placebo.

Infants and Children

The FDA pediatric approval of palonosetron was based on a phase III, multicenter, international, randomized, double-blind, non-inferiority trial of children aged 0 to younger than 17 years scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of malignant disease (Kovacs, 2016). Between September 2011 and October 2012, a total of 502 subjects were randomly assigned to receive up to 4 cycles of 10 μg/kg palonosetron (n=169), or 20 μg/kg of palonosetron on day one (n=169), or three 150 μg/kg doses of ondansetron on day 1, scheduled 4 hours apart (n=164). Of these, 166, 165 and 162 subjects, respectively, were included in the final efficacy analysis. Non-inferiority versus ondansetron was demonstrated for 20 μg/kg of palonosetron in the acute phase; however, non-inferiority versus ondansetron was not demonstrated for 10 μg/kg palonosetron in the acute phase. Complete response rates (no vomiting, retching, or rescue medication) were 59.4% for palonosetron and 58.6% for ondansetron. Approximately 55% of study participants received adjuvant corticosteroids; emetogenic chemotherapies included doxorubicin, cyclophosphamide, ifosfamide, cisplatin, dactinomycin, carboplatin, and daunorubicin. In the first treatment cycle, treatment-emergent adverse events occurred in 134 (80%) of 167 children who received 10 μg/kg palonosetron, 113 (69%) of 163 who received 20 μg/kg palonosetron, and 134 (82%) of 164 who received ondansetron. The most common drug-related treatment-emergent adverse events were nervous system disorders, mainly headaches.

Additional Considerations

The American Society of Clinical Oncology (ASCO) (2017) includes the following drugs as high and moderate emetic risk intravenous antineoplastic agents*:

- Anthracycline/cyclophosphamide combination
- Carmustine
- Cisplatin
- Cyclophosphamide ≥ 1,500 mg/m²
- Dacarbazine
- Mechlorethamine
- Streptozocin
- Alemtuzumab
- Azacitidine
The NCCN Practice Guidelines in Oncology for Antiemesis (V3.2018) recommends intravenous palonosetron as a preferred 5-HT3 antagonist for moderately emetogenic chemotherapy when the regimen includes dexamethasone but does not include a neurokinin-1 receptor antagonist (NK1 RA). When an NK1 RA is used in the regimen, a single dose of palonosetron has not shown better results than a single dose of a first-generation 5-HT3 antagonist.

The NCCN drug compendium (2018) has category 1 recommendations for the use of palonosetron in combination with dexamethasone prior to intravenous antineoplastic therapy that is moderate or highly emetogenic. For highly emetogenic chemotherapy, the NCCN recommends a 3-drug regimen that includes an NK1 RA.

NCCN includes the following combinations:

- high emetic risk in combination with or without aprepitant, fosaprepitant, or rolapitant
- moderate emetic risk as a preferred agent with or without aprepitant, fosaprepitant, or rolapitant
- high or moderate emetic risk in combination with olanzapine

Contraindications, Warnings and Precautions, Drug Interactions, and Use in Specific Populations

The FDA prescribing information (2015) for palonosetron (Aloxi) includes the following contraindications, warnings and precautions, drug interactions, and use in specific populations:

Contraindications

Aloxi is contraindicated in individuals known to have hypersensitivity to the drug or any of its components.

Warnings and Precautions

- Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other selective 5-HT3 receptor antagonists.
- Serotonin syndrome has been reported with 5-HT3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs.

Drug Interactions

The potential for clinically significant drug interactions with palonosetron appears to be low.
Use in Specific Populations

- Chemotherapy-Induced Nausea and Vomiting
  Pediatric use: Safety and effectiveness in neonates (less than 1 month of age) have not been established.
- Postoperative Nausea and Vomiting
  Safety and effectiveness in patients below the age of 18 years have not been established.

The NCCN states that “depending on the route of administration and dose, 5-HT3 RAs may increase the risk of developing prolongation of the QT interval of the ECG.” The warning is not included on the palonosetron drug inserts. Caution and monitoring should be used for individuals with QT prolongation risk factors.

Definitions

Emetogenic: Having the capacity to induce vomiting.

References

Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:

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This document addresses the use of Zoledronic acid, also known as Zoledronate, which is available under the brand names Reclast® and Zometa®, as well as in generic form. This drug is a member of bisphosphonate class of drugs which are calcium regulators. Zoledronic acid is specifically used to inhibit bone resorption.

**Note:** Please see the following for more information related to the treatment of pathologic bone loss:

- [CG-DRUG-73 Denosumab (Prolia®, Xgeva™)](#)

**Clinical Indications**

**Medically Necessary:**

The use of zoledronic acid is considered **medically necessary** for any of the following conditions:

- Bone metastases documented on imaging or bone pain associated with imaging-documented metastases from breast, prostate, lung, kidney, thyroid, or other solid tumors; **or**
- Breast cancer, prevention of bone loss secondary to adjuvant hormone therapy (that is, aromatase inhibitors); **or**
- Breast cancer, early stage, premenopausal – prevention of bone loss secondary to ovarian dysfunction induced by adjuvant chemotherapy therapy; **or**
- Glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months; **or**
- Hypercalcemia of malignancy, treatment; **or**
- Multiple myeloma; **or**
- Osteoporosis, treatment to increase bone mass in men; **or**
- Osteoporosis, treatment and prevention – in postmenopausal women; **or**
- Paget’s disease of bone in men and women – treatment indicated with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease; **or**
- Prevention of osteoporosis during androgen deprivation therapy in prostate cancer.
Not Medically Necessary:

The use of zoledronic acid is considered **not medically necessary** when the criteria above have not been met and for all other indications.

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**Discussion/General Information**

Zoledronic acid, also known as zoledronate, is available under the brand names Reclast and Zometa, as well as in generic form. This drug is a member of bisphosphonate class of drugs which are calcium regulators. Zoledronic acid is specifically used to inhibit bone resorption. In vitro, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone, including osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. It is frequently used to treat individuals at risk for significant bone loss either due to a specific disease state or due to the result of another medical therapy.

**Bone metastases from kidney cancer**

Lipton and others (2003) reported on the results of a study investigating the use of zoledronic acid in 74 subjects with bone metastases from advanced renal cell carcinoma (RCC). This study was a retrospective subset analysis of a randomized controlled trial (RCT) involving 74 subjects with RCC. All subjects were originally randomized to receive zoledronic acid 4 mg, or 8 mg, or placebo every 3 weeks for 9 months along with concomitant antineoplastic therapy. Zoledronic acid (4 mg) was reported to significantly reduce the proportion of subjects with a skeletal-related event (SRE) compared with placebo (37% vs. 74%, p=0.015). In addition, zoledronic acid significantly reduced the mean skeletal morbidity rate compared with placebo (2.68 vs. 3.38, p=0.014) and extended the time to the first event (p=0.006). A multiple event analysis demonstrated that the risk of developing an SRE was reduced by 61% compared with placebo (hazard ratio [HR], 0.394, p=0.008). Finally, the median time to progression of bone lesions was significantly longer for subjects who were treated with zoledronic acid (p=0.014 vs. placebo).

**Bone metastases from non-small cell lung cancer**
Rosen (2003) published the results of a phase III, double-blind, randomized trial comparing zoledronic acid for the treatment of bone metastases from solid tumors other than breast and prostate cancer. In this study, 773 subjects were randomized to either 4 mg or 8 mg of zoledronic acid or placebo treatment. During the study, the 8 mg dose was eventually reduced to 4 mg due to concerns over renal safety. The proportion of subjects experiencing a SRE was 38% for the 4 mg zoledronic acid group, 35% for the zoledronic 8/4 mg group, and 44% in the placebo group (p=0.127 and p=0.025 for the 4 mg and 8/4 mg groups vs. placebo, respectively). The median time until the first SRE was 230 days and 163 days for the 4 mg zoledronic acid and placebo group, respectively (p=0.023). A multiple event analysis looking at the risk of developing skeletal events identified a significant benefit to the use of zoledronic acid. (HR, 0.732, p=0.017).

**Bone metastases from thyroid cancer**

Orita (2011) reported on a nonrandomized controlled study involving 50 subjects with bone metastases from differentiated thyroid carcinoma. No bisphosphonate therapy was given to 28 subjects and 22 subjects received zoledronic acid. The authors reported that SREs occurred in significantly lower frequency in the zoledronic acid group (3/22 subjects, 14%) than the control group (14/28, 50%) (p=0.007). The use of zoledronic acid significantly retarded the onset of the first SRE (p=0.04). Two subjects in the zoledronic acid group developed bisphosphonate-related osteonecrosis of the jaw versus none in the control group.

A large double-blind, placebo-controlled trial by Rosen and colleagues (2004) involved 773 subjects with solid tumors (n=11 with thyroid carcinoma) who were randomized to receive either zoledronic acid (4 mg or 8 mg) or placebo via a 15-minute infusion every 3 weeks for 21 months. The 8 mg dose was later reduced to 4 mg (8/4 mg group). The reported results indicated that fewer subjects in the zoledronic acid group developed at least 1 SRE at 21 months vs. placebo group subjects (39% of those treated at the 4 mg dose [p=0.127] and 36% of those treated at the 8/4-mg dose [p=0.023], compared with 46% of those treated with placebo). Furthermore, 4 mg of zoledronic acid significantly delayed the median time to first SRE (236 days with 4 mg vs. 155 days with placebo; p=0.009) and significantly reduced the annual incidence of SREs (1.74 per year with the 4 mg dose vs. 2.71 per year with placebo; p=0.012). Moreover, the 4 mg dose of zoledronic acid was found to reduce the risk of developing a skeletal event by 31% (HR, 0.693, p=0.003). Zoledronic acid was found to be well tolerated with long-term use; the most commonly reported adverse events in all treatment groups included bone pain and the transient, acute-phase reactions of nausea, anemia, and emesis.

**Breast cancer**

Hershman (2008) conducted a multicenter, randomized, double-blind, placebo-controlled, phase III study involving 101 premenopausal women receiving adjuvant chemotherapy for early-stage breast cancer. Subjects were selected to receive treatment with either placebo or zoledronic acid at baseline, 6 months, and at 12 months. The primary endpoint of change in lumbar spine bone mineral density (LS-BMD) was evaluated; secondary endpoints included change in femoral neck BMD (FN-BMD) and total hip BMD (TH-BMD). Overall, 96 subjects (95%) completed the 24 week evaluation, and 85 (84%) completed the final follow-up evaluation at 52 weeks. At 24 weeks and 52 weeks, the authors reported percentage change in LS-BMD, FN-BMD, and TH-BMD vs. baseline in the zoledronic acid group. In comparison, the placebo group had significant decreases in LS-BMD at 24 weeks (-2.98%) and at 52 weeks (-4.39%). Total hip BMD and FN-BMD were also significantly decreased vs. baseline (-2.08% and -1.5%, respectively, at 52 weeks). There were significant differences in measurements between the two groups at 24 and 52 weeks with regard to markers of bone resorption and formation, including serum C-telopeptide of type I collagen (CTX) and bone-specific alkaline phosphatase (BSAP), indicating favorable results for the zoledronic acid group (p<0.001). BSAP increased significantly between 24 and 36 weeks in the placebo arm (p<0.001); CTX increased significantly between 12 and 24 weeks in the placebo arm (p<0.001). The percentage of subjects who experienced adverse events was similar between the treatment arms, with the exception of eye discomfort, which was more common in the zoledronic acid arm vs placebo arm (47% vs 25%; p<0.01). There were no reports of renal function changes, osteonecrosis of the jaw, or cancer recurrence during the 52 week period.

In another study, the same group (Hershman, 2010) reported the results of a secondary analysis of a previously published multicenter, randomized, double-blind, placebo-controlled, phase III study. In the initial study, 101 premenopausal female subjects undergoing adjuvant chemotherapy for early-stage breast cancer were randomized to receive either zoledronic acid or placebo every 3 months for 12 months to assess effects on LS-BMD. At 24 months, 62 women (61%) completed evaluations to determine if effects persist after completion of therapy. In the zoledronic acid group, the percentage change in LS-BMD at 24 months was not significantly different when compared to baseline and 12 months (-0.6%). In contrast, when compared to baseline, the placebo group experienced a 6.3% decrease in LS-BMD at 24 months (p<0.05). Femoral neck BMD and TH-BMD measurements remained stable in the
Zoledronic acid in premenopausal women with early-stage breast cancer was shown to prevent bone loss during adjuvant goserelin plus tamoxifen or anastrozole therapy and improved bone mineral density at 5 years (Gnant, 2008). In a prospective study of a randomized, open-label, phase III study (n=1803) (Austrian Breast and Colorectal Cancer Study Group trial-12 [ABCSDG-12]), 404 premenopausal women who underwent surgery for breast cancer and who were scheduled to receive goserelin for 3 years were randomized to endocrine therapy alone (goserelin and anastrozole or goserelin and tamoxifen; n=199) or endocrine therapy concurrent with zoledronic acid (goserelin, anastrozole, and zoledronic acid or goserelin, tamoxifen, and zoledronic acid; n=205). After 3 years of treatment, endocrine therapy alone caused significant loss of BMD at the lumbar spine (-11.3%, p<0.0001) and trochanter (-7.3%, p<0.0001). At 2 years following completion of treatment, subjects not receiving zoledronic acid still had decreased BMD at both sites compared with baseline (lumbar spine, -6.3%, p=0.001; trochanter, -4.1%, p=0.058). In contrast to these findings, subjects who received zoledronic acid had stable BMD at 36 months (lumbar spine, +0.4%; trochanter, +0.8%) and increased BMD at 60 months at both sites (lumbar spine, +4.0%, p=0.02; trochanter, +3.9%, p=0.07) compared with baseline.

The ZO-FAST trial, an open-label RCT published by Coleman (2013), involved 1065 postmenopausal women with hormone receptor-positive early-stage breast cancer receiving adjuvant letrozole randomly assigned to receive immediate zoledronic acid or delayed zoledronate (initiated for fracture or on-study BMD decrease). In the final analysis at 60 months, the authors reported significant improvement in LS-BMD in the immediate treatment groups vs. the delayed treatment group (mean change in LS-BMD, 4.3% vs. -5.4%, respectively; p<0.0001). Furthermore, immediate treatment appeared to reduce the risk of disease-free survival (DFS) events by 34% (HR, 0.66, p=0.0375) with fewer local (0.9% vs. 2.3%) and distant (5.5% vs. 7.7%) recurrences when compared to delayed treatment.

The Zometa-Femara Adjuvant Synergy Trial (Z-FAST), an open-label RCT involving 602 subjects treated with either immediate zoledronic acid or delayed administration in postmenopausal women with early breast cancer receiving adjuvant letrozole demonstrated that early treatment could prevent cancer treatment-induced bone loss (Bru�sky, 2007). Subjects were randomized to receive letrozole with either upfront zoledronic acid (n=301) or delayed zoledronic acid (n=301) initiated when either lumbar spine or total hip T-scores decreased to less than -2 or a nontraumatic fracture occurred. At 12 months, only 25 (8.3%) of subjects in the delayed group had received treatment with zoledronic acid. At the same time point, there were 500 evaluable subjects (83%) in which a positive percent change in BMD occurred in the immediate group and a negative percent change in BMD was reported in the delayed group. An overall mean percent difference between the groups of 4.4% (p=0.0001) for LS-BMD and 3.3% (p=0.0001) for TH-BMD was reported at 12 months. In a subset of 212 subjects, the difference in percent change of serum bone turnover markers between the immediate and delayed groups was -35% for N-telopeptide (NTX) and -33% for BSAP at 12 months. Compared to baseline measurements, both NTX and BSAP significantly increased in the delayed group (NTX, p=0.0001; BSAP, p=0.0006) and significantly decreased in the immediate group (NTX, p=0.013; BSAP, p=0.0001). In another subset of 300 subjects used in a safety analysis, the incidence of adverse events and treatment-related withdrawals were similar between groups; however, bone pain occurred more frequently in the immediate group (11.3% vs 4%).

Gnant (2007) reported the results of a randomized, phase III, open-label study involving 401 premenopausal subjects with stage I to II, estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer with no prior adjuvant therapy. Subjects were randomized into 4 groups: (1) treatment with goserelin and tamoxifen either with zoledronic acid (n=100), or (2) without zoledronic acid (n=103), or (3) treatment with goserelin and anastrozole either with zoledronic acid (n=104), or (4) without zoledronic acid (n=94). At 36 months, results from 114 subjects showed that the treatment groups without zoledronic acid had significant decreases in BMD compared with baseline (LS-BMD, -14.4%, p<0.0001; trochanter, -8.2%, p=0.0005) and T-scores (LS-BMD, -1.4, p<0.0001; trochanter, -0.6, p=0.0017). In the treatment groups containing zoledronic acid, BMD remained stable compared with baseline and T-scores significantly improved (p<0.0001) compared with adjuvant endocrine therapy alone. Adverse events were mild to moderate in severity and were consistent with known toxicities associated with each drug. Zoledronic acid use was not associated with renal dysfunction and the addition of zoledronic acid did not add significant toxicity to the other treatment groups. No subjects experienced bone fractures or jaw osteonecrosis.

Aside from the bone mineral density benefits derived from zoledronic acid for individuals who have undergone treatment for breast cancer, it has also been postulated that additional benefits may be possible in relation to the...
reduction in the rates of breast cancer recurrence. A meta-analysis published by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG, 2015) evaluated the impact of adjuvant bisphosphonate therapy on breast cancer recurrence. This report involved data from 26 trials encompassing 18,766 subjects with a median follow-up of 5.6 years. The authors stated that 3453 subjects experienced recurrence and 2106 had died during the study periods reported. Recurrence rates in the overall study population were not found to be significantly different. However, they found that bisphosphonates had a greater impact on preventing distant recurrence vs. local contralateral recurrence (p=0.01). This effect was attributed mainly to a reduction in bone metastases (10-year risk 7.8 vs. 9.0; relative risk [RR], 0.83, p=0.004). The effect of bisphosphonates in reducing bone recurrence in women 55 years of age and older was significant (p=0.02). Among the 4616 women 45 years of age and younger included in the study with bone recurrence, treatment group allocation had no significant impact (p=0.97). Alternatively, for women 55 years of age and older, the treatment group demonstrated a highly significant benefit from bisphosphonate therapy (p=0.002). Regarding the use of zoledronic acid specifically, their analysis showed significant benefits in such treatment, regardless of dose frequency (every 6 months vs. monthly) or duration of treatment (2 years vs. 3-5 years) (p=0.037). For pre-menopausal women, treatment with bisphosphonates appeared to provide little benefit with regard to bone metastases or breast cancer mortality. Conversely, in postmenopausal women, both were significantly improved (recurrence: RR, 0.86, p=0.002; distant recurrence: RR, 0.82, p=0.0003; bone recurrence: RR, 0.72, p=0.0002; breast cancer mortality: RR, 0.82, p=0.002). The absolute gain for bone recurrence was calculated to be 2.2%, and for breast cancer mortality 3.3%. This study also reported on bone fracture risk, with the use of bisphosphonates improving 5-year fracture rates from 6.3% to 5.1%, with little gain in the first year and the most benefit seen in years 2-4.

Grant and colleagues in the Austrian Breast and Colorectal Cancer Study Group (ABCSG) have reported on the results of a long-term study of 1803 subjects with breast cancer assigned to one of 4 groups: (1) goserelin plus tamoxifen (n=451), (2) goserelin plus tamoxifen plus zoledronic acid (n=449), (3) goserelin plus anastrozole (n=453), and (4) goserelin plus anastrozole plus zoledronic acid (n=450) (Grant, 2009, 2011, 2015). In their first report from 2009, after a median follow-up of 47.8 months, 137 events had occurred, with disease-free survival rates of 90.8% in the group that received endocrine therapy alone vs. 94.0% in the group that received endocrine therapy with zoledronic acid. They reported that the addition of zoledronic acid to endocrine therapy resulted in an absolute reduction of 3.2% and a relative reduction of 36% in the risk of disease progression (p=0.01). However, the addition of zoledronic acid was not noted to significantly reduce the risk of death (p=0.11). The results of an interim analysis were reported in 2011, with a median follow-up of 62 months. They stated that zoledronic acid continued to reduce risk of disease-free survival events overall (p=0.009). However, this result was not found to be significant when the tamoxifen group arms and anastrozole arms were assessed separately (p=0.067 and p=0.061, respectively). They also noted that zoledronic acid did not significantly affect risk of death (p=0.09). Bone pain was reported in 601 patients (349 patients on zoledronic acid vs 252 not on zoledronic acid). Most recently, the results with a 94.4-month median follow-up was reported in 2015. The relative risks of disease progression and death were reported to continue to be reduced by zoledronic acid, although no longer significant at the predefined significance level (HR, 0.77, p=0.042 for progression and HR, 0.66, p=0.064 for death). The absolute risk reductions with zoledronic acid were 3.4% for disease free survival and 2.2% for overall survival.

In 2016, Kroep and colleagues reported the results of a meta-analysis of four studies assessing the impact of zoledronic acid in subjects with breast cancer receiving neoadjuvant chemotherapy or neoadjuvant chemotherapy plus zoledronic acid. Data was available for 735 subjects for measurement of pathological complete response in the breast (pCRb) and for 552 subjects for measurement of pathological complete response breast and lymph nodes (pCR). In the total study population of 750 subjects, the addition of zoledronic acid to neoadjuvant chemotherapy did not increase pCRb or pCR rates. However, the authors reported that for postmenopausal subjects, the addition of zoledronic acid resulted in a significant, near doubling of the pCRb rate (10.8% for the chemotherapy only group vs. 17.7% for the chemotherapy plus zoledronic acid group; odds ratio [OR], 2.14). Their conclusions were that the addition of zoledronic acid to neoadjuvant chemotherapy had no impact on pCR. However, it may augment the effects of chemotherapy in postmenopausal individuals with breast cancer.

Ishikawa (2017) reported the results of an RCT involving 188 postmenopausal subjects with triple-negative breast cancer assigned to undergo therapy with either chemotherapy alone (n=95) or chemotherapy plus zoledronic acid (n=93). Chemotherapy consisted of four cycles of FEC100 followed by 12 cycles of paclitaxel weekly. Zoledronic acid was given 3-4 times weekly for 7 weeks. The authors reported no significant survival benefit to the addition of zoledronic acid, with the 3-year disease free survival rate of 84.6% for the chemotherapy alone group and 90.8% for the chemotherapy plus zoledronic acid group (p=0.188).

Glucocorticoid-induced osteoporosis
The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial demonstrated that a single dose of zoledronic acid was noninferior to once daily oral risedronate for the prevention and treatment of glucocorticoid-induced osteoporosis in the multicenter, randomized, double-blind, double-placebo study involving 833 subjects who received treatment with prednisolone daily (Reid, 2009). Subjects were randomized in a 1:1 ratio to receive either a single dose of zoledronic plus a daily placebo, or daily oral risedronate plus a single IV placebo. The study groups were further divided into treatment and prevention subgroups. The primary outcome was the percent change from baseline in BMD of the lumbar spine (L1 to L4) at 12 months. Efficacy analysis was performed on the modified intent-to-treat (mITT) population, defined as subjects who received study medication and had baseline and at least one post-baseline BMD measurement. The mITT population included 568 women (68%), of whom, 373 (66%) were menopausal. While the number of baseline fractures was similar between groups in the treatment arm, more subjects in the zoledronic acid prevention group had baseline fractures. The mITT analysis revealed a single IV dose of zoledronic acid was noninferior to once daily oral risedronate 5 mg for the treatment and prevention of glucocorticoid-induced osteoporosis. In the treatment subgroup, the mean percent change from baseline in BMD at 12 months was 4.06% vs 2.71% in the zoledronic acid and risedronate groups, respectively. In the prevention subgroup, the mean percent change from baseline in BMD at 12 months was 2.6% vs 0.64% in the zoledronic acid and risedronate groups, respectively. Within the first 3 days of study drug administration, adverse events were significantly higher in the zoledronic acid treatment and prevention subgroups compared with risedronate. After 3 days, the incidence of events was similar between drug groups. Serious adverse events included worsening rheumatoid arthritis in the treatment subgroup (zoledronic acid, 8% vs risedronate, 6%) and pyrexia in the prevention subgroup (zoledronic acid, 15% vs risedronate, 2%).

In an unpublished pivotal trial data detailed in the Product Information for Reclast, zoledronic acid increased LS-BMD more than an oral bisphosphonate in a randomized, multicenter, double-blind, active controlled, 1-year study (n=833). Subjects treated with 7.5 mg/day or more of oral prednisone or its equivalent, were randomized to treatment for 1 year with either 1 dose of zoledronic acid or to an oral daily bisphosphonate. Subjects were stratified either to the treatment group defined as receiving 3 months or less of corticosteroid treatment prior to randomization, or the prophylaxis group, defined as greater than 3 months of corticosteroid treatment prior to randomization. For the treatment group, the mean increase in LS-BMD at 1 year for the zoledronic acid group was 4.1% vs. 2.7% for the bisphosphonate group. This was a treatment difference of 1.4% (p<0.001) for the treatment group. For prevention, the mean increase in the LS-BMD at 1 year was 2.6% in the zoledronic acid group vs. 0.6% for the bisphosphonate group. This was a treatment difference of 2% (p<0.001) for the prophylaxis group.

Hypercalcemia of malignancy

Major and colleagues (2001) conducted a pooled analysis of two concurrent, randomized, double-blind, double-dummy clinical trials, in which subjects with moderate to severe hypercalcemia of malignancy (HCM) were assigned to receive a single dose of zoledronic acid 4 mg via a 5 minute IV infusion (n=86), zoledronic acid 8 mg (n=98) via a 5 minute IV infusion, or pamidronate 90 mg (n=103) via 2 hour infusion. To maintain the blind, zoledronic acid therapy was administered simultaneously with IV hydration (500 mL of IV fluids over 4 hours). All subjects received 250 mL of IV fluids before infusion of study drug. The remaining portion of the required IV hydration was administered as part of a double-dummy infusion. Bone metastases at baseline existed in 144 subjects (52.4%). Assessment of corrected serum calcium (CSC) at day 10 revealed complete responses (CR) [defined as reduction in CSC to concentrations equal to or less than 10.8 mg/dL] in 88.4% (p=0.002) and 86.7% (p=0.015) of subjects receiving zoledronate 4 mg and 8 mg, respectively. By comparison, 69.7% of pamidronate-treated subjects attained CR status. The onset of CSC normalization occurred as early as 4 days after treatment in approximately 50% of subjects receiving zoledronate (4 mg, 45.3%; 8 mg, 55.6%) compared with 33.3% of pamidronate subjects. A total of 15 subjects were refractory to treatment with either agent. The median time to relapse in the zoledronate 4 mg group was 30 days (p=0.001) and 40 days in the zoledronate 8 mg (p=0.007). Both were significantly longer vs. the median time to relapse of 17 days in pamidronate subjects. A group of 70 subjects who were initially refractory to treatment or experiencing relapse after initial CR were re-treated with zoledronate 8 mg. Complete response was attained in 36 subjects (52%) by day 10, with a median response-duration of 15 days.

Multiple myeloma and bone metastasis from solid tumors

Morgan et al. (2010) reported an open label, randomized controlled study involving 1960 subjects with newly diagnosed multiple myeloma comparing 4 mg zoledronic acid as an infusion every 3-4 weeks (n=981; 555 on intensive chemotherapy, 426 on non-intensive chemotherapy) vs. 1600 mg oral clodronate acid daily (n=979; 556 on intensive chemotherapy, 423 on non-intensive chemotherapy). All subjects also received intensive or non-intensive induction chemotherapy. The primary endpoints were overall survival (OS), progression-free survival (PFS), and overall response rate. At the time of study cutoff, subjects received bisphosphonates for a median of 350 days before
disease progression, with a median of 3.7 years follow-up. The authors reported that zoledronic acid reduced mortality by 16% vs. clodronic acid (HR, 0.84, p=0.0118), and extended median OS by 5.5 months (50.0 months vs. 44.5 months; p=0.04). Zoledronic acid also significantly increased median PFS by 2.0 months (19.5 months vs. 17.5 months; p=0.07). Rates of complete, very good partial, or partial response did not differ significantly between the zoledronic acid and clodronic acid groups for subjects receiving intensive induction chemotherapy (432 subjects [78%] vs. 422 [76%]; p=0.43) or non-intensive induction chemotherapy (215 [50%] vs. 195 [46%]; p=0.18). Zoledronic acid was associated with higher rates of confirmed osteonecrosis of the jaw (35 [4%]) than was clodronic acid (3 [<1%]).

Additional results from the same study were reported in 2011 (Morgan, 2011). The researchers reported that at a median follow-up of 3.7 years, subjects in the zoledronic acid group had a lower incidence of SREs than did those in the clodronic acid group (265 [27%] vs. 346 [35%], respectively; HR, 0.74, p=0.0004). Zoledronic acid was also associated with a lower risk of any SRE in the subsets of subjects with bone lesions (233 [35%] of 668 vs. 292 [43%] of 682 with clodronic acid; HR, 0.77, p=0.0038) and without bone lesions at baseline (29 [10%] of 302 vs. 48 [17%] of 276 with clodronic acid; HR, 0.53, p=0.0068). Fewer subjects in the zoledronic acid group had vertebral fractures than did those in the clodronic acid group (50 [5%] in the zoledronic acid group vs. 88 [9%] in the clodronic acid group; p=0.0008), other fractures (45 [5%] vs. 66 [7%]; p=0.04), and new osteolytic lesions (46 [5%] vs. 95 [10%]; p<0.0001). The authors concluded that the results of their study support the early use of zoledronic acid rather than clodronic acid in subjects with newly diagnosed multiple myeloma for the prevention of skeletal-related events, irrespective of bone disease status at baseline.

In another publication, the same group presented an analysis investigating the optimal therapy regimens for different subject populations in the MRC Myeloma IX trial. They examined traditional and thalidomide-based induction and maintenance regimens and IV zoledronic acid and oral clodronate in all enrolled subjects (Morgan, 2012). Zoledronic acid was reported to improve OS compared with clodronic acid independently of sex, stage, or myeloma subtype, most profoundly in subjects with baseline bone disease or other SREs. In subjects treated for ≥ 2 years, zoledronic acid improved OS vs. clodronic acid from randomization (p=0.02) and also from first on-study disease progression (median, 34 months for zoledronic acid vs 27 months for clodronate; p=0.03). The investigators concluded that zoledronic acid demonstrated greater benefits than clodronic acid.

Osteoporosis in men

Zoledronic acid significantly reduced the risk of vertebral fracture among men with osteoporosis in a 24 month, multicenter, double-blind, placebo-controlled, randomized trial involving 1199 male subjects with primary or hypogonadism-induced osteoporosis (Boonen, 2012). Subjects were allocated to receive two doses of zoledronic acid 5 mg (n=588) or placebo (n=611), infused at baseline and at 12 months. The primary outcome of the rate of new morphometric vertebral fractures over 24 months was reported as 1.6% in the zoledronic acid group vs. 4.9% in the placebo group, representing a 67% reduction in RR associated with zoledronic acid (RR, 0.33; 95% confidence interval [CI], 0.16 to 0.7; p=0.002). Additional clinical benefits in the zoledronic acid group compared with the placebo group at 24 months included fewer moderate to severe new vertebral fractures (RR reduction, 63%; p=0.03) and less height loss (-2.2 mm vs. -4.5 mm; p=0.002). Lumbar spine BMD, TH-BMD, and FN-BMD were all significantly greater in the zoledronic acid group over a 24-month period (all p<0.05 vs. placebo), and bone turnover markers were significantly lower in men who received zoledronic acid (p<0.05 vs. placebo). Subjects with low serum levels of total testosterone demonstrated similar results. Adverse events were reported more often in the zoledronic acid group and included arthralgia, extremity pain, pyrexia, or influenza-like symptoms. However, the incidence of serious adverse events were similar between groups (zoledronic acid group, 25.3%; the placebo group, 25.2%), with the exception of the incidence of myocardial infarction (MI), with 9 subjects in the zoledronic acid group having MIs vs. 2 men in the placebo group (p=0.03).

Osteoporosis, treatment and prevention in postmenopausal women

Data from an unpublished study submitted to the FDA for Reclast (see package insert) included 582 postmenopausal female subjects randomly assigned in a double-blind fashion into 1 of 3 treatment groups: (1) zoledronic acid at randomization and at 12 months (n=198); (2) zoledronic acid at randomization and placebo at 12 months (n=181); and (3) placebo at randomization and at 12 months (n=202). Subjects were further classified into 2 strata: (1) women less than 5 years from menopause (n=224); and (2) women 5 years or more from menopause (n=357). In treatment group 1, there were 77 subjects in stratum 1 and 121 in stratum 2; in group 2, there were 70 subjects in stratum 1 and 111 in stratum 2. No stratification data were provided for the control group. LS-BMD was significantly increased across both strata in comparison to placebo at month 24. In group 2, the increase was 4% in stratum 1 and 4.8% in stratum 2, in comparison to a decrease of 2.2% in stratum 2 and a 0.7% decrease in stratum 2 in the control...
group. Overall, treatment with zoledronic acid and placebo at month 12 resulted in an increase in LS-BMD of 6.3% in stratum 1 and 5.4% in stratum 2 over 24 months compared with placebo (both \(p<0.0001\)). Total hip BMD was also significantly increased across both strata compared with placebo at 24 months, with a 2.6% increase in stratum 2 and 2.1% in stratum 2 for group 2 vs. a 2.1% decrease in stratum 1 and 1% decrease in stratum 2 of control group subjects. Overall, treatment with zoledronic acid and placebo at month 12 resulted in an increase in TH-BMD of 4.7% in stratum 2 and 3.2% in stratum 2 over 24 months vs. placebo (both \(p<0.0001\)).

Black (2007) reported the results of a 3 year, double-blind, placebo-controlled study of postmenopausal women with evidence of osteoporosis from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly - Pivotal Fracture Trial (HORIZON-PFT) \((n=7765)\). This study involved 768 subjects randomized to receive either zoledronic acid \((n=3889)\) or placebo \((n=3876)\) at baseline, 12 months, and 24 months. The investigators reported that the 3 year incidence of new vertebral fractures was reduced for the zoledronic acid group \((3.3\%, n=92)\) vs. the placebo group \((10.9\%, n=310)\) \((RR, 0.3, p=0.001)\). The incidence of hip fractures was also reduced in the zoledronic acid group \((1.4\%, n=52)\) vs. placebo \((2.5\%, n=88)\) \((HR, 0.59, p=0.002)\). They also reported significant reductions in the zoledronic acid group vs. the placebo group in the incidence of nonvertebral fractures \((8\% vs. 10.7\%; HR, 0.75)\), all clinical fractures \((8.4\% vs. 12.8\%; HR, 0.67)\) and clinical vertebral fractures \((0.5\% vs. 2.6\%; HR, 0.23)\) \((p<0.001 for all comparisons)\). Significant increases in the zoledronic acid group vs. placebo were reported for TH-BMD \(+(6.02\%)\), LS-BMD \(+(6.71\%)\), and FN-BMD \(+(5.06\%)\) \((p<0.001)\). At 12 months, the biochemical markers of bone resorption and formation \((CTX and NTX)\) were all significantly reduced for the zoledronic acid group vs. placebo \((p<0.001 for all comparisons)\). The number of subjects reporting any adverse event was higher for the zoledronic acid group compared with placebo \((95.5\% vs 93.9\%; p=0.002)\). However, the difference between groups for serious adverse events was not statistically significant.

A randomized, double-blind, dose-ranging study over 1 year involving postmenopausal women was conducted by Reid and colleagues (2002). Subjects were assigned to receive either placebo \((n=59)\) or IV infusions of zoledronic acid in one of the following dose regimens: a single infusion every 3 months of zoledronic acid at the following dose strengths: (1) 0.25 mg \((n=60)\); (2) 0.5 mg \((n=58)\); (3) 1 mg \((n=53)\); or (4) 2 mg every 6 months \((n=61)\); or (5) 4 mg zoledronic acid given once at baseline \((n=52)\). Throughout the duration of the study, all groups receiving zoledronic acid showed progressive increases from baseline in mean BMD of the lumbar spine vs. the placebo group \((p<0.001)\). No significant differences between the five zoledronic acid dosing groups were noted with regard to post-treatment BMD. Subjects treated with zoledronic acid also showed progressive improvements in FN-BMD compared with the placebo group, with improvements in the treatment groups ranging between 3.1% and 3.5% at 12 months vs. a mean decline of 0.4% in the placebo group \((p=0.001)\). With the exception of the 4-dose regimen of zoledronic acid 0.25 mg, all other dosing regimens of zoledronic acid provoked significant increases in BMD of the distal radius compared with radius BMD in the placebo group \((p<0.05, all comparisons)\). Subjects treated with zoledronic acid showed notable decreases in serum markers of bone turnover \((CTX and NTX; creatinine ratio)\). Treatment-related adverse events occurred with significantly greater frequency in the zoledronic acid treatment groups, with musculoskeletal pain, nausea, and fever reported most frequently; most of these events were rated as mild in severity. Finally, serum calcium concentrations declined significantly from baseline to 1 month in all zoledronic acid groups subjects \((mean reduction of 0.08 mmol/L; p<0.05)\). No significant changes in serum calcium concentrations were noted in the placebo groups at 3 months or thereafter.

In 2015, Greenspan and others reported the results of a double-blind, placebo-controlled RCT involving 181 frail women over the age of 65 years old with a history of vertebral or hip fracture or a measured bone BMD below the treatment cutoff for osteoporosis. Subjects were randomly assigned in a 1:1 fashion to undergo a single IV infusion of either 5 mg of zoledronic acid or placebo. Subjects were evaluated at 12 and 24 months. The primary outcome was percent change in BMD of the hip and spine at 12 months. Secondary outcomes included adverse events and bone turnover markers. In the intent-to-treat analysis, 89 subjects were in the experimental group and 92 were included in the control group. However, in the experimental group, 75 (84.3%) subjects completed DEXA scans at 12 months and 60 (67.4%) at 24 months. In the control group, these numbers were 83 (90.2%) and 72 (78.3%), respectively. The authors reported that mean total hip BMD increased significantly more in the experimental group vs. controls at both 12 and 24 months \((2.8\% vs. -0.5\%, and 2.6\% vs. -1.5\%, respectively; p<0.001 for both)\). Similar findings were reported for mean spine BMD \((3.0\% vs. 1.1\% at 12 months, 4.5\% vs. 0.7\% at 24 months, respectively; p<0.001 for both)\). Bone resorption, as measured by C-telopeptide cross-links type 1 collagen, decreased in the experimental group at both 12 and 24 months \((p=0.01)\) whereas it was increased in the control group at both time points \((p<0.05)\). A total adverse event rate of 97% was reported, with a serious adverse event rate of 64%. No between group differences were reported, including the number of deaths, fractures, or cardiac events \((p=0.68 for total adverse events and p=0.29 for serious adverse events, respectively)\).

Grey (2017) reported the results of a 3-year open label extension of placebo-controlled RCT involving 160 postmenopausal women with osteopenia who were assigned to receive treatment with 1 mg, 2.5 mg or 5 mg of
zoledronic acid, or placebo. Significant loss to follow-up was reported, with 34 (21%) subjects withdrawing from the study. However, all 160 were included in the analysis of BMD and bone turnover. In the axial skeleton, statistically significant increases in BMD compared with placebo were observed for the 1 mg, 2.5 mg and 5 mg doses for 3–4 years, 4–5 years and at least 5 years, respectively. Each dose produced its largest effect on BMD at 2 years, with mean increases in spine and hip BMD reported as 5.0% and 2.6% for the 1 mg group respectively; 5.7% and 4.1% for the 2.5 mg group, respectively; and 5.7% and 4.7% for the 5 mg group, respectively. The authors reported that spine BMD returned to baseline level 5 years after administration in both the 1 mg and 2.5 mg groups, but remained above baseline in the group that received the 5 mg. Hip BMD returned to baseline level at 2.5 years in the 1 mg group and at 4.5 years in the 2.5 mg group, but remained above baseline levels 5 years after administration in the 5 mg group. The per-protocol analysis resulted in similar results. They also noted that each dose of zoledronic acid substantially reduced bone turnover markers soon after administration, after which each marker of bone turnover slowly increased toward the values reported in the placebo group. No difference in fracture rates was reported between the zoledronic acid groups and the placebo group.

**Paget’s disease**

The package insert for Reclast describes the results of two unpublished identical, 6 month, randomized, double-blind trials addressing the treatment of Paget’s disease of the bone. These studies involved 347 subjects with serum alkaline phosphatase (SAP) levels at least twice the age-specific upper limit who were randomized to a single 5 mg IV infusion of zoledronic acid (n=176) or daily oral risedronate 30 mg for 2 months (n=171). Therapeutic response was defined as either normalization of SAP or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. The zoledronic acid subjects achieved therapeutic response at a 96% rate, vs. 74% of risedronate subjects. Most zoledronic acid subjects achieved therapeutic response within 63 days of initiation of treatment. Additionally, 89% of the zoledronic acid group achieved normalization of SAP levels by 6 months vs. 58% of subjects receiving risedronate (p<0.0001). No differences were reported with regard to demographics or disease severity in the zoledronic acid group. In subjects who previously received oral bisphosphonate therapy, the therapeutic response rates were 96% in the zoledronic acid group and 55% in the risedronate group. The response rates in subjects who did not receive previous treatment were 98% and 86% for zoledronic acid and risedronate, respectively.

**Prevention of skeletal-related events in men with prostate cancer**

In 2004, Saad and others published the results of a placebo-controlled randomized clinical trial involving 122 subjects with hormone-refractory metastatic prostate cancer. At 24 months follow-up, fewer subjects in the zoledronic acid group had at least one SRE vs. the placebo group (38% vs. 49%, p=0.028) and the annual incidence of SREs was 0.77 for the zoledronic acid group versus 1.47 for the placebo group (p=0.005). The median time to the first SRE was significantly longer in the zoledronic acid group vs. the placebo group (488 days vs. 321 days, p=0.009). Finally, compared with placebo, treatment with zoledronic acid reduced the ongoing risk of SREs by 36% (RR, 0.64, p=0.002). The authors concluded that treatment with zoledronic acid resulted in significantly lower incidence of SREs when compared to placebo, regardless of whether subjects had a previous SRE.

The same group reported the results of a randomized, placebo-controlled, phase III trial in 422 men with hormone-refractory prostate cancer and bone metastases (Saad, 2005). This study enrolled 422 subjects who were randomized to receive zoledronic acid or placebo. Subjects received zoledronic acid or placebo for a 15 month core phase, with the option to continue therapy for 9 more months in the extension phase of the study. Among all subjects, zoledronic acid significantly reduced the incidence of a second on-study SRE (p=0.017) and significantly delayed the median time to second SRE compared with placebo at 15 months (p=0.006). Among 144 subjects with a history of SREs before study entry (34%), zoledronic acid significantly reduced the skeletal morbidity rate by 65% (p=0.036) and reduced the overall risk of developing an SRE by 40% (p=0.028) compared with placebo at 24 months.

In an additional report of retrospective exploratory analyses to determine whether long-term treatment with zoledronic acid provides continuing efficacy, Saad (2007) looked at the data collected from 132 subjects involved in an extension phase of the study. For these subjects, it was reported that zoledronic acid significantly delayed the onset of first SRE (p=0.009) and decreased the risk of developing an SRE by 53% compared with placebo (p=0.022). The authors concluded that their analysis confirmed their previously reported results that suggest long-term treatment with zoledronic acid provides continuing clinical benefit in subjects with advanced prostate cancer, even after the occurrence of SREs.

**Prevention or treatment of osteoporosis during androgen deprivation therapy**
Smith and others (2003) conducted a randomized, double-blind, placebo-controlled, multicenter trial in 106 men with non-metastatic prostate cancer (stage M0). Subjects were randomized to receive 1 year of treatment with either zoledronic (n=55) or placebo (n=51). The authors designed the study to include the analysis of primary efficacy variables in 4 subgroups; (1) subjects receiving a gonadotropin-releasing hormone (Gn-RH) agonist alone, (2) receiving a Gn-RH agonist and antiandrogen, (3) baseline BMD T-score -1 or greater, and (4) baseline BMD T-score -2 or lower. Completion of the trial was reported for 47 subjects in the zoledronic acid group and 43 in the placebo group. At 1 year, LS-BMD in the zoledronic group was increased vs. a decrease of BMD in the placebo group (mean percent change 7.8%, p<0.001). The authors noted that antiandrogen had no impact on zoledronic acid efficacy. Lumbar spine BMD in the zoledronic acid group increased 5.6% from baseline (p=0.001) vs. a decrease of 2.2% from baseline in the placebo group (p=0.0012). Significant increases in BMD in the zoledronic acid group were reported in the femoral neck, trochanter, and total hip with corresponding decreases seen in the placebo group (p<0.001 for all comparisons). Grade 3 or 4 toxicities were reported in both groups; 24% in the zoledronic group and 39% in the placebo group. The most common toxicities reported in the zoledronic and placebo groups, respectively, were hot flushes (58% vs 51%), fatigue (38% vs 35%), arthralgias (22% vs 14%), constipation (16% in each group), and urinary frequency (15% vs 22%).

Prostate cancer

A randomized, placebo-controlled, double-blind clinical trial comparing zoledronic acid with placebo in subjects with bone metastases associated with hormone-refractory prostate cancer was published by Saad and others (2002). Subjects were randomized to receive either zoledronic acid 4 mg (n=214) or 8 mg (subsequently reduced to 4 mg due to renal function deterioration, 8/4 group) (n=221), or placebo (n=208) every 3 weeks for 15 months. There were significantly fewer SREs in the 4 mg zoledronic acid group vs. the placebo group (33% and 44% respectively, p=0.021). The proportion of subjects receiving 8/4 mg zoledronic acid who experienced a SRE was 38% (p=0.222). The median time to the first SRE was reported as being 321 days in the placebo group vs. 363 days the group receiving 8/4 mg zoledronic acid (p=0.491). In 4 mg zoledronic acid median SRE was not reached during the study period due to low numbers of subjects experiencing SREs (p=0.011). Urinary markers of bone resorption were significantly decreased in subjects receiving either dose of zoledronic acid (p=0.001). In addition, pain and analgesic scores increased more in subjects receiving placebo compared with subjects receiving zoledronic acid.

Wirth and colleagues (2015) reported the results of an RCT of zoledronic in the prevention of bone metastases in patients with high-risk non-metastatic prostate cancer. A total of 1433 subjects were randomized to receive standardized localized prostate cancer therapy alone or standard therapy plus 4 mg of zoledronic acid IV every 3 months for ≤ 4 years. Of that population, 1393 subjects were used for intention-to-treat (ITT) efficacy analyses, with 1040 patients having available bone imaging studies. Bone imaging detected new bone metastases in 88 of 515 subjects (17.1%) in the zoledronic group and 89 of 525 subjects (17.0%) in the control group (p=0.95). In the ITT population (n=1393), the Kaplan-Meier estimated proportion of bone metastases after a median follow-up of 4.8 years was 14.7% in the zoledronic acid group versus 13.2% in the control group (p=0.65). The authors concluded that zoledronic acid was demonstrated to be ineffective for the prevention of bone metastases in high-risk individuals with localized prostate cancer.

In 2016, three studies were published addressing the efficacy of zoledronic acid in subjects with prostate cancer. The first, by Vale et al. was a meta-analyses of aggregate data from large RCTs combining docetaxel or bisphosphonates with standard of care in hormone-sensitive prostate cancer. They identified seven eligible trials involving bisphosphonates for men with M1 disease. The survival results from three of these trials (n=2740) demonstrated that addition of bisphosphonates improved survival (p=0.025). However, they found no evidence of a benefit from the addition of zoledronic acid (p=0.323). Of 17 trials of bisphosphonates for men with M0 disease, survival results from four trials (n=4079) demonstrated no evidence of benefit from the addition of zoledronic acid (p=0.782). They concluded that no evidence exists to suggest that zoledronic acid improves survival in men with M1 or M0 disease. James and others (2016b) reported the results of the STAMPEDE trial, involving 2962 subjects with high-risk, locally advanced, metastatic or recurrent prostate cancer who were starting first-line long-term hormone therapy. Subjects were stratified and randomized in a 2:1:1:1 fashion to: (1) standard of care only (SOC-only; control), (2) standard of care plus zoledronic acid (SOC + ZA), (3) standard of care plus docetaxel (SOC + Doc), or (4) standard of care with both zoledronic acid and docetaxel (SOC + ZA + Doc). Median follow-up was 43 months. The authors reported that the median overall survival was 71 months for SOC-only group, not reached for the SOC + ZA group (HR, 0.94, p=0.450), 81 months for the SOC + Doc group (HR, 0.78, p=0.006), and 76 months for SOC + ZA + Doc (HR, 0.82, p=0.022). Grade 3-5 adverse events were reported for 399 (32%) patients receiving SOC, 197 (32%) receiving SOC + ZA, 288 (52%) receiving SOC + Doc, and 269 (52%) receiving SOC + ZA + Doc. They concluded that zoledronic acid showed no evidence of survival improvement and should not be part of standard of care for this population. James (2016a) also reported the results of the TRAPEZE trial, which evaluated the clinical effectiveness and palliative benefits of combining docetaxel, zoledronic acid, and Sr89 on
subjects with bony metastatic CRPC. Overall, 349 of 757 subjects (46%) completed docetaxel treatment. The clinical progression-free survival did not reach statistical significance for either Sr89 or zoledronic acid. However, zoledronic acid did have a significant effect on skeletal-related event-free interval (HR, 0.78, p=0.01). Additionally, no impact on overall survival are noted for zoledronic acid (HR, 0.99, p=0.91). They concluded that zoledronic acid did not improve clinical progression free survival or overall survival, but it did significantly improve median skeletal-related event-free interval and reduced total skeletal-related event-free by around one-third, suggesting a role as post-chemotherapy maintenance therapy.

Other indications

Zhao and others (2017) published a network meta-analysis of medical therapies for low bone mineral density in individuals with Crohn’s disease. The analysis included 12 studies involving 920 subjects who received a variety of treatments, including alendronate, etidronate, ibandronate, pamidronate, phylloquinone, risedronate, and zoledronic acid. Only two of the studies included involved zoledronic acid, with a total of 27 subjects. The authors reported that, compared with placebo, zoledronate provided a statistically significant increasing LS-BMD (standardized mean difference=2.74). Additionally, surface under the cumulative ranking area (SUCRA) analysis identified that zoledronic acid might have the highest probability to be the best treatment for increasing LS-BMD in individuals with Crohn’s disease (SUCRA=2.5%). They concluded that zoledronic acid might have the highest probability to be the best therapeutic strategy for increasing LS-BMD. However, these conclusions are of limited utility given the small number of subjects involved in the studies included.

Nationally recognized recommendations

The use of zoledronic acid has become widely accepted as a standard therapy for the prevention and treatment of conditions related to bone loss. Such use is recommended by both the National Comprehensive Cancer Network (NCCN, 2018) and the American Society of Clinical Oncology (ASCO) for cancer-related conditions (Angel, 2013 Dhesy-Thind, 2017; Kyle, 2007; Van Poznak, 2011, 2017). The American Association of Clinical Endocrinologists (Watts, 2010), the American College Physicians (ACP; Quaseem, 2008, 2017), and the American College of Obstetricians and Gynecologists (ACOG, 2012) all recommend the use of zoledronic acid for the treatment of osteoporosis.

Warnings and Adverse Events

The FDA-approved prescribing information provides the following warnings and adverse event information for Zometa:

- Patients being treated with Zometa should not be treated with Reclast.
- Adequately rehydrate patients with hypercalcemia of malignancy prior to administration of Zometa and monitor electrolytes during treatment.
- Renal toxicity may be greater in patients with renal impairment. Do not use doses greater than 4 mg. Treatment in patients with severe renal impairment is not recommended. Monitor serum creatinine before each dose.
- Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting Zometa. Avoid invasive dental procedures.
- Severe incapacitating bone, joint, and/or muscle pain may occur. Discontinue Zometa if severe symptoms occur.
- Zometa can cause fetal harm. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy. These fractures may occur after minimal or no trauma. Evaluate patients with thigh or groin pain to rule out a femoral fracture. Consider drug discontinuation in patients suspected to have an atypical femur fracture.
- Hypocalcemia: Correct before initiating Zometa. Adequately supplement patients with calcium and vitamin D. (5.10)
- The most common adverse events (greater than 25%) were nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea.
The FDA-approved prescribing information provides the following warnings and adverse event information for Reclast:

- Patients receiving Zometa should not receive Reclast.
- Hypocalcemia may worsen during treatment. Patients must be adequately supplemented with calcium and vitamin D.
- A single dose should not exceed 5 mg and the duration of infusion should be no less than 15 minutes. Renal toxicity may be greater in patients with underlying renal impairment or with other risk factors, including advanced age or dehydration. Monitor creatinine clearance before each dose.
- Osteonecrosis of the Jaw (ONJ) has been reported. All patients should have a routine oral exam by the prescriber prior to treatment.
- Atypical Femur Fractures have been reported. Patients with thigh or groin pain should be evaluated to rule out a femoral fracture.
- Pregnancy: Reclast can cause fetal harm. Women of childbearing potential should be advised.
- Severe Bone, Joint, and Muscle Pain may occur. Withhold future doses of Reclast if severe symptoms occur.
- The most common adverse reactions (greater than 10%) were pyrexia, myalgia, headache, arthralgia, pain in extremity. Other important adverse reactions were flu-like illness, nausea, vomiting, diarrhea, and eye inflammation.

| Definitions |

Antineoplastic therapy: Any medical therapy intended to prevent, inhibit, or halt the development or growth of tumors.

Aromatase inhibitor: A class of drugs used in the treatment of breast cancer and ovarian cancer in postmenopausal women.

Glucocorticoid: A class of adrenal steroid hormones that bind to the glucocorticoid receptor, which are present in almost every human cell and which are essential for the utilization of carbohydrate, fat and protein by the body and for normal response to stress. Glucocorticoid drugs are widely used for the suppression of inflammation in chronic inflammatory diseases such as asthma, rheumatoid arthritis, and inflammatory bowel disease.

Hypercalcemia: A condition characterized by abnormally high blood levels of calcium. It is defined as an albumin-corrected calcium (cCa) of greater than or equal to 12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL = Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin [g/dL]).

Osteoporosis: A disease condition characterized by clinically significant loss of bone mass and/or bone density.

| References |


Government Agency, Medical Society, and Other Authoritative Publications:


   - Kidney cancer (V3.2018). Revised February 6, 2018

**Index**

Osteoporosis
Osteopenia
Reclast
Zoledronate
Zoledronic acid
Zometa
The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

### Document History

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<td>05/03/2018</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Hematology/Oncology Subcommittee review. The document header wording updated from “Current Effective Date” to “Publish Date.” Updated Discussion and References sections.</td>
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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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This document addresses fosaprepitant (Emend, Merck & Co., Inc., Whitehouse Station, NJ), a human substance P/neurokinin-1 (NK-1) receptor antagonist. Given intravenously (IV), fosaprepitant is used for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy.

**Clinical Indications**

**Medically Necessary:**

Fosaprepitant is considered **medically necessary** in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy.

**Not Medically Necessary:**

Fosaprepitant is considered **not medically necessary** for all other indications.

**Coding**

*The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

**HCPCS**

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**ICD-10 Diagnosis**

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Chemotherapy-induced nausea and vomiting is a known side effect of chemotherapy. There are three types of chemotherapy-induced nausea and vomiting: acute, occurring within the first 24 hours following chemotherapy; delayed, occurring more than 24 hours after chemotherapy; and anticipatory emesis, occurring prior to treatment as a conditioned response in those who have developed nausea and vomiting during previous chemotherapy. The goal of antiemetic therapy is the prevention and management of chemotherapy-induced nausea and vomiting.

Fosaprepitant (Merck & Co., Inc., Whitehouse Station, NJ) was initially approved by the United States (U.S.) Food and Drug Administration (FDA) in 2008. Fosaprepitant is given via IV in combination with other antiemetic agents for the prevention of nausea and vomiting associated with highly and moderately emetogenic chemotherapy. Fosaprepitant is given on the first day of chemotherapy. In 2016, the Product Information label for fosaprepitant was updated to note that the drug has not been studied for the treatment of established nausea and vomiting.

The National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®, 2018) has defined chemotherapeutic agents as high emetic risk when they have a 90% or greater frequency of causing emesis. A moderate emetic risk is defined as 30%-90% frequency of causing emesis. NCCN includes category 1 recommendations for the use of fosaprepitant in those undergoing treatment with high or moderate emetic risk agents.

In 2016, Ruhlmann and associates, studied the use of fosaprepitant in the prevention of radiation induced nausea and vomiting. In a multinational, randomized, double-blind, placebo-controlled phase 3 trial, women with cervical cancer scheduled to receive radiotherapy and weekly cisplatin were randomized to receive either single doses of IV fosaprepitant (n=118) or a saline placebo (n=116) in combination with IV palonosetron and oral dexamethasone prior to cisplatin administration. The primary endpoint was the proportion of individuals with sustained no emesis at 5 weeks of treatment. Secondary endpoints measured the proportion of individuals with a complete response (no emesis and no use of rescue medications). The proportion of individuals with sustained no emesis at 5 weeks (competing risk analysis) was 48.7% (95% confidence interval [CI] 25.2–72.2) for the placebo group compared with 65.7% (95% CI, 42.2–89.2) for the fosaprepitant group. The overall complete response rate, defined as no emesis and no rescue medications, over the course of treatment was higher in the fosaprepitant group compared to the placebo group (24% in the fosaprepitant group compared to 14% in the placebo group; p=0.007). There were no serious adverse events which were considered drug related. The authors noted that future studies might explore newer NK-1 receptor antagonists other drugs which appear to be effective against chemotherapy-related nausea in addition to emesis.

A study by Saito and colleagues (2013) reported on the safety and efficacy of single-dose fosaprepitant following treatment with cisplatin. In this multicenter, placebo-controlled, double-blind, randomized parallel study, the control group (n=167) received intravenous (IV) placebo, granisetron and dexamethasone while the treatment group (n=173) received IV fosaprepitant, granisetron and dexamethasone in the intention-to-treat analysis. The primary endpoint was the percentage of participants who had a complete response (no emesis and no rescue therapy) over the entire treatment course. The percentage of participants with a complete response was 64% in the treatment group compared with 47% in the placebo group (p=0.0015). The fosaprepitant regimen was more effective than the control regimen in both the acute (0-24 hour post chemotherapy) phase (94% versus 81%, p=0.0006) and the delayed (24-120 hour post chemotherapy) phase (65% versus 49%, p=0.0025).

In a 2011 study by Grunberg and colleagues, fosaprepitant was compared to apreptinat, the oral form of fosaprepitant approved by the FDA in 2003. The authors sought to determine whether a single intravenous dose of fosaprepitant was non-inferior to a 3 day oral apreptinat regimen. The phase III, double-blind study included 2322 participants who were randomly assigned to one of two treatment arms: the fosaprepitant group (n=1147) or the apreptinat group (n=1175). The primary endpoint was complete response defined as no vomiting or retching with no rescue medication during overall phase, defined as 0 to 120 hours following initiation of chemotherapy. Secondary endpoints were the proportion of participants with complete response in the delayed phase defined as 25 to 120 hours after initiation of chemotherapy, and the proportion of participants with no vomiting in the overall phase. The participants completed a daily diary for 5 days following the start of chemotherapy and kept track of vomiting or retching episodes, the use of any rescue therapy, and nausea ratings. For the primary endpoint, 71.9% (95% CI, 69.1% to 74.5%) of participants in the fosaprepitant group reported complete response compared to 72.3% (95% CI, 69.6% to 74.9%) in the apreptinat group. For the secondary endpoint, 74.3% (95% CI, 71.6% to 76.9%) of participants reported complete response in the fosaprepitant group compared to 74.2% (95% CI, 71.6% to 76.8%) in the apreptinat group. For the secondary endpoint of no vomiting during overall phase, 72.9% (95% CI, 70.2% to 75.5%) of participants in the fosaprepitant
group reported no vomiting compared to 74.6% (95% CI, 71.9% to 77.1%) in the aprepitant group, supporting the non-inferiority of intravenous fosaprepitant to oral aprepitant.

**Definitions**

Emetogenic: Having the capacity to induce vomiting.

High risk: Emesis that has been documented to occur in more than 90% of patients.

Moderate risk: Emesis that has been documented to occur in 30% to 90% of patients.

**References**

**Peer Reviewed Publications:**


**Government Agency, Medical Society, and Other Authoritative Publications:**


**Websites for Additional Information**


Index

Emend
Fosaprepitant

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

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<td>05/03/2018</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Hematology/Oncology Subcommittee review. The document header wording updated from &quot;Current Effective Date&quot; to &quot;Publish Date.&quot; Updated Discussion, References and Websites sections.</td>
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<td>05/02/2018</td>
<td>Hematology/Oncology Subcommittee review. Updated Discussion, References and Websites sections.</td>
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<td>Hematology/Oncology Subcommittee review. Updated Description, Discussion, Definitions, References and Websites sections. Removed ICD-9 codes from Coding section.</td>
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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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Subject: Laronidase (Aldurazyme®)

Guideline #: CG-DRUG-58

Publish Date: 10/17/2018

Status: Reviewed

Last Review Date: 09/13/2018

Description

This document addresses the clinical indications for laronidase (Aldurazyme, BioMarin Pharmaceutical Inc., Novato, CA and Genzyme Corporation, Cambridge, MA), a polymorphic variant of the human enzyme, alpha-L-iduronidase. Laronidase is an enzyme replacement therapy (ERT) approved by the U.S. Food and Drug Administration (FDA) for the treatment of individuals with Mucopolysaccharidosis I, including Hurler syndrome, Hurler-Scheie syndrome, as well as those with Scheie syndrome who have moderate to severe symptoms.

Clinical Indications

Medically Necessary:

Laronidase is considered medically necessary for the treatment of an individual with Mucopolysaccharidosis I (MPS I) when the following criteria are met:

A. Diagnosis of any of the following MPS I syndromes:
   1. Hurler syndrome; or
   2. Hurler-Scheie syndrome; or
   3. Scheie syndrome, moderate to severe manifestations including any of the following:
      a. Cardiac valve abnormalities (such as aortic or mitral valve regurgitation, with or without insufficiency or stenosis); or
      b. Corneal clouding, open-angle glaucoma, and retinal degeneration, progressive; or
      c. Craniofacial or growth retardation; or
      d. Frequent, moderate to severe upper respiratory infections; or
      e. Hepatosplenomegaly; or
      f. Hernias (such as hiatal, inguinal, or umbilical); or
      g. Neurological symptoms resulting from cervical instability or cervical spinal cord compression; or
      h. Skeletal and joint involvement, progressive (such as, arthropathy, back pain, joint stiffness, lumbar spondylolisthesis, lumbar spinal compression, osteopenia, or osteoporosis); and

B. Diagnosis is confirmed by either of the following:
   1. Documented deficiency in alpha-L-iduronidase enzyme activity of less than 10% of the lower limit of normal range as measured in fibroblasts or leukocytes; or
Not Medically Necessary:

Laronidase is considered **not medically necessary** for all other indications, including the treatment of an individual with the Scheie form of MPS I who has mild symptoms.

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**Description/General Information**

**Description of the Condition**

MPS I is an inherited autosomal recessive lysosomal storage disease caused by a deficiency of α-L-iduronidase, a lysosomal enzyme required for the catabolism (breakdown) of complex carbohydrates known as glycosaminoglycans (GAGs). Reduced or absent L-iduronidase activity blocks the degradation of GAG substrates dermatan sulfate and heparin sulfate and leads to accumulation of these substrates throughout the body, resulting in progressive damage to a broad range of tissues (Aldurazyme Product Information [PI] Label, 2013). MPS I has historically been divided into three broad groups based on severity of symptoms: Hurler syndrome (MPS I-H, severe), Hurler-Scheie syndrome (MPS I-HS, intermediate), and Scheie syndrome (MPS I-S, attenuated). MPS I is now viewed as a continuous spectrum of disease, with the most severely affected individual on one end, the less severely affected (attenuated) on the other end, and a wide range of different severities in between. The population frequency of MPS I is estimated to be approximately 1 in 100,000 births, with MPS I-H the most common and MPS I-S the rarest of the subtypes (National Institute of Neurological Disorders and Stroke [NINDS], 2017).

Children with MPS I inherit a defective gene from both their mother and father with symptoms generally beginning between ages 3 and 8. In the most severe form of MPS I, developmental delay is evident by the end of the first year, and children usually stop developing between ages 2 and 4. Following this is progressive mental decline and loss of physical skills. Children with severe MPS I often die before age 10 from obstructive airway disease, respiratory infections, or cardiac complications. Although symptoms generally begin to appear after age 5 in children with attenuated MPS I, the diagnosis is most commonly made after age 10. At the opposite end of the spectrum, children with Scheie syndrome are intellectually normal and may have a normal life span; however, many will become disabled due to degenerative bony disease, corneal opacity and valvular heart disease and longevity is dependent upon the particular syndrome (Jameson, 2016; NINDS, 2017). In a review article, Thomas and colleagues (2010) state:

> Using natural history data from the uniquely large population of 78 Scheie patients enrolled in the MPS I Registry, we characterized the onset and prevalence of clinical manifestations and explored reasons for delayed diagnosis of the disease. Median patient age was 17.5 years; 46% of the patients were male, and 88% were Caucasian. Of 25 MPS I-related clinical features, cardiac valve abnormalities, joint contractures, and corneal clouding were each reported by > 80% and all three by 53% of patients. Carpal tunnel syndrome, hernia, coarse facial features, and hepatomegaly were each reported by >5 0% of patients. Age at onset of
The clinical features varied widely between individuals, but the median age at onset was 3 years for hernia and between 5 and 12 years for most features, including coarse facial features, hepatomegaly, joint contractures, bone deformities, cardiac valve abnormalities, cognitive impairment, and corneal clouding. Carpal tunnel syndrome, cardiomyopathy, and myelopathy arose more commonly during adolescence or adulthood...Scheie syndrome usually emerges during childhood, and recognition of attenuated MPS I requires awareness of the multisystemic disease manifestations and their diverse presentation.

The clinical manifestations of MPS I syndromes may include inhibited growth (short stature), developmental delay/learning disabilities, abnormal gait (especially toe walking), abdominal protrudence due to hepatosplenomegaly, hernias, impaired vision (corneal clouding), hearing loss, impaired cardiac and pulmonary function (including frequent respiratory infections, noisy breathing, heart murmur), skeletal malformations, and often, neurological abnormalities (including mental dysfunction). The most suggestive rheumatological feature of MPS I is development of joint pain and joint contractures at an early age without concomitant inflammation. Other common bone and joint feature (subtle or overt) include claw hand, spinal deformity (gibbus, kyphosis, lordosis, and scoliosis) and radiologic evidence of dysostosis multiplex. Distinguishing clinical features of MPS I relative to other MPS disorders include progressive corneal clouding and cognitive impairment (but rarely with overt behavioral issues) (Lehman, 2011; NINDS, 2017).

**Diagnosis of the Condition**

A diagnostic workup in an individual with MPS I typically demonstrates elevated levels of urinary GAG (that is, MPS quantitative urine) and increased amounts of both dermatan and heparan sulfate detected on thin-layer chromatography. Reduced or absent activity of α-L-iduronidase in blood spots, fibroblasts, leukocytes, or whole blood can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the *IDUA* gene allows for detection of the disease-causing mutation in affected individuals and subsequent carrier detection in relatives. To date, a clear genotype-phenotype correlation has not been established.

In a GeneReviews®, Clarke (2016) states that MPS I should be suspected in individuals with the following suggestive clinical and supportive laboratory findings:

**Clinical findings**

- Coarse facial features
- Early frequent upper-respiratory infections including otitis media
- Inguinal or umbilical hernia
- Hepatosplenomegaly
- Characteristic skeletal and joint findings (gibbus deformity; limitation of joint range of motion)
- Characteristic ocular findings (corneal clouding)
  
  Note: Clinical findings vary by disease severity. Clinical findings alone are not diagnostic.

**Supportive laboratory findings**

Analysis of urinary GAG (i.e., heparan and dermatan sulfate) may be quantitative (measurement of total urinary uronic acid) or qualitative (GAG electrophoresis to analyze the specific GAGs excreted).

- Neither the quantitative nor the qualitative method can diagnose a specific lysosomal enzyme deficiency, including MPS I; however, an abnormality detected by either or both methods indicates the likely presence of an MPS disorder.
- GAG electrophoresis can exclude and include certain MPS disorders; however, definitive diagnosis requires additional testing.
- Both methods have reduced sensitivity, particularly when urine is dilute.

To establish a definitive diagnosis of MPS I (Clarke, 2016), the following molecular genetic testing is recommended:

The diagnosis of MPS I is established in a proband with the suggestive clinical and laboratory findings (above) and either identification of biallelic pathogenic variants in *IDUA* on molecular genetic testing or detection of deficient activity of the lysosomal enzyme α-L-iduronidase. Molecular testing approaches can include single-gene testing and use of a multi-gene panel.
The detection rate for pathogenic variants by sequence analysis of the *IDUA* gene in 85 individuals (Beesley, 2001) and 102 individuals (Bertola, 2011) with MPS I was reported at 95%-97% (that is, the proportion of probands with pathogenic variants detectable by sequence analysis alone).

**Clinical Safety and Effectiveness of Laronidase for MPS I Syndromes**

Laronidase therapy in individuals with MPS I is intended to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG. The effects of intravenously (IV) administering laronidase on cells within the central nervous system (CNS) cannot be inferred from activity in sites outside the CNS. The ability of laronidase to cross the blood brain barrier has not been evaluated in animal models or clinical studies (Aldurazyme PI Label, 2013).

The American College of Medical Genetics (ACMG) publication on the diagnosis and management of lysosomal storage diseases addresses several syndromes including MPS I. The ACMG guidelines describe how weekly treatment with 0.58 mg/kg/dose of laronidase improved forced vital capacity (FVC), reduced symptoms of airway obstruction, and exercise tolerance increased as demonstrated by improved 6-minute walk distance (6MWD) test results. Liver and spleen volumes were reduced to near normal levels and both weight and height growth trended towards normalization (Wang, 2011).

In 2003, the FDA approved laronidase as an orphan drug for use in the treatment of individuals diagnosed with MPS I with Hurler or Hurler-Scheie syndrome and for those with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected individuals with the Scheie form have not been established. Laronidase has been shown to improve pulmonary function and walking capacity. Laronidase has not been evaluated for effects on the CNS manifestations of the disorder (Aldurazyme PI Label, 2013; Wang, 2011).

In a 26 week, randomized, double-blind, placebo-controlled phase 3 study (n=45, age range, 6 to 43 years) laronidase improved FVC and the 6MWD in individuals with Hurler or Hurler-Scheie forms of MPS I (Wraith, 2004). At baseline, all participants had a percent of predicted normal FVC of 77% or less with a mean baseline percent of predicted normal FVC of 48% ± 15% in the laronidase arm and 54% ± 16 % in the placebo arm. Laronidase was administered 0.58 mg/kg of body weight once weekly (n=22) or placebo (n=23) once weekly. The mean baseline 6MWD was 319 ± 131 meters and 367 ± 114 meters. Relative to baseline, after 26 weeks of either laronidase or placebo once weekly. Laronidase significantly improved FVC compared with placebo (mean FVC change, 1% ± 7% vs. -3% ± 7%, respectively; mean difference, 4%; mean difference, 2%; 95% confidence [CI], 0.4% to 7%; p=0.02). At 26 weeks, laronidase improved 6MWD from baseline, but the improvement was not statistically significant (mean 6MWD change from baseline, 28 meters vs. -11 meters, respectively; mean difference, 38 meters; median difference, 39 meters, 95% CI, -2 to 79; p=0.07). Although liver size and urinary GAG levels were decreased among participants receiving laronidase compared with placebo, no laronidase-treated participants achieved the normal range for urinary GAG levels over the 26-week study period. In the 4-year, open-label, phase 3 extension study (Clarke, 2009), long-term treatment with laronidase maintained an improvement in 6MWD over an additional 182 weeks in participants with Hurler or Hurler-Scheie forms of MPS I. Mean urinary GAG level decreases reported at 182 weeks were similar to those reported after 26 weeks.

In a phase 2 trial, Kakkis and colleagues (2001) reported that laronidase infusions were associated with clinical and biochemical improvements in a small cohort of children, adolescents, and a single adult with MPS I. A total of 10 participants (n=9, 5 to 17 years; n=1, 22 years) with MPS I (predominately Hurler-Scheie syndrome) experienced significant reductions in hepatosplenomegaly and urinary GAG excretion (63%, mean reduction from baseline), and improvement in some signs and symptoms during one year of treatment with weekly laronidase. There was a significant increase reported in the rate of growth in height (2.8 to 5.15 cm/year) and weight (1.7 to 3.8 kg/year) in prepubertal participants. The degree of elbow extension and shoulder flexion increased significantly from baseline in evaluable participants, however, knee extension was unaffected. A trend towards improvement of airway function and endurance/performance of daily activities was reported, but the investigators did not perform statistical analyses. Cardiac function improved subjectively (1 or 2 New York Heart Association classes), but this improvement was not confirmed by echocardiography. No improvement was reported in corneal clouding. A limitation of this study was the lack of a control group to confirm these outcomes.

The safety and effectiveness of laronidase in children younger than 5 years of age were reported in a prospective, open-label, uncontrolled, multinational study (n=20) of 16 children with Hurler syndrome and 4 children with Hurler-Scheie syndrome (Wraith, 2007). Clinical improvements in hepatomegaly, left ventricular hypertrophy, and apnea/hypopnea index were noted in 94% of children with weekly laronidase at week 52. Four children underwent dosage increases for the last 26 weeks because of elevated urinary GAG levels at week 22. The mean urine GAG level declined by approximately 50% by 13 weeks and was sustained thereafter. No participant reached the normal
range for urinary GAG levels for the study duration. The change in urinary GAG levels in children 6 years or younger was similar to the urinary GAG changes observed in older individuals (6 through 43 years of age).

Laraway and colleagues (2016) retrospectively evaluated the long-term outcomes of laronidase therapy in 35 individuals with attenuated MPS I (Hurler-Scheie and Scheie syndrome) for up to 10 years (mean follow-up, 6.1 years) following initiation of therapy. Case notes, laboratory results and data from clinical trials was analyzed for urinary GAG levels, FVC, 6MWD test, height-for-age Z score, cardiac valve function, corneal clouding, and visual acuity. Of the 35 individuals, one discontinued laronidase after 1 year (declined weekly intravenous infusions) and 3 individuals died during follow-up. Baseline urinary GAG data were available for 91% (32 of 35) individuals. Mean urinary GAG levels decreased by more than 50% from baseline within 6 months of laronidase therapy regardless of age at initiation with reductions remaining between 50% and 90% of baseline values throughout follow-up. The percentage of reduction from baseline was statistically significant (p<0.001) at all time points (6 months to 7 years). There were no statistically significant changes in mean FVC, 6MWD test, or height-for-age Z score. At the last assessment, disease remained stable in mitral and aortic valve function (65%, 22 of 34 individuals), corneal clouding (78%, 18 of 23 individuals), and visual acuity (33%, 8 of 24 individuals) with some improvement in visual acuity in 42% (10 of 24) of individuals. Individuals of younger age who initiated treatment at less than 10 years of age maintained disease measures (that is, FVC, 6MWD test, and height) closer to norms than those individuals aged 10 or older at treatment initiation. Fewer children aged less than 10 years at treatment initiation experienced mitral and aortic valve deterioration compared with those aged 10 years or older (14% vs. 40%, respectively). Limitations of this study include difficulties in accurately assessing cardiac function by echocardiography, and only subjective and non-standardized assessment of stenosis/regurgitation was reported. Other limitations include heterogeneity of the study population, which may have affected outcome measures known to be affected by demographics such as age, sex and ethnicity in individuals with MPS I.

Perez-Lopez and colleagues (2017) performed a systematic review of the evaluable randomized trials or observation studies to assess effectiveness variables modified in individuals with MPS I who initiated laronidase as adults (≥ 18 years). A meta-analysis of studies evaluating the same effectiveness outcomes was performed and the evidence was rated according to GRADE criteria. Heterogeneity was assessed by the Chi-squared test and the I-squared statistic. Case reports were excluded from meta-analysis and their main outcomes were evaluated separately. The primary outcome was the reduction of urine GAG levels in terms of: 1) percentage of individuals with reduction in baseline urine GAG levels; and 2) percentage of individuals with normalization of urine GAG levels. A total of 19 studies and 12 case reports were reviewed. Use of laronidase resulted in decreased urine GAG levels (high evidence) and liver volume (high evidence), improved 6MWD test (moderate evidence) and increased blood anti-laronidase antibody levels (high evidence). There was no conclusive results (low or very low evidence) regarding improvement/stabilization of respiratory function, change in shoulder flexion, cardiac improvement/stabilization, improvement in symptoms of nocturnal hypoventilation and sleep apnea, improvement in quality of life, visual acuity, otolaryngologic function, bone mineral density or effectiveness of intrathecal therapy. Limitations of this analysis include lack of specific studies in the target population (that is, laronidase initiated at ≥ 18 years) and very few randomized clinical trials; thus, data was extracted mainly from subgroup analyses of observational studies that included all MPS I subjects. There was also significant heterogeneity between study designs and the evaluated clinical outcomes; however, no publication bias was observed in reporting of positive outcomes of laronidase therapy (vs. no effect) in the evaluated studies.

Dornelles and colleagues (2017) published a systematic review and meta-analysis aimed to evaluate the efficacy and safety of laronidase in individuals of any age with MPS I. The first study selection included randomized controlled trials; however, since less than five trials were identified, prospective studies were included. Studies with overlapping data were excluded. Primary inferences were based on random-effects models and the GRADE criteria was used for assessment of study quality. Search results yielded four studies for quantitative synthesis. Two of the studies were randomized controlled trials and the others were quasi-experimental or open-label, nonrandomized trials. Through the meta-analysis, the authors found the following outcomes: adverse events (65%; 95%CI 53, 76), apnea-hypopnea index (not significant), urinary GAG [mean change -65.5 μg/mg creatinine (95%CI -68.8, -62.3)], liver volume [mean change -31.03% (95%CI -36.1, -25.9)], left ventricular mass index [mean change -1.8 (95%CI -2.32, -0.25)], and performance in the 6-minute walk test (not significant). The authors concluded that laronidase is safe to use and effectively reduces liver volume, urinary GAG, and left ventricular mass index. Study limitations included few studies meeting criteria for the meta-analysis due to MPS I being a rare disorder, lack of data for each phenotype, and unclear or high risk of selection and performance bias in the included randomized control trials.

In the clinical studies and post-marketing safety experience with laronidase, approximately 1% of participants experienced severe or serious allergic reactions. In participants with MPS I, pre-existing upper airway obstruction may have contributed to the severity of some reactions. The most commonly reported infusion reactions occurring in at least 10% of infants and children 6 months of age and older were pyrexia, chills, blood pressure increased,
tachycardia, and oxygen saturation decreased. The development of antibodies against exogenous enzyme did not appear to correlate with infusion reactions or response to laronidase. The most frequently occurring adverse reactions occurring in at least 10% of children 6 years and older are rash, upper respiratory tract infection, injection site reaction, hyperreflexia, paresthesia, flushing, and poor venous access. It has been observed that most individuals develop antibodies by week 12 of laronidase infusion; therefore, individuals are routinely premedicated one hour before the infusion begins with antihistamines and antipyretics (Aldurazyme PI Label, 2013).

**FDA Black Box Warnings and Additional Information for Use of Laronidase**

The PI Label (Aldurazyme, 2013) for laronidase includes the following Black Box warning:

**WARNING: RISK OF ANAPHYLAXIS**

Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME infusions. Therefore, appropriate medical support should be readily available when ALDURAZYME is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions, and require additional monitoring.

**Dosing Information and Use in Specific Populations**

- The recommended dosage regimen of ALDURAZYME is 0.58 mg/kg of body weight administered once weekly as an intravenous (IV) infusion.
- The safety and effectiveness of ALDURAZYME was assessed in a 52-week, open-label, uncontrolled clinical study in 20 patients with MPS I, ages 6 months to 5 years old, and was found to be similar to the safety and effectiveness of ALDURAZYME in pediatric patients 6 to 18 years, and adults.
- A registry for pregnant women is available. Pregnant women with MPS I should be encouraged to enroll in the MPS I Registry.

**Warnings and Precautions**

- Anaphylaxis and Allergic Reactions: Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME infusion and up to 3 hours after infusion. Appropriate medical support and monitoring measures should be readily available when ALDURAZYME is administered. If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion and initiate appropriate treatment, which may include ventilatory support, treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids.
- Risk of Acute Respiratory Complications: Patients with acute febrile or respiratory illness at the time of ALDURAZYME infusion may be at greater risk for infusion reactions. Consider delaying ALDURAZYME infusion. Sleep apnea is common in MPS I patients. Evaluation of airway patency should be considered prior to initiation of treatment with ALDURAZYME. Appropriate respiratory support should be available during infusion.
- Risk of Acute Cardiorespiratory Failure: Caution should be exercised when administering ALDURAZYME to patients susceptible to fluid overload. Consider a decreased total infusion volume and infusion rate when administering ALDURAZYME to these patients. Appropriate medical monitoring and support measures should be available during infusion.
- Infusion Reactions: Pretreatment is recommended prior to the infusion to reduce the risk of infusion reactions and may include antihistamines, antipyretics, or both. If infusion reactions occur, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

**Definitions**

6-minute walk distance (6MWD) test: A standardized test that measures how far a person can walk on a hard, flat surface in 6 minutes and has been used to assess endurance in several MPS syndromes (ATS, 2002).
Dysostosis multiplex: A complex of multiple skeletal abnormalities affecting the bones of the face, spine, ribs and extremities.

Enzyme replacement therapy (ERT): A treatment provided via intravenous infusion to provide enzymes in an individual unable to make sufficient amounts of that enzyme on their own.

Forced vital capacity (FVC): A measurement of the volume of air which can be forcibly exhaled from the lungs after taking the deepest breath possible; FVC is used assess the presence and severity of lung diseases.

Hurler syndrome (MPS I-H, severe): The most common and severe subtype of MPS I syndrome. Symptoms of MPS I-H are reported as follows (Wang, 2011):

- General: Early (< 12 months) onset, rapid disease progression, hepatosplenomegaly, hernias (inguinal, umbilical, and hiatal), and death in first decade if untreated
- Cognition: Normal early development, developmental delay/plateau, and neurocognitive decline
- Neurologic: Communicating hydrocephalus
- Ophthalmologic: Corneal clouding and open-angle glaucoma
- Otolaryngological: Chronic recurrent rhinitis, persistent nasal discharge, obstructive sleep apnea, recurrent acute otitis media, and mixed hearing loss
- Cardio: Valvular dysplasia and insufficiency, cardiomyopathy, cor pulmonale (especially with sleep apnea), myocardial infarction
- Orthopedic: Vertebral dysplasia, kyphosis/lumbar gibbus, hip dysplasia/dislocation, global restriction of joint mobility, carpal tunnel syndrome, short stature, and osteopenia/osteoporosis

Hurler-Scheie syndrome (MPS I-HS, intermediate): Also classified as combined “intermediate/attenuated” MPS I-HS. Symptoms of MPS I-HS are reported as follows (Wang, 2011):

- General: Intermediate onset, hepatomegaly, and hernias (inguinal, umbilical, and hiatal)
- Cognition: Learning disability possible and attention deficit possible
- Neurologic: Cervical spinal cord compression and cervical instability
- Ophthalmologic: Corneal clouding and open-angle glaucoma
- Otolaryngological: Chronic recurrent rhinitis, persistent nasal discharge, obstructive sleep apnea, recurrent acute otitis media, and mixed hearing loss
- Cardio: Valvular dysplasia and insufficiency, cor pulmonale (especially with sleep apnea)
- Orthopedic: Vertebral dysplasia, kyphosis/lumbar gibbus, hip dysplasia/dislocation, global restriction of joint mobility, carpal tunnel syndrome, short stature, and osteopenia/osteoporosis

Molecular genetic testing: Testing that involves the analysis of deoxyribonucleic acid (DNA), either through linkage analysis, sequencing, or one of several methods of mutation detection.

Mutation: A permanent, transmissible change in genetic material.

Proband: A term used in medical genetics to refer to the first affected family member with a known pathogenic genetic mutation.

Scheie syndrome (MPS I-S, attenuated): The rarest subtype of MPS I syndrome which leads to difficulty in developing characteristic phenotypic descriptions. Symptoms of MPS I-S are reported as follows, and may be mild, or moderate to severe (Wang, 2011):

- General: Childhood onset, hernias (inguinal, umbilical, and hiatal) and normal life expectancy
- Cognition: Typically no symptoms
- Neurologic: Cervical spinal cord compression and cervical instability
- Ophthalmologic: Corneal clouding, open-angle glaucoma, and retinal degeneration
- Otolaryngological: None identified
- Cardio: Valvular dysplasia and insufficiency
- Orthopedic: Lumbar spondylolisthesis, lumbar spinal compression, joint stiffness, carpal tunnel syndrome, milder short stature, and osteopenia/osteoporosis

Sequence analysis: Process by which the nucleotide sequence is determined for a segment of DNA. Also referred to as gene sequencing.

**References**

**Peer Reviewed Publications:**


**Government Agency, Medical Society, and Other Authoritative Publications:**


Websites for Additional Information


Index

Aldurazyme
Laronidase
MPS I
Mucopolysaccharidosis I

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

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<td>09/13/2018</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information, References, and Websites for Additional Information sections. MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Minor punctuation change to Clinical Indications. Updated Discussion/General Information, Definitions, References, and Websites for Additional Information sections.</td>
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<td>Reviewed</td>
<td>11/02/2017</td>
<td>MPTAC review. Initial document development.</td>
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<td>New</td>
<td>11/03/2016</td>
<td>MPTAC review. Initial document development.</td>
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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member’s card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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©CPT Only - American Medical Association
This document addresses intravenous, subcutaneous, and inhalation administration of prostacyclin analogues for the treatment of pulmonary arterial hypertension, (also referred to as idiopathic pulmonary arterial hypertension or IPAH), a life-threatening disease characterized by sustained elevations of pulmonary artery pressure with associated thickening of the pulmonary arteries and narrowing of the blood vessels.

The U.S. Food and Drug Administration (FDA) approved the following infusion and inhalation prostacyclin analogues for use in pulmonary arterial hypertension:

- Epoprostenol (Veletri®, Actelion Pharmaceuticals US, Inc., South San Francisco, CA);
- Epoprostenol sodium (Flolan®, GlaxoSmithKline, Research Triangle Park, NC);
- Iloprost (Ventavis®, Actelion Pharmaceuticals US, Inc., South San Francisco, CA);
- Treprostinil (Remodulin® and Tyvaso®, United Therapeutics Corporation, Research Triangle Park, NC).

Note: Please see the following related document for additional information:

- CG-SURG-79 Implantable Infusion Pumps

Clinical Indications

Diagnostic Criteria for Pulmonary Arterial Hypertension (PAH):

- Adult and pediatric PAH: Right heart catheterization which shows a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest; a pulmonary capillary wedge pressure (PCWP), mean pulmonary artery wedge pressure (PAWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units (ACCF/AHA Hoeper, 2013; Ivy, 2013; AHA/ATS Abman, 2015).

Criteria for Vasodilator Response:

- A favorable response is defined as a fall in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output, when challenged with inhaled nitric oxide, intravenous epoprostenol or intravenous adenosine.
Medically Necessary:

Continuous intravenous infusion of epoprostenol sodium (prostacyclin, PGI2, Veletri, Flolan) is considered medically necessary as a treatment for individuals who meet all of the following criteria:

- Meets the diagnostic criteria for PAH (above); and
- Demonstrates an unfavorable acute response to vasodilators; and
- Meets one of the following selection criteria with New York Heart Association Functional Class III or IV symptoms:
  - World Health Organization (WHO) Group I* idiopathic pulmonary arterial hypertension including all subtypes of WHO Group I PAH; or
  - Pulmonary hypertension associated with connective tissue disorders (for example, scleroderma, systemic sclerosis, etc.); or
  - Pulmonary hypertension associated with congenital heart defects.

Continuous subcutaneous infusion of treprostinil sodium (Remodulin) is considered medically necessary as a treatment for individuals who meet all of the following criteria:

- Meets the diagnostic criteria for PAH (above); and
- Demonstrates an unfavorable acute response to vasodilators; and
- Meets one of the following selection criteria with New York Heart Association functional Class II, III, or IV symptoms:
  - World Health Organization (WHO) Group I* idiopathic pulmonary arterial hypertension including all subtypes of WHO Group I PAH; or
  - Pulmonary hypertension associated with connective tissue disorders (for example, scleroderma, systemic sclerosis, etc.); or
  - Pulmonary hypertension associated with congenital heart defects.

Continuous intravenous infusion of treprostinil sodium (Remodulin) is considered medically necessary for treatment of individuals who meet criteria for treprostinil treatment above when there is documented inability to tolerate treatment by subcutaneous infusion.

Inhalation therapy with iloprost (Ventavis) inhalation solution or Tyvaso inhalation solution* (treprostinil) is considered medically necessary as a treatment for individuals who meet all of the following criteria:

- Meets the diagnostic criteria for PAH (above); and
- Demonstrates an unfavorable acute response to vasodilators; and
- Meets one of the following selection criteria with New York Heart Association (NYHA) Functional Class III or IV symptoms:
  - World Health Organization (WHO) Group I* idiopathic pulmonary arterial hypertension including all subtypes of WHO Group I PAH; or
  - Pulmonary hypertension associated with connective tissue disorders (for example, scleroderma, systemic sclerosis, etc.); or
  - Pulmonary hypertension associated with congenital heart defects.

*FDA approved labeling for Tyvaso (treprostinil) inhalation solution states for use in the treatment of pulmonary arterial hypertension (WHO Group I) in individuals with NYHA Functional Class III symptoms to improve exercise ability (FDA, 2013).

Continuous infusion of epoprostenol or treprostinil is considered medically necessary for individuals with severe PAH refractory to medical therapy with calcium channel blockers.

Not Medically Necessary:

Use of epoprostenol, treprostinil or iloprost is considered not medically necessary as a treatment for individuals appropriate for treatment with calcium channel blockers:
• Individuals who demonstrate a favorable acute hemodynamic response to vasodilators at cardiac catheterization who are deemed appropriate by the treating physician for a trial of calcium channel blocker treatment, or
• Individuals who demonstrated a favorable acute hemodynamic response to vasodilators but have not become refractory to, or unable to, tolerate therapeutic doses of calcium channel antagonists.

Continuous intravenous infusion of treprostinil sodium (Remodulin) is considered not medically necessary for treatment of individuals when inability to tolerate treatment by subcutaneous infusion has not been documented.

The use of epoprostenol, treprostinil, or iloprost is considered not medically necessary for all other applications in the absence of WHO Group I PAH including those with WHO Group II to V* pulmonary hypertension and for other causes of pulmonary hypertension, including, but not limited to, left ventricular failure, left sided valvular heart disease, chronic pulmonary diseases, and alveolar hypoventilation syndromes.

*See the Definitions section of this document for a description of the WHO Classification System.

**Coding**

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**HCPCS**

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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>J1325</td>
<td>Injection, epoprostenol; 0.5 mg [Flolan, Veletri]</td>
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<tr>
<td>J3285</td>
<td>Injection, treprostinil, 1 mg [Remodulin]</td>
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<tr>
<td>J7686</td>
<td>Treprostinil, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, 1.74 mg [TYVASO]</td>
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<td>K0455</td>
<td>Infusion pump used for uninterrupted parenteral administration of medication (e.g., epoprostenol or treprostinil)</td>
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<tr>
<td>Q4074</td>
<td>Iloprost, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, up to 20 micrograms [Ventavis]</td>
</tr>
<tr>
<td>S0155</td>
<td>Sterile diluant for epoprostenol, 50 ml [diluant for Flolan]</td>
</tr>
<tr>
<td>S9347</td>
<td>Home infusion therapy, uninterrupted, long-term, controlled rate intravenous or subcutaneous infusion therapy (e.g., epoprostenol)</td>
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**ICD-10 Diagnosis**

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<td>Primary pulmonary hypertension</td>
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<td>I27.20</td>
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<td>I27.21</td>
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<td>I27.83</td>
<td>Eisenmenger’s syndrome</td>
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<td>I27.89</td>
<td>Other specified pulmonary heart diseases</td>
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<td>M34.0</td>
<td>Progressive systemic sclerosis</td>
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<td>M34.81</td>
<td>Systemic sclerosis with lung involvement</td>
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<tr>
<td>M34.9</td>
<td>Systemic sclerosis, unspecified</td>
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<tr>
<td>Q20.0-Q24.9</td>
<td>Congenital malformations of heart</td>
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**Discussion/General Information**

PAH is a life-threatening disease characterized by sustained elevations of the mPAP, thickening of the pulmonary arteries and narrowing of the blood vessels. As the disease progresses, the right side of the heart becomes enlarged and may fail. The diagnosis and treatment of PAH is complex and continues to be refined. Medical management consists of diuretics, supplemental oxygen, anticoagulants, calcium channel blockers, endothelin receptor antagonists (bosentan [Tracleer, Actelion Pharmaceuticals US, Inc., South San Francisco, CA]), and continuous infusion of prostacyclin (epoprostenol) or prostacyclin analog (treprostinil) or inhaled iloprost. Lung or heart-lung transplantation has been performed in individuals who are refractory to medical management.
The clinical effectiveness and safety of prostacyclin infusion therapy by continuous intravenous (IV) infusion of epoprostenol sodium (Flolan), continuous subcutaneous infusion of treprostinil sodium (Remodulin), and inhalation therapy with iloprost (Ventavis) inhalation solution for treatment of individuals with idiopathic pulmonary arterial hypertension (IPAH) or pulmonary arterial hypertension (PAH) associated with connective tissue disorders, such as scleroderma or congenital heart defects, is well documented in the peer-reviewed medical literature. These therapies improve cardiopulmonary hemodynamics, exercise tolerance and quality of life in many individuals. In addition, epoprostenol has been shown to enhance survival for individuals who have been unresponsive to conventional therapy. Continuous IV epoprostenol infusions are reserved for those who are unresponsive to conventional therapy, and may be used either as long-term therapy or as a bridge to transplantation. Epoprostenol is contraindicated in individuals with congestive heart failure (CHF) due to severe left ventricular systolic dysfunction and those with hypersensitivity to epoprostenol or to structurally related compounds. It is not recommended for treatment in the following diagnoses: diseases of the left atrium or ventricle (for example, cardiomyopathy, CHF), diseases of mitral or aortic valves, chronic obstructive pulmonary disease (COPD) or disorders of alveolar hypoventilation.

In a retrospective study of 557 consecutive subjects with IPAH, it was observed that 70 individuals demonstrated an acute hemodynamic response to vasodilators at cardiac catheterization, defined in this study as at least a 20% decrease in both mPAP and PVR (Sitbon, 2005). Badesch and colleagues (2007) state:

Treatment with oral calcium channel blockers in this group of acute responders resulted in a long term response, (defined as subjects in NYHA Class I or II with a sustained hemodynamic improvement at one year without the addition of prostanoids or endothelin receptor antagonists) in only 54%, representing 6.8% of the total number of individuals studied. It is strongly recommended, therefore, that individuals treated with calcium channel antagonists are followed closely with reassessment at three months to ensure they have improved to NYHA Functional Class I or II. If this improvement is not observed, additional or alternative therapy should be instituted.

**Prostacyclin Analogues as Monotherapy for PAH**

In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of the screening, management, and treatments of PAH (McCrary, 2013). The authors searched the literature through July 2012 using broad inclusion criteria (diagnosis of PAH in individuals of any age; randomized controlled trials [RCTs], or observational studies; all sample sizes). They identified 27 RCTs (3587 participants) and nine observational studies that evaluated the comparative effectiveness and safety of monotherapy or combination therapy for PAH. Data from the observational studies was considered unusable. Twenty-two RCTs (adult-only participants) compared a single drug (monotherapy) to placebo or standard therapy, defined as supportive treatment (diuretics, oxygen, digoxin, and/or oral anticoagulants) with or without calcium channel blockers; eight RCTs studied prostanoids; eight studied endothelin-receptor antagonists; and six studied phosphodiesterase type 5 (PDE-5) inhibitors. The median trial duration was 12 weeks (range 4-24). Based on low strength of evidence, prostanoids were associated with lower mortality compared with standard therapy/placebo (odds ratio [OR], 0.52; 95% confidence interval [CI]; 0.29-0.95). Moderate strength of evidence for each drug class supported an association with improved 6-minute walk distance (6MWD); treatment effects (mean difference in distance walked, intervention - standard therapy/placebo) were 27.9 meters (95% CI; 10.3-45.4) for prostanoids. There was insufficient evidence to form a conclusion concerning an association between use of prostanoids and rates of hospitalization. Low strength of evidence for each drug class supported an association with improvements in most hemodynamic measures (PVR, mPAP, and cardiac index). However, the clinical significance of the observed treatment effect magnitudes is unclear. Among commonly reported adverse events, high strength of evidence supported a greater incidence of jaw pain and cough with aerosolized prostanoid than with placebo. Based on moderate strength of evidence, the incidence of flushing was greater with aerosolized prostanoids than with standard therapy/placebo.

**Prostacyclin Analogues in Combination Therapy for PAH**

In March 2009, the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) Expert Consensus Document on Pulmonary Hypertension was released. This document includes the following information:

In general, patients with poor prognostic indexes should be initiated on parenteral therapy, while patients with class II or early II symptoms commonly commence therapy with either endothelin receptor antagonists or PDE-5 inhibitors...Caution is recommended against widespread treatment of non-PAH PH until patient benefit has been proven in clinical trials. On the topic of combination therapy, while it is an attractive theoretical
option in PAH, there are still ongoing trials investigating its safety and efficacy. Benefit of combination therapy has been suggested in several smaller, open label observational studies but randomized controlled trials are needed and in process… (McLaughlin, 2009).

The safety and efficacy of combination therapy for PAH with various oral agents (vasodilators, endothelin-receptor antagonists, and PDE-5 inhibitors) and with oral agents and prostacyclin analogues continues to be studied with some early results that suggest improved short-term clinical outcomes. However, most authors acknowledge the need for further study to fully investigate the long-term efficacy and safety of combination therapy in PAH based on larger, well designed, controlled, clinical trials (Bai, 2011; Benza, 2008; Benza, 2011; Fox, 2011; Frantz, 2012; McLaughlin, 2010).

The 2013 AHRQ comparativeness effectiveness review also included five RCTs of combination therapies for PAH. Treatments from different classes of drugs were combined in the meta-analyses of this review; all treatment combinations were add-on therapies. Evidence was insufficient to form any conclusion about combination therapy, in comparison to continuation of monotherapy, for the outcomes of mortality or hospitalization. Low strength of evidence supported an association between greater improvement in the 6MWD with combination therapy, compared to continued monotherapy (mean difference in distance walked 23.9 meters [95% CI; 8.0-39.9]). Because the magnitude of the treatment effect is less than the commonly accepted minimal important difference of 33 meters, the clinical significance of this finding is uncertain (McCorry, 2013).

Other Considerations

In 2013, the Fifth World Symposium on pulmonary hypertension (PH) (WSPH; Nice, France) reached consensus to maintain the general scheme of previous clinical classifications for PH, including some proposed modifications and updates related to pediatric PH. The proposed change is to withdraw persistent PH of the newborn (PPHN) from Group 1 because the classification carries more differences than similarities with other PAH subgroups, thus designating PPHN as a separate number “1.” PAH associated with chronic hemolytic anemia was moved from Group 1 PAH to Group 5, (that is, unclear/multifactorial mechanism). In addition, specific items related to pediatric PH were added, in order to create a comprehensive, common classification for both adults and children, adding congenital or acquired left heart inflow/outflow obstructive lesions and congenital cardiomyopathies to Group 2 and segmental PAH added to Group 5. There were no changes to Groups 2, 3, and 4. In summary, individuals in Group 1 are considered to have PAH, (including IPAH), and the remaining four groups are considered to have PAH as follows: PAH due to left heart disease (Group 2), PAH due to chronic lung disease and/or hypoxia (Group 3), chronic thromboembolic PH (CTEPH - Group 4), and PAH due to unclear multifactorial mechanisms (Group 5) (Simonneau, 2013). To date, the proposed modifications to the clinical classifications of PH in this 2013 consensus document differ from the earlier clinical classifications of PH (Simonneau, 2004); however, the latter remain in use by the ACCF/AHA in their 2009 expert consensus document on PH (McLaughlin, 2009).

The American College of Chest Physicians (ACCP) updated guidelines for the medical therapy of PAH clarify that an acute response to vasodilators is defined as a fall in mPAP of at least 10 mm Hg to 40 mm Hg or lower, with an unchanged or increased cardiac output when challenged with inhaled nitric oxide, IV epoprostenol or IV adenosine (Badesch, 2007).

For individuals with IPAH and a favorable response to acute vasodilator challenge, treatment with an appropriate oral calcium channel antagonist should be considered prior to the use of epoprostenol, treprostinil, or iloprost. If a calcium channel antagonist is used, close follow-up is recommended with reassessment after three months to verify that the person has improved to NYHA Functional Class I or II (Badesch, 2007).

There is insufficient published evidence to support the use of epoprostenol, treprostinil, or iloprost for the treatment of PAH resulting from disorders other than those meeting the medical necessity criteria in this document.

Prostacyclin Analogues for the Treatment of PAH

Veletri (epoprostenol) received FDA approval on August 25, 2010 for continuous IV infusion for the treatment of PAH. The current FDA-approved labeling includes indications and usage for Veletri for the treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly individuals with NYHA Functional Class III or IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases (Veletri Product Information, 2016).
Treprostinil (Remodulin) was originally approved as a subcutaneous infusion. In 2004, the FDA approved IV use of treprostinil (Remodulin), “For those who are not able to tolerate a subcutaneous infusion for the treatment of PAH in patients with NYHA Class II, III, IV symptoms to diminish symptoms associated with exercise.” Because Remodulin also inhibits platelet aggregation, there is potential for increased risk of bleeding, particularly among individuals maintained on anticoagulants. During clinical trials, however, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatory, opioids, corticosteroids, and other medications. The current FDA-approved labeling indications and usage state:

In patients with pulmonary arterial hypertension requiring transition from Flolan (eprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition (Remodulin Product Information, 2013).

While local site reactions may be lessened by continuous IV infusion of eprostenol, this route exposes the individual to IV catheter-related complications, such as sepsis and venous thromboembolism. Due to the shorter half-life of treprostinil, when given intravenously as compared to subcutaneously, the IV route may increase the risks related to abrupt cessation in the delivery of the medication, as occurs with pump malfunction. Accordingly, Remodulin is preferably infused subcutaneously, but can be administered by a central IV line if the subcutaneous route is not tolerated, due to severe site pain or reaction. An uncontrolled study demonstrated that transition from IV eprostenol to subcutaneous Remodulin can be successfully achieved without major adverse side effects.

Iloprost (Ventavis) inhalation solution is a synthetic analogue of prostacyclin, which dilates systemic and pulmonary arterial vascular beds resulting in improvement in exercise capacity and the symptoms associated with PAH. Ventavis was FDA-approved on August 17, 2004 for, “The treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms.” According to the FDA approval information, in controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration (Olschewski, 2002). Ventavis is intended for inhalation administration only via the pulmonary drug delivery device, the I-neb® AAD® System, and has not been studied with any other nebulizers. The current FDA-approved labeling includes the following warnings and precautions:

Ventavis inhalation can induce bronchospasm. Bronchospasm may be more severe or frequent in patients with a history of hyperreactive airways. Ventavis has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections. Safety and efficacy in pediatric patients has not been established (Ventavis Product Information, 2017).

On July 30, 2009, the FDA approved another inhalation form of treprostinil, Tyvaso inhalation solution for the treatment of PAH. The current FDA-approved labeling states:

Tyvaso is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosantan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration (Tyvaso Product Information, 2017).

In an updated supplemental approval letter from the FDA regarding Tyvaso, revisions were approved for the ‘Use in Specific Populations’ section of the labeling for pregnancy to remove the language, “Tyvaso should be used during pregnancy only if clearly needed.” Additional outcomes data was provided in this 2014 letter and in another update in 2016, both regarding animal study results, and the following was also noted regarding long term results of the pivotal human trial with no change to the FDA approved labeling indications (FDA Prescribing Information for Tyvaso, 2017):

In long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (N=206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. These uncontrolled observations do not allow comparison with a control group not given Tyvaso and cannot be used to determine the long-term effect of Tyvaso on mortality (FDA, August 2014).
New York Heart Association (NYHA) Functional Classification for Heart Failure symptoms:

Class I: No limitation with ordinary physical activity;
Class II: Slight limitation with fatigue, dyspnea, palpitations, or angina resulting from ordinary physical activity;
Class III: Marked limitation; symptomatic with less than ordinary activity;
Class IV: Symptoms present while at rest.

Pulmonary arterial hypertension (PAH): A class of diseases categorized by persistently increased blood pressure in the pulmonary artery, which transports blood from the right ventricle of the heart to the lungs. This can lead to significant and potentially lethal damage to the heart, and may even require lung or heart-lung transplantation if not adequately controlled. PAH is defined by the 2009 ACCF/AHA Expert Consensus document (McLaughlin, 2009) and by updated specialty society guidelines for adults and children (ACCF/AHA Hoeper, 2013; Ivy, 2013; AHA/ATS Abman, 2015) as a:

1. mean pulmonary artery pressure (mPAP) greater than 25 mm Hg (McLaughlin, 2009) or mPAP greater than or equal to 25 mm Hg at rest (Hoeper and Ivy, 2013; Abman, 2015); and
2. pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg (all guidelines); and
3. pulmonary vascular resistance (PVR) greater than 3 Wood units (all guidelines).

Pulmonary arterial hypertension (PAH) WHO Clinical Classification System: The changes in defining and classifying pulmonary hypertension were developed by the 2009 ACCF/AHA Expert Consensus Task Force on Pulmonary Hypertension (McLaughlin, 2009). Persons in Group 1 are considered to have pulmonary arterial hypertension (PAH or idiopathic PAH/IPAH), and the remaining four groups are considered to have PH (secondary PH) (Simonneau, 2004).

Table 1. Revised WHO Classification of Pulmonary Hypertension (PH)

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
       1.3.1. Connective tissue disorder
       1.3.2. Congenital systemic-to-pulmonary shunts
       1.3.3. Portal hypertension
       1.3.4. HIV infection
       1.3.5. Drugs and toxins
          Other (thyroid disorders, glycogen storage disease, Gaucher’s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
   1.4. Associated with significant venous or capillary involvement
       1.4.1. Pulmonary veno-occlusive disease (PVOD)
       1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   1.5. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension associated with left heart diseases
   2.1. Left-sided atrial or ventricular heart disease
   2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with respiratory diseases and/or hypoxemia (including COPD)
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Sleep disordered breathing
   3.4. Alveolar hypoventilation disorders
   3.5. Chronic exposure to high altitude
   3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
   4.1. Thromboembolic obstruction of proximal pulmonary arteries
   4.2. Thromboembolic obstruction of distal pulmonary arteries
   4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis).
   
   Scleroderma: A systemic disorder of connective tissue characterized by induration and thickening of the skin, abnormalities of the blood vessels, and fibrotic degenerative changes in various body organs.

   The World Health Organization (WHO) Classification System: Is used to describe IPAH and other causes of secondary PH. IPAH is characterized by a sustained level of mPAP without apparent cause. The estimated incidence of IPAH is 1 to 2 cases per 1 million persons in the general population. During childhood, the condition affects both genders equally; after puberty, it is more common in women than men and is most prevalent in persons 20 to 40 years of age. If untreated, the median survival from time of diagnosis is less than 2.8 years. Unexplained shortness of breath and fatigue are common early symptoms; angina and syncope are seen in advanced disease stages. Secondary PH (WHO Groups 2-5) occurs as a complication of pulmonary, cardiac and extrathoracic conditions. Common causes include scleroderma and its variants (such as, the CREST syndrome), and various congenital heart defects. In individuals with secondary PH, management is directed at early recognition and treatment of the underlying disease and may also include therapy for the hypertension itself.

   World Health Organization (WHO) - functional classification for Pulmonary Arterial Hypertension:

   - **Class I:** no limitation of clinical activity; ordinary physical activity does not cause dyspnea or fatigue;
   - **Class II:** slight limitation in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest;
   - **Class III:** marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest;
   - **Class IV:** unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity (Rich, 1998).

   **References**

   **Peer Reviewed Publications:**

Lung Transplant. 2006; 25(11):1353
Government Agency, Medical Society, and Other Authoritative Publications:


17. Pohar R, Clark M, Spry C. Drugs for pulmonary arterial hypertension: a systematic review of the clinical-effectiveness of combination therapy. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

Index

Epoprostenol Sodium
Flolan
Remodulin
Iloprost
Iloprost
Veleti
Ventavis
Treprostinil
Tyvaso

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

<table>
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<th>Status</th>
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<tr>
<td>Reviewed</td>
<td>01/24/2019</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. References were updated. MPTAC review. Moved content of DRUG.00004 Prostacyclin Infusion Therapy and Inhalation Therapy for Treatment of Pulmonary Arterial Hypertension to new clinical utilization management guideline document with the same title. Revised the diagnostic criteria for adult and pediatric PAH in the Clinical Indications section, for clarification and consistency with updated specialty society guideline recommendations. The Discussion, Definitions and References sections were updated.</td>
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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member’s card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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©CPT Only - American Medical Association
This document addresses the following medications used to treat retinal vascular conditions of the eye:

I. Pegaptanib (Macugen®, Bausch & Lomb, Bridgewater, NJ)
II. Bevacizumab (Avastin®, Genentech, Inc., San Francisco, CA)
III. Ranibizumab (Lucentis®, Genentech, Inc., San Francisco, CA)
IV. Aflibercept (Eylea®, Regeneron, Tarrytown, NY)

Note: Please see the following related documents for additional information:

- [CG-DRUG-64 FDA-Approved Biosimilar Products](#)
- [CG-DRUG-68 Bevacizumab (Avastin®) for Non-Ophthalmologic Indications](#)
- [CG-DRUG-91 Intravitreal Corticosteroid Implants](#)

Note: Please refer to [CG-DRUG-64 FDA-Approved Biosimilar Products](#) for additional information on clinical criteria for review of a biosimilar product to an already FDA-approved anti-vascular endothelial growth factor agent addressed in CG-DRUG-90.

### Clinical Indications

I. Pegaptanib (Macugen)

**Medically Necessary:**

A series of intravitreal injections with pegaptanib is considered *medically necessary* as a treatment of:

A. Established neovascular "wet" age-related macular degeneration.

**Not Medically Necessary:**

The use of intravitreal pegaptanib is considered *not medically necessary* for all other conditions including, but not limited to:
A. Diabetic eye disease
B. As a treatment of other forms of age-related macular degeneration to prevent progression to neovascular “wet” age-related macular degeneration.

II. Bevacizumab (Avastin)

Medically Necessary:

A series of intravitreal injections with bevacizumab is considered medically necessary as a treatment for any of the following:

A. Diabetic macular edema; or
B. Proliferative diabetic retinopathy with or without diabetic macular edema; or
C. Established neovascular “wet” age-related macular degeneration; or
D. Macular edema from branch retinal vein occlusion; or
E. Macular edema from central retinal vein occlusion; or
F. Neovascular glaucoma; or
G. Other rare causes of choroidal neovascularization for one or more of the following conditions:
   1. angioid streaks; or
   2. choroiditis (including, but not limited to histoplasmosis induced choroiditis); or
   3. degenerative myopia (idiopathic); or
   4. retinal dystrophies; or
   5. trauma; or
H. Pseudoxanthoma elasticum; or
I. Radiation retinopathy; or
J. Retinopathy of prematurity.

Not Medically Necessary:

The use of intravitreal bevacizumab is considered not medically necessary for any other condition not listed above as medically necessary.

III. Ranibizumab (Lucentis)

Medically Necessary:

A series of intravitreal injections with ranibizumab is considered medically necessary as a treatment for any of the following:

A. Choroidal neovascularization associated with myopic degeneration; or
B. Diabetic macular edema; or
C. Proliferative diabetic retinopathy with or without diabetic macular edema; or
D. Established neovascular “wet” age-related macular degeneration; or
E. Macular edema from branch retinal vein occlusion; or
F. Macular edema from central retinal vein occlusion; or
G. Radiation retinopathy.

Not Medically Necessary:

The use of intravitreal ranibizumab is considered not medically necessary for any other condition not listed above as medically necessary.

IV. Aflibercept (Eylea)

Medically Necessary:
A series of intravitreal injections with aflibercept is considered **medically necessary** as a treatment for **any** of the following:

A. Diabetic macular edema; or  
B. Proliferative diabetic retinopathy with or without diabetic macular edema; or  
C. Established neovascular "wet" age-related macular degeneration; or  
D. Macular edema from branch retinal vein occlusion; or  
E. Macular edema from central retinal vein occlusion; or  
F. Radiation retinopathy.

**Not Medically Necessary:**

The use of intravitreal aflibercept is considered **not medically necessary** for any other condition not listed above as medically necessary.

**Clinically Equivalent Cost Effective Agents**

Note: When anti-vascular endothelial growth factor is determined to be medically necessary based on the clinical criteria above, the benefit plan may have in addition a medically necessary criterion that the treatment be cost effective.

A benefit plan may select any one or more of the following as clinically equivalent cost effective anti-vascular endothelial growth factor agents: Pegaptanib (Macugen), Bevacizumab (Avastin), Ranibizumab (Lucentis), Aflibercept (Eylea). A list of one or more cost effective anti-vascular endothelial growth factor agents for each plan is available [here](#).

In benefit plans where there is a requirement to use a cost effective anti-vascular endothelial growth factor agent, requests for an anti-vascular endothelial growth factor agent that is not cost effective may be approved when the following criteria are met:

A. The individual has had a trial of and is intolerant to one cost effective agent; or  
B. For the prescribed indication, the cost effective agent(s) is/are not FDA-approved or does not meet the off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use (see below); or  
C. The prescribed indication is neovascular age-related macular degeneration and Pegaptanib (Macugen) is the sole cost effective anti-vascular endothelial growth factor agent selected by a benefit plan.

**FDA-approved Indications or Indications Meeting off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pegaptanib (Macugen)</th>
<th>Bevacizumab (Avastin)</th>
<th>Ranibizumab (Lucentis)</th>
<th>Aflibercept (Eylea)</th>
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<tr>
<td>Diabetic macular edema</td>
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<td>X</td>
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<tr>
<td>Macular edema following retinal vein occlusion</td>
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<tr>
<td>Myopic choroidal neovascularization</td>
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<td>Y</td>
<td></td>
<td>X</td>
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<tr>
<td>Neovascular age-related macular degeneration</td>
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<td>Neovascular glaucoma</td>
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<td></td>
<td>Y</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td></td>
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</tr>
</tbody>
</table>

X = FDA-approved Indications (excluding cosmetic indications)  
Y = Indications Meeting off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use
The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

I. Intravitreal injections of pegaptanib [Macugen]

CPT
67028  Intravitreal injection of a pharmacologic agent [when specified as intravitreal injection of pegaptanib, in conjunction with the HCPCS code listed below]

HCPCS
J2503  Injection, pegaptanib sodium, 0.3 mg [Macugen]

ICD-10 Diagnosis
H35.3210-H35.3293  Exudative age-related macular degeneration

II. Intravitreal injections of bevacizumab [Avastin]

CPT
67028  Intravitreal injection of a pharmacologic agent [when specified as intravitreal injection of bevacizumab, in conjunction with the HCPCS code(s) listed below]

HCPCS
C9257  Injection, bevacizumab, 0.25 mg [Avastin]
J3490  Unclassified drugs [when specified as Avastin intravitreal or biosimilar bevacizumab-awwb (Mvasi) intravitreal]
J3590  Unclassified biologics [when specified as Avastin intravitreal or biosimilar bevacizumab-awwb (Mvasi) intravitreal]
J9035  Injection, bevacizumab, 10 mg [when specified as Avastin intravitreal]
Q5107  Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg

ICD-10 Diagnosis
B39.0-B39.9  Histoplasmosis
E08.311-E08.3519  Diabetes mellitus due to underlying condition with diabetic retinopathy with macular edema [includes only codes E08.311 and ranges E08.3211-E08.3219, E08.3311-E08.3319, E08.3411-E08.3419, E08.3511-E08.3519, and E08.3519 when specified as proliferative diabetic retinopathy]
E08.3521-E08.3599  Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy [without macular edema]
E09.311-E09.3519  Drug or chemical induced diabetes mellitus with diabetic retinopathy with macular edema [includes only codes E09.311 and ranges E09.3211-E09.3219, E09.3311-E09.3319, E09.3411-E09.3419, E09.3511-E09.3519, and E09.3519 when specified as proliferative diabetic retinopathy]
E09.3521-E09.3599  Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy [without macular edema]
E10.311-E10.3519  Type 1 diabetes mellitus with diabetic retinopathy with macular edema [includes only codes E10.311 and ranges E10.3211-E10.3219, E10.3311-E10.3319, E10.3411-E10.3419, E10.3511-E10.3519, and E10.3519 when specified as proliferative diabetic retinopathy]
E10.3521-E10.3599  Type 1 diabetes mellitus with proliferative diabetic retinopathy [without macular edema]
E11.3521-E11.3599  Type 2 diabetes mellitus with proliferative diabetic retinopathy [without macular edema]

Other specified diabetes mellitus with proliferative diabetic retinopathy [without macular edema]

Other vascular disorders of iris and ciliary body (neovascularization)

Other specified diabetes mellitus with proliferative diabetic retinopathy [without macular edema]

Chorioretinal disorders in diseases classified elsewhere

Central retinal vein occlusion, right eye, with macular edema

Central retinal vein occlusion, left eye, with macular edema

Central retinal vein occlusion, bilateral, with macular edema

Central retinal vein occlusion, unspecified eye, with macular edema

Tributary (branch) retinal vein occlusion, right eye, with macular edema

Tributary (branch) retinal vein occlusion, left eye, with macular edema

Tributary (branch) retinal vein occlusion, bilateral, with macular edema

Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema

Background retinopathy and retinal vascular changes

Retinopathy of prematurity

Exudative age-related macular degeneration

Angioid streaks of macula

Hereditary retinal dystrophy

Unspecified retinal disorder [specified as radiation retinopathy]

Glucoma secondary to other eye disorders [neovascular glaucoma]

Other specified glaucoma [neovascular glaucoma]

Degenerative myopia

Degenerative myopia with choroidal neovascularization

Other specified congenital malformations of skin [pseudoxanthoma elasticum]

Radiation sickness, unspecified [specified as radiation retinopathy]

III. Intravitreal injections of ranibizumab [Lucentis]

CPT

67028 Intravitreal injection of a pharmacologic agent [when specified as intravitreal injection of ranibizumab, in conjunction with the HCPCS code listed below]

HCPCS

J2778 Injection, ranibizumab; 0.1 mg [Lucentis]

ICD-10 Diagnosis

Diabetes mellitus due to underlying condition with diabetic retinopathy with macular edema [includes only codes E08.311 and ranges E08.3211-E08.3219, E08.3311-E08.3319, E08.3411-E08.3419, E08.3511-E08.3519, and E08.319 when specified as proliferative diabetic retinopathy]

Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy [without macular edema]

Drug or chemical induced diabetes mellitus with diabetic retinopathy with macular edema [includes only codes E09.311 and ranges E09.3211-E09.3219, E09.3311-E09.3319, E09.3411-E09.3419, E09.3511-E09.3519, and E09.319 when specified as proliferative diabetic retinopathy]

Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy [without macular edema]

Type 1 diabetes mellitus with diabetic retinopathy with macular edema [includes only codes E10.311 and ranges E10.3211-E10.3219, E10.3311-E10.3319, E10.3411-E10.3419, E10.3511-E10.3519, and E10.319 when specified as proliferative diabetic retinopathy]

Type 2 diabetes mellitus with proliferative diabetic retinopathy [without macular edema]


Other specified diabetes mellitus with proliferative diabetic retinopathy [without macular edema]

Other vascular disorders of iris and ciliary body (neovascularization)

Central retinal vein occlusion, right eye, with macular edema

Central retinal vein occlusion, left eye, with macular edema

Central retinal vein occlusion, bilateral, with macular edema

Central retinal vein occlusion, unspecified eye, with macular edema

Tributary (branch) retinal vein occlusion, right eye, with macular edema

Tributary (branch) retinal vein occlusion, left eye, with macular edema

Tributary (branch) retinal vein occlusion, bilateral, with macular edema

Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema

Exudative age-related macular degeneration

Unspecified retinal disorder [specified as radiation retinopathy]

Degenerative myopia

Degenerative myopia with choroidal neovascularization

Radiation sickness, unspecified [specified as radiation retinopathy]

Intravitreal injection of aflibercept [Eylea]

Intravitreal injection of a pharmacologic agent [when specified as intravitreal injection of aflibercept]

Injection, aflibercept, 1 mg [Eylea]

Diabetes mellitus due to underlying condition with diabetic retinopathy with macular edema [includes only codes E08.311 and ranges E08.3211-E08.3219, E08.3311-E08.3319, E08.3411-E08.3419, E08.3511-E08.3519, and E08.319 when specified as proliferative diabetic retinopathy]

Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy [without macular edema]

Drug or chemical induced diabetes mellitus with diabetic retinopathy with macular edema [includes only codes E09.311 and ranges E09.3211-E09.3219, E09.3311-E09.3319, E09.3411-E09.3419, E09.3511-E09.3519, and E09.319 when specified as proliferative diabetic retinopathy]

Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy [without macular edema]

Type 1 diabetes mellitus with diabetic retinopathy with macular edema [includes only codes E10.311 and ranges E10.3211-E10.3219, E10.3311-E10.3319, E10.3411-E10.3419, E10.3511-E10.3519, and E10.319 when specified as proliferative diabetic retinopathy]

Type 1 diabetes mellitus with proliferative diabetic retinopathy [without macular edema]


Type 2 diabetes mellitus with proliferative diabetic retinopathy [without macular edema]

Age-related macular degeneration (AMD) is an eye disease characterized by progressive degeneration of the macula, the central part of the retina at the back of the eye. When this is caused by the development of abnormal blood vessels develop behind the retina, the condition is commonly referred to as "wet" or neovascular AMD. These new blood vessels tend to be fragile and leak blood and fluid. The blood and fluid raise the macula from its normal position at the back of the eye. With wet AMD, loss of central vision can occur quickly. AMD is the leading cause of severe vision loss in people over 55 years of age in the developed world. The neovascular "wet" form of this disease represents 10% of the overall disease prevalence but is responsible for roughly 90% of the vision loss due to AMD. It is more common in Caucasians and its incidence increases with age as it is estimated that 10 to 15% of individuals older than 80 years have some form of AMD.

Vascular endothelial growth factor (VEGF), a cytokine, appears to have a key role in the angiogenesis and vascular permeability associated with wet AMD. Overexpression of VEGF is also thought to contribute to diabetic retinopathy, and other retinal disorders associated with neovascularization. Research focused on development of compounds designed to bind to and inhibit VEGF can be an effective treatment for AMD.

Retinal vein occlusion occurs when there is a blockage of the blood supply from the retina. Depending on where the blockage occurs, the condition can be characterized as central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO). This condition most often affects older individuals and can be caused by a blood clot, diabetes, glaucoma, atherosclerosis or hypertension. Symptoms include sudden blurred vision or loss of vision. Retinal vein occlusion is the second most common type of retinal vascular disease and is estimated to involve 180,000 eyes per year.

The macula is the part of the eye where sharp, straight-ahead vision occurs. Fluid can leak into the center of the macula, causing the macula to swell, resulting in blurred vision. Common in diabetics, this is known as diabetic macular edema (DME).

Infants born before 31 weeks gestation are at risk for retinopathy of prematurity, the development of abnormal retinal fibrovascular tissue and blindness. With appropriate screening and treatment, the incidence of blindness in infants due to retinopathy of prematurity is relatively low (approximately 1 case in 820 infants).

Intraocular injections pose a risk for infection, retinal detachment and traumatic lens injury. These injections require the treating physician to adhere to appropriate aseptic technique, educate individuals regarding worrisome symptoms and monitor individuals after each injection as increases in intraocular pressure have been seen.

I. Pegaptanib (Macugen)

Neovascular (wet) Age-Related Macular Degeneration (AMD)
In 2004, the United States Food and Drug Administration (FDA) approved pegaptanib for the treatment of neovascular (wet) AMD. Two concurrent, prospective randomized, double blind controlled clinical trials were used as the basis of approval from the FDA (VEGF [vascular endothelial growth factor] Inhibition Study in Ocular Neovascularization [VISION] Clinical Trial Group, 2006a, VISION Clinical Trial Group, 2006b). The populations of
these studies included all forms of wet AMD. While on average, both treated and control groups continued to experience vision loss, the rate of vision decline in the treated group was slower than that in the control group.

Since that time, research has continued to be reported on the use of pegaptanib for neovascular AMD. Friberg and colleagues (2010) reported on a prospective, phase IV, open-label, uncontrolled study for the use of pegaptanib as maintenance therapy for neovascular AMD after induction therapy. Pegaptanib was given every 6 weeks for 48 weeks with follow-up to week 54. A total of 568 participants were enrolled and 487 participants completed the 54-week study. Mean visual acuity improved during the induction from 49.6 letters to 65.5 letters and was 61.8 letters at week 54. Pegaptanib was well tolerated with a total of 468 participants reporting one or more adverse events, 350 participants experienced an ocular adverse event and 112 participants had one or more serious adverse events. The authors conclude that this maintenance therapy may be a viable option for those individuals who respond initially to induction therapy.

There is little published data about the long-term use of intravitreal pegaptanib. In a 2015 study by Inoue and colleagues, the authors reported on the results of a 3-year follow-up of pegaptanib given as maintenance treatment for neovascular AMD. Sixteen of 20 eyes were available for follow-up after 3 years. Best corrected visual acuity improved from 0.56 ± 0.31 before treatment to 0.24 ± 0.25 at baseline and was 0.25 ± 0.28 at 156 weeks. Central foveal thickness was also assessed and found to have decreased. No severe side effects were reported during follow-up. Studies with larger group sizes are necessary to continue to assess long-term use.

Diabetic Macular Edema (DME)
In 2011, Sultan and colleagues reported on a randomized, double-masked, 2-year trial of pegaptanib, as an off-label use, for DME. A total of 288 participants were enrolled to receive intravitreal pegaptanib (n=145) or sham injections (n=143). Sham injections weren’t injections but rather a dynamic minimization procedure of an empty barrel of a needleless syringe designed to mimic the intravitreal injection. A total of 230 participants completed 54 weeks of treatment and 207 participants completed 2 years of treatment. During year 1, injections were administered every 6 weeks for a total of nine injections. Treatment effect was assessed 6 weeks after each injection. After 18 weeks, participants could receive laser photocoagulation (of which 84 participants did). Participants were still evaluated every 6 weeks during year 2 to determine if a medication injection was required. Forty-nine (49) participants in the pegaptanib group and 25 participants in the sham group reported a visual acuity improvement of greater than 10 letters at week 54. While this study does suggest the potential benefit of pegaptanib for DME, the study did not compare pegaptanib to other available VEGF inhibitors or support the conclusion that pegaptanib is as good as or better than the current standard of care for DME.

Other literature for Macugen for DME includes retrospective analyses (Querques, 2009a; Querques, 2009b) and small group sizes (Rinaldi, 2013). Insufficient data is available for the use in other ophthalmologic processes such as diabetic retinopathy (Dahr, 2007; Krzystolik, 2006; Gonzalez, 2009).

II. Bevacizumab (Avastin)
Neovascular (wet) AMD
Bevacizumab, which was initially approved by the FDA in 2004 for the treatment of metastatic colon cancer, is a monoclonal antibody that binds to VEGF. Intravitreal usage of bevacizumab is a non-FDA approved use which has been widely reported by practicing ophthalmologists to be beneficial in select individuals with neovascular AMD.

Arevalo and colleagues (2010) report the results of a 24-month study in which 180 subjects received at least one injection of intravitreal bevacizumab for subfoveal choroidal neovascularization (CNV) secondary to AMD. Individuals received best-corrected visual acuity testing, ophthalmoscopic exam, optical coherence tomography and fluorescein angiography at baseline and at 1, 3, 6, 12, and 24 months thereafter. Systemic adverse events included elevated blood pressure, cerebrovascular accidents, myocardial infarctions, iliac artery aneurysms, toe amputations and death. Ocular complaints included bacterial endophthalmitis, tractional retinal detachments, uveitis and rhegmatogenous retinal detachment and vitreous hemorrhage. At 24 months, all individuals showed stability or improvement in best-corrected visual acuity, optical coherence tomography and fluorescein angiography.

Tufail et al (2010) randomized 131 subjects to either intervention with intravitreal bevacizumab or standard treatment of photodynamic treatment with verteporfin, pegaptanib or sham control for AMD with 54-week follow-up. In the bevacizumab group, more letters were gained from baseline when compared to the standard treatment group.
**Diabetic Retinopathy**

In a 2015 study by Manabe and colleagues, the authors investigated the use of bevacizumab for proliferative diabetic retinopathy prior to surgery. A total of 66 eyes of 62 participants were randomized to either intravitreal bevacizumab (n=34 eyes) or sham control group (n=32). Following surgery (within 4 weeks), the frequency of reoperation was 20.6% (7/34 eyes) in the sham group and 3.1% (1/32 eyes) in the bevacizumab group; recurrent vitreous hemorrhage occurred in 23.5% (8/34 eyes) in the sham group and 3.1% (1/32 eyes) in the bevacizumab group. At 1 month following surgery, best-corrected visual acuity improved in both the bevacizumab and sham groups, however the visual improvement did not differ significantly between the two groups. While this study has limitations including a short observation period and multiple surgeons performing the surgery, injection of bevacizumab for proliferative diabetic retinopathy decreased the incidence of reoperation due to early postoperative vitreous hemorrhage.

In a Cochrane review (Smith, 2015) the authors reported on the use of bevacizumab prior to having vitrectomy for proliferative diabetic retinopathy to avoid postoperative vitrectomy cavity hemorrhage. After review of 12 randomized controlled trials with a total of 654 eyes, the authors concluded that the participants who received bevacizumab in addition to pars plana vitrectomy were less likely to have postoperative vitrectomy cavity hemorrhage when compared to pars plana vitrectomy alone. However, the effect of pre- or intraoperative bevacizumab on the incidence of late postoperative hemorrhage was uncertain. Several of the included studies were unclear when describing the randomization methods. Due to significant study heterogeneity, the authors were unable to give an estimate of the effect of bevacizumab on postoperative visual acuity.

**DME and Retinal Vein Occlusion**

Since ranibizumab is derived from the same parent molecule as the full-length humanized anti-VEGF antibody bevacizumab, specialty consensus suggests that bevacizumab may be appropriate for the same disorders as ranibizumab including branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and DME. Intravitreal bevacizumab has also been suggested for CRVO (Costa, 2007; Mohamed, 2007; Moschos, 2008; Rosenfeld, 2005), BRVO (Ahmadi, 2009; Gunduz, 2008; Kreutzer, 2008; Rensch, 2009) and DME (Arevalo, 2007; Arevalo, 2009; Haritoglou, 2008).

Soehillian (2012) reported on the 24-month findings of a trial comparing bevacizumab monotherapy to bevacizumab with intravitreal triamcinolone acetonide versus photoacoagulation as a treatment for DME. A total of 150 eyes were included in the study. The eyes were randomly assigned to 1 of 3 study arms: the bevacizumab group, the bevacizumab/triamcinolone acetonide group, or the photocoagulation group. At the end of the 24-month study period, 39 eyes remained in the bevacizumab group, 36 eyes remained in the bevacizumab/triamcinolone acetonide group, and 38 eyes remained in the photocoagulation group. Whenever indicated, retreatment was performed at 3-month intervals. The bevacizumab group had 39 eyes which required retreatment, 27 eyes in the bevacizumab/triamcinolone acetonide group required retreatment, and 31 eyes in the photocoagulation group required retreatment. The visual acuity improved the most in the bevacizumab group at month 6, but did not sustain up to 24 months and the difference between the groups was not significant at all visits. But the mean visual acuity was greater in the bevacizumab group compared to the other groups and in the bevacizumab/triamcinolone acetonide group compared to the photocoagulation group.

**Neovascular Glaucoma**

Neovascular glaucoma is a severe form of glaucoma caused by the growth of new blood vessels which obstruct aqueous humor outflow. This causes an increase in intraocular pressure (IOP). In a study by Costagliola (2008), 23 individuals were scheduled to receive intravitreal injections of bevacizumab at 4 week intervals. At the end of the scheduled protocol (three injections of intravitreal bevacizumab), IOP was reduced, and visual acuity, pain and edema were significantly improved.

**CNV**

There are rare causes of CNV (degenerative myopia [idiopathic], angiod streaks, trauma, choroiditis, retinal dystrophies, and ocular histoplasmosis) for which there are no approved therapies. There is an unmet medical need for treatment and the extremely low incidence of disease will make comparative treatment trials challenging. There is strong biologic plausibility from small case series that intravitreal bevacizumab may be of benefit (Chan, 2007b; 2008b). Specialty consensus opinion also suggests that the drug may be used for these rare disorders due to the lack of other available treatment. A retrospective case series by Cionni and colleagues (2012) reported on the long-term outcomes of intravitreal bevacizumab for the treatment of CNV due to presumed ocular histoplasmosis. A total of 117 eyes received intravitreal bevacizumab and 34 eyes received a combination of intravitreal bevacizumab and photodynamic therapy. The mean follow-up was 21.1 months. Visual acuity was measured at baseline, 12 months and 24 months. There was no significant difference in the number of eyes with a 3-line gain between the bevacizumab group and the bevacizumab and photodynamic therapy groups. The number of participants with a gain
of 3 or more lines of vision was 39/104 eyes. At 1 year, 84/104 eyes showed maintained or improved visual acuity. At 2 years, 17/57 eyes continued to maintain a 3-line gain in visual acuity.

Radiation Retinopathy
Radiation retinopathy occurs following irradiation for tumors or inflammation of the choroid, retina, orbit, and paranasal sinuses. It is a rare and progressive disease resulting in loss of vision. It has been treated with laser photocoagulation. The anti-VEGF drugs have been studied to treat this condition. In a study by Finger and colleagues (2008a), 21 participants with radiation retinopathy received intravitreal bevacizumab every 6-12 weeks. In 18 of the participants, visual acuity was stable or improved. Three participants regained two or more lines of visual acuity. No adverse effects were reported. Although this is a small group size with a short-term follow-up, the condition is rare enough that no real case-control or randomized studies can be effectively carried out and no other effective therapy can be used.

A study by Finger (2016) reviewed the charts of 120 individuals who received intravitreal anti-VEGF therapy for radiation maculopathy. A total of 99 participants were available for analysis for measuring visual acuity and central foveal thickness. There was a mean treatment interval of 38 months with a mean observation period of 6.75 years. A total of 20 participants lost three or more lines of visual acuity (measured by Early Treatment Diabetic Retinopathy Study [ETDRS] Charts). Before beginning anti-VEGF treatment, 69 participants had visual acuity better than or equal to 20/40 and 99 participants had visual acuity better than or equal to 20/200. Following the last treatment, 65 participants had visual acuity better than or equal to 20/40 and 96 participants had acuity better than or equal to 20/200. Central foveal thickness was measured using optical coherence tomography. There were 63 participants with initial central foveal thickness values available. At the 3-month interval, 15/63 had thickness which was within 10 μm of baseline, 39 participants had improved thickness. There were no treatment-related retinal detachments or vitreous hemorrhages reported. The study limitations include increasing technology/techniques over the 10-year time span and the retrospective, uncontrolled study design.

Retinopathy of Prematurity
Retinopathy of prematurity is a leading cause of childhood blindness throughout the world. For neonates, it is believed that exposure to high levels of oxygen obliterates the vessels in the retina. Current treatment is peripheral retinal ablation with laser therapy which is destructive (that is, the laser destroys the majority of cells that produce VEGF in the retina), has complications and does not prevent all vision loss. Bevacizumab is an emerging treatment for retinopathy of prematurity. There have been several small case series studies which have shown improvement in retinopathy of prematurity after use of intravitreal bevacizumab (Ahmed, 2010; Erol, 2010; Wu, 2011). Mintz-Hittner and colleagues (2011) reported on a controlled (but not masked) study of 150 infants with retinopathy of prematurity who were randomized to receive either intravitreal bevacizumab or conventional laser therapy. The primary outcome was whether retinopathy of prematurity recurred in the eyes and required re-treatment using bevacizumab before 54 weeks postmenstrual age. In infants with zone I retinopathy of prematurity, 94% had no evidence of recurrence compared to 58% of the infants treated with conventional laser therapy. In addition, there were more structural complications (need for vitrectomy, detachment, macular dragging) in the infants treated with laser therapy. The authors concluded that:

Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina.

The limited number of infants studied makes it difficult to draw conclusions regarding the safety of this treatment. The authors noted that the “study was too small to address the question of whether intravitreal bevacizumab is safe” and that additional research is necessary. However, the primary alternative treatment is also not without risk. Laser photocoagulation requires intubating, sedating, and immobilizing the child and may permanently destroy the peripheral retina. The available scientific literature suggests that intravitreal bevacizumab for retinopathy of prematurity improves net health outcomes and is at least as beneficial as the established alternatives at this time. Martínez-Castellanos and colleagues (2013) reported on 18 eyes of 13 children with retinopathy of prematurity who received intravitreal bevacizumab. Follow-up was 5 years. During that time, all of the children showed initial regression of neovascularization and visual acuity was preserved. Although 1 child showed delay in growth and neurodevelopment, the others were all within the normal range. The results are suggestive that intravitreal bevacizumab for retinopathy of prematurity preserves ocular function and development.

Other Retinal Conditions
There are other rare eye disorders in which bevacizumab is being used. Coats’ disease is a very rare disorder in
which there is an abnormal development of blood vessels behind the retina. The retinal capillaries break open, leaking the serum portion of blood into the back of the eye. This causes the retina to swell and can cause retinal detachment. The most common treatments for Coats’ disease are laser photoagulation and cryotherapy. Wang and colleagues (2011) reported on 3 individuals with Coats’ disease who received a treatment of bevacizumab combined with laser photoagulation. Fundus photography and fluorescein angiography showed regression of the vascular dilatation and the aneurismal appearance of the telangiectasia areas. Optical coherence tomography showed a decrease of the macular edema and fluid. Visual improvement was noted. Ramasubramanian and colleagues (2012) reported a retrospective analysis of 8 individuals with Coats’ disease who had received laser photoagulation and/or cryotherapy and bevacizumab injections. After a mean follow-up of 8.5 months, retinopathy resolved in all 8 individuals, Coats’-related subretinal fluid resolved in all 8 individuals and retinal exudation resolved in 6 individuals. This was not without side effects. Four individuals developed vitreous fibrosis following the bevacizumab injections, and 3 individuals then progressed on to traction retinal detachment. The authors concluded that “Caution is advised in the use of bevacizumab for patients with Coats’ disease.” A retrospective review by Ray and colleagues (2013) reported on the use of bevacizumab plus ablative therapy versus the use of ablative therapy alone. Ten children with Coats’ disease received intravitreal bevacizumab and were compared to 10 children who received ablative therapy. In the bevacizumab group, the eyes required more treatments over a longer period of time compared to the ablative group, but all the children were successfully treated. In the ablative group, 2 of the children failed ablative therapy. The authors state that while bevacizumab may play a role in the treatment of Coats’ disease, there is no decrease in the time it takes to reach full treatment.

III. Ranibizumab (Lucentis)

Neovascular (wet) AMD

On June 30, 2006, the FDA approved ranibizumab for the treatment of individuals with neovascular “wet” AMD. The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study was a 2-year, double-blind, sham-controlled study in which 716 randomly assigned individuals with AMD received either monthly intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) or sham injections for 24 months (Boyer, 2007; Rosenfeld, 2006). Results were reported at 12 months and 24 months. At 12 months, 94.5% of the 0.3 mg dose group and 94.6% of the 0.5 mg dose group lost fewer than 15 letters, as compared with 62.2% of individuals receiving sham injections. Visual acuity improved by 15 or more letters in 24.8% of the 0.3 mg dose group and 33.8% of the 0.5 mg dose group, as compared with 5.0% of the sham-injection group. Mean increases in visual acuity were 6.5 letters in the 0.3 mg group and 7.2 letters in the 0.5 mg group, as compared with a decrease of 10.4 letters in the sham-injection group. The benefit in visual acuity was maintained at 24 months. During 24 months, presumed endophthalmitis was identified in 5 individuals (1.0%) and serious uveitis in 6 individuals (1.3%) given ranibizumab. A subgroup analysis compared efficacy outcomes across subgroups based on individuals’ gender, age, baseline visual acuity score, baseline CNV lesion size, CNV lesion type, and duration of neovascular AMD (Boyer, 2007). Ranibizumab treatment was associated with an average increase from baseline visual acuity in all subgroups evaluated and was superior to sham treatment across all subgroups. Predictors of visual acuity outcomes were, in decreasing order of importance, baseline visual acuity score, CNV lesion size, and age.

The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) Study is a 2-year, multicenter, double-blind study, in which 423 individuals with AMD were randomly assigned to monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) plus sham verteporfin therapy or monthly sham injections plus active verteporfin therapy (Brown, 2006). The primary end point was the proportion of individuals losing fewer than 15 letters from baseline visual acuity at 12 months. Of the 423 individuals enrolled, 94.3% of those given 0.3 mg of ranibizumab and 96.4% of those given 0.5 mg lost fewer than 15 letters, as compared with 64.3% of those in the verteporfin group (p<0.001 for each comparison). Follow-up is continued through 2 years of treatment (Brown, 2009). Of the 423 individuals who started the study, at least 77% in each group have completed the 2-year study. Consistent with the results measured at month 12, at month 24 the visual acuity benefit from ranibizumab therapy showed 89.9% to 90% had lost less than 15 letters from baseline versus 65.7% of individuals treated with verteporfin therapy.

In 2011, the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group reported on a comparison between ranibizumab and bevacizumab for the treatment of neovascular AMD. Using a single-blind, noninferiority study, 1208 individuals were randomized to receive either intravitreal injections of ranibizumab or bevacizumab monthly or as needed. The primary outcome was the change in mean visual acuity at 1 year when compared to baseline. Visual acuity improved from baseline to 1 year when the drugs were given monthly and when the drugs were given as needed. The results were inconclusive when bevacizumab was given as needed when compared to bevacizumab given monthly. Results were also inconclusive when bevacizumab was given as needed when compared to ranibizumab given monthly.
The CATT Research Group (2012) has published their 2-year results for ranibizumab and bevacizumab for treatment of neovascular AMD. The year 2 of CATT was done to describe the longer-term effects of the original four treatment groups and to describe the impact of switching from monthly to as-needed treatment after a year of monthly treatment. Primary outcome measure was mean change in visual acuity. After 2 years, there were 1030 individuals still available for visual acuity score assessment. Most of the mean visual acuity changes occurred during year 1 with little change during year 2. At 2 years, the mean increase in letters of visual acuity was 8.8 in the group who received ranibizumab monthly, 7.8 in the group who received bevacizumab monthly, 6.7 in the group who received ranibizumab as-needed, and 5.0 in the group who received bevacizumab as-needed. For both ranibizumab and bevacizumab, the mean change in visual acuity at 2 years was similar in the as-needed group to the group which switched from monthly to as-needed treatment.

CVN
CVN is a complication of different diseases which affect the posterior segment of the eye. It has the potential to cause blindness. This loss of vision is usually caused by hemorrhage, leakage and fibrosis. Other than AMD, pathological myopia is the most common condition associated with CVN. In a 2014 randomized study by Wolf and colleagues, the authors reported on 277 participants with myopic CNV who received ranibizumab or photodynamic therapy. There were three treatment arms; group I included 106 participants who received ranibizumab once and then thereafter as needed based on visual acuity, group II included 116 participants who received ranibizumab once and then as needed based on disease activity criteria, group III included 55 participants who received photodynamic therapy once and disease activity treated with ranibizumab or photodynamic therapy only at investigators’ discretion from month 18.

In August 2012, the FDA approved ranibizumab for DME. Current treatment for DME includes laser photocoagulation, intravitreal triamcinolone acetonide and pars plana vitrectomy. Triamcinolone acetonide and pars plana vitrectomy have limited efficacy and significant side effects. A 2012 article by Nguyen and colleagues reports on the safety and efficacy of intravitreal ranibizumab in individuals with DME. The article discussed two parallel, phase III, double-masked, sham-injection-controlled, randomized design studies. The primary outcome was the proportion of individuals who gained greater than or equal to 15 letters of visual acuity from baseline at 24 months. In the Ranibizumab Injection in Subjects with clinically significant macular edema with center involvement Secondary to diabetes mellitus (RISE) portion of the study, 377 participants were randomized to one of three arms; 127 to sham injections, 125 to 0.3 mg injection of ranibizumab, and 125 to 0.5 mg injection of ranibizumab. The second study was Ranibizumab Injection in subjects with clinically significant macular edema with center involvement secondary to Diabetes mellitus (RIDE) and consisted of 382 participants who were randomized to sham injection (n=130), 0.3 mg ranibizumab injection (n=125) and 0.5 mg ranibizumab injection (n=127). For the RISE portion, at 24 months, 44.8% of participants who received 0.3 mg injection of ranibizumab and 39.2% of participants who received 0.5 mg injection of ranibizumab gained greater than or equal to 15 letters compared to 18.1% of individuals who received sham injections. In the RID portion, corresponding proportions were 33.6%, 45.7% and 12.3%, respectively. Vision changes were observed as early as 7 days after the first injection of ranibizumab. All of the 759 participants from both trials had diabetic retinopathy with DME.

In a phase IIIb prospective study by Pearce and colleagues (2015), the authors evaluated the use of ranibizumab in 109 participants with DME. In this study, the participants received an initial three monthly injections of ranibizumab and then had subsequent bi-monthly follow-up from months 6-18 based on the results of best-corrected visual acuity and optical coherence tomography. A total of 100 participants completed the 12-month portion of the study and 99 participants completed 18 months. At baseline, the best-corrected visual acuity was 62.9 letters. The mean change in best-corrected visual acuity from baseline to month 6 was +6.6 letters (95% confidence interval [CI], 4.9-8.3). The mean change in best-corrected visual acuity at 12 months following bi-monthly treatment of ranibizumab was +4.8 letters (95% CI, 2.9-6.7; p<0.001). At 18 months, best-corrected visual acuity was +6.5 letters (95% CI, 4.2-8.8). At month 12, 24.8% of participants gained ≥ 10 letters and 13.8% of participants gained ≥ 15 letters. At month 18, 34.9% gained ≥ 10 letters and 19.3% gained ≥ 15 letters.

In February 2015, the FDA expanded their indications for ranibizumab to include diabetic retinopathy in individuals with DME. According to the FDA labeling, the safety and efficacy of the expanded indication was supported by the RISE and RIDE trials.

Diabetic Retinopathy and Radiation Retinopathy
As noted above, ranibizumab is derived from the same parent molecule as the full-length humanized anti-VEGF
antibody bevacizumab which suggests that bevacizumab may be appropriate for the same disorders as ranibizumab. The studies by Finger, 2008 and Finger, 2016 are summarized above. The Manabe, 2015 study is summarized above.

In a study published by the Writing Committee for the Diabetic Retinopathy Clinical Research Network in 2015, the authors reported on a randomized trial comparing ranibizumab to panretinal photocoagulation in 305 participants with proliferative diabetic retinopathy. A total of 203 eyes received panretinal photocoagulation and 191 eyes received intravitreal ranibizumab. Panretinal photocoagulation was completed in one to three visits. Participants received ranibizumab at baseline and every 4 weeks through 12 weeks. After 12 weeks re-treatment was determined based on investigator assessment of neovascularization. Of the participants in the panretinal photocoagulation group, there were 72 eyes that received ranibizumab at baseline and an additional 36 eyes that received ranibizumab during the subsequent 2 years. At the 2-year follow-up, the mean visual acuity letter score improvement in the ranibizumab group was +2.8 and +0.2 in the panretinal photocoagulation group. There were no significant differences in adverse events reported between the two groups.

Retinal Vein Occlusion
The use of ranibizumab has been suggested for the treatment of retinal vein occlusion and in June 2010, the FDA approved ranibizumab for macular edema following retinal vein occlusion. The Diabetic Retinopathy Clinical Research Network (Elman, 2010) reports on 1-year and 2-year data for ranibizumab for DME. In this phase III study, a total of 854 study eyes were randomized to one of four treatment arms: sham injection plus prompt laser, ranibizumab plus prompt laser, ranibizumab plus deferred laser, or triamcinolone plus prompt laser. Approximately half of the eyes treated with ranibizumab had a greater than 10-letter gain from baseline and approximately 30% gained greater than 15 letters (equivalent to three lines on the eye chart). For the eyes treated with ranibizumab plus laser, the results were similar whether the laser was prompt or delayed. Additional studies are reporting outcomes data on the use of ranibizumab for DME (Nguyen, 2010).

In 2010, Massin et al, reports the Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study). Individuals (n=151) with DME were randomized to receive intravitreal ranibizumab or sham. At 12 months, the ranibizumab group had an improvement of 7.8 letters compared with -0.1 letters in the sham group. Best-corrected visual acuity in the ranibizumab group improved by 10.3 letters from baseline compared to a decline of 1.4 letters from baseline in the sham group. While this study suggests ranibizumab is effective in improving best-corrected visual acuity for those with DME, further clinical trials are necessary to confirm long-term safety and efficacy.

Campochiaro and colleagues (2010) reported on the 6-month results of a phase III study assessing the safety and efficacy of intracocular injections of ranibizumab for those with BRVO. A total of 397 individuals were randomized to receive either intraocular injection of ranibizumab or sham injections. There was a mean improvement of 7.5 letters 1 week after the first treatment with the ranibizumab injections. After 6 months of treatment with ranibizumab there was a mean improvement of between 3 and 4 lines of vision compared to 1.5 lines in the sham group. At 6-month follow-up there was a 65% improvement for those treated with ranibizumab versus 42% for those in the sham group.

Retinopathy of Prematurity
Ranibizumab is a treatment under consideration for retinopathy of prematurity. Several small case series studies have shown improvement in retinopathy of prematurity after use of intravitreal ranibizumab (Eells, 2017; Gunay, 2017; Kabatas, 2017; Zhang, 2017). Huang (2017) conducted a larger, retrospective review of ranibizumab use to mitigate retinopathy of prematurity by a single provider, in a single institution in China. One hundred forty-five individuals, 283 eyes were reviewed, including only those subjects who consented to ranibizumab use, and excluding subjects lost to follow-up. A total of 266 eyes (94.0%) showed a positive response, defined as regression with or without reactivation. While 127 eyes (48% of the eyes initially showing a positive response) failed to sustain improvement and required additional laser treatment and an additional 8 eyes that sustained regression also received additional laser treatments to address a persistent, large avascular area. The authors acknowledge the limitations of the study, including the lack of a control, a single-center, a limited Asian population, and that a comprehensive capture of systemic side effects was not performed.

IV. Aflibercept (Eylea)

Neovascular (wet) AMD
On November 18, 2011, the FDA approved aflibercept for the treatment of individuals with neovascular “wet” AMD. Heier and colleagues (2012) reported on two phase-III studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) in which participants were treated and evaluated for efficacy of aflibercept versus ranibizumab. A total of 2419 participants were enrolled in the two studies and were randomly assigned to one of four
treatment arms with three of the treatment arms receiving varying doses of aflibercept and one treatment arm receiving ranibizumab. The primary endpoint was visual acuity at 1 year (losing less than 15 letters of visual acuity at week 52 compared to baseline). Intravitreal aflibercept was dosed monthly or every 2 months after three initial monthly doses showed similar efficacy and safety outcomes as the monthly doses of ranibizumab. The groups who received intravitreal aflibercept had best corrected visual acuity within 0.5 letters of the ranibizumab group. Side effects were similar among the treatment groups.

Macular Edema and CRVO
The FDA approved aflibercept for the treatment of diabetic macular edema following CRVO in September 2012. The approval was based on two randomized, multi-center, double-masked, sham-controlled studies in individuals with macular edema following CRVO. The published study, Boyer and colleagues (2012), reported on the 6-month results of the phase III Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion [CRVO] (COPERNICUS). This study enrolled 189 eyes with macular edema secondary to CRVO. The primary endpoint was the number of eyes with a gain of 15 letters or more in best corrected visual acuity from baseline to week 24. Participants were randomly assigned in a 3:2 ratio to receive either receive aflibercept (n=115 eyes) or sham injections (n=74 eyes) every 4 weeks for 24 weeks. Assessments were performed on day 1, at week 4, and every 4 weeks thereafter to week 24. Assessments included a full ocular exam, visual acuity testing, slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure measurement and optical coherence tomography. Examiners were masked to treatment assignment. The National Eye Institute 25-item Visual Function Questionnaire was administered at baseline and at week 24. At the 24-week assessment, 110 participants in the aflibercept group remained and 60 participants in the sham group remained. The aflibercept group had a mean gain of 17.3 ± 12.8 letters at 24 weeks compared with a mean loss of 4.0 ± 18.0 letters in the sham group. At week 24, the aflibercept group showed an improvement of 7.2 points in the National Eye Institute 25-item Visual Function Questionnaire total score compared to an improvement of 0.8 points in the sham group. Visual acuity maintained throughout the course of the 24-week study.

DME and Diabetic Retinopathy
In July 2014, the FDA approved aflibercept for the treatment of diabetic macular edema. In a 2014 article by Korobelnik and colleagues, the authors reported the outcome results of two parallel, phase III DME studies (the VISTA and VIVID). A head-to-head comparison was made between intravitreal aflibercept and macular laser photocoagulation for individuals with diabetic macular edema. Using the results of the two similarly designed, double-masked, randomized, phase III trials, a total of 872 eyes were included. Participants who received aflibercept received injections every 4 weeks or every 8 weeks after 5 monthly doses. The primary endpoint was the change from baseline in best-corrected visual acuity in ETDRS letters at week 52. For those who received the intravitreal aflibercept, the mean best-corrected visual acuity gains from baseline to week 52 were 12.5 (in the every 4 week group) and 10.7 (in the every 8 week group) compared to 0.2 letters in the laser group in one trial and 10.5 and 10.7 versus 1.2 letters in the other trial. Secondary endpoints at week 52 included the proportion of eyes that gained ≥ 15 letters from baseline and the mean change from baseline in central retinal thickness. The corresponding proportions of eyes gaining ≥ 15 letters were 41.6% and 31.1% versus 7.8% (p<0.0001) in one trial, and 32.4% and 33.3% versus 9.1% (p<0.0001) in the second trial. Mean reductions in central retinal thickness were 185.9 and 183.1 versus 73.3 µm (p<0.0001) in one trial, and 195.0 and 192.4 versus 66.2 µm (p<0.0001) in the second trial. At week 52, those in the group who received intravitreal aflibercept showed superiority in functional and anatomic endpoints when compared to the laser group. All of the participants from both trials had diabetic retinopathy with DME at baseline.

In 2015, Brown and colleagues reported on the 100-week results from the VISTA and VIVID trials. The participants received aflibercept every 4 weeks, every 8 weeks, or laser treatment. The best-corrected visual acuity at 100 weeks in the every 4 week group of aflibercept was 11.5 letters, 11.1 letters in the every 8 week group, and 0.9 letters in the laser group in the VIVID study. In the VISTA study, the every 4 week group gained 11.4 letters, 9.4 letters in the every 8 week group, and 0.7 letters in the laser group. In the VISTA study, a total of 3.2% of participants lost ≥ 15 letters in the every 4 week group, 0.7% of participants lost ≥ 15 letters in the every 8 week group and 9.7% of participants lost ≥ 15 letters in the laser group. In the VIVID study, 2.2% of participants lost ≥ 15 of letters in the every 4 week group, 1.5% of participants lost ≥ 15 letters in the every 8 week group and 12.9% of participants lost ≥ 15 letters in the laser group.

In March 2015, the FDA expanded the indication for aflibercept to include diabetic retinopathy with DME based on the VIVID and VISTA studies.

In a 2015 study by the Diabetic Retinopathy Clinical Research Network, the authors reported on the 1-year outcome of safety and efficacy of a head-to-head comparison of aflibercept, bevacizumab and ranibizumab in the treatment of DME. Individuals were randomized to receive either aflibercept (n=224), bevacizumab (n=218) or ranibizumab.
During the first year, visits occurred every 4 weeks. Each visit involved best-corrected visual acuity (as measured by ETDRS) and optical coherence tomography to measure central subfield thickness. In the aflibercept group, the mean improvement in the visual acuity letter score was 13.3 and the central subfield thickness decreased by $169 \pm 138 \mu m$. In the bevacizumab group the mean improvement in visual acuity letter score was 9.7 with a central subfield thickness decrease of $101 \pm 121 \mu m$. In the ranibizumab group the mean improvement in visual acuity letter score was 11.2 with a decreased central subfield thickness of $147 \pm 134 \mu m$. Although the participants who received aflibercept showed a greater improvement in visual acuity, the difference was driven by the eyes with the worse visual acuity at baseline. For the participants with an initial visual-acuity letter score of 78 to 69, 20 participants had a mean improvement of 8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab. For the participants with an initial letter score less than 69, the mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab. Adverse events included 2 participants who received aflibercept and ranibizumab with injection-related infectious endophthalmitis (both nonstudy eyes). While the injections improved vision, there were no differences among the groups if the initial visual acuity loss was mild; aflibercept was more effective at improving vision if the initial visual acuity levels were worse.

**Diabetic Retinopathy and Radiation Retinopathy**

As noted above, the anti-VEGF agents are derived from the same parent molecule as the full-length humanized anti-VEGF antibody bevacizumab which suggests that aflibercept may be appropriate for the same disorders as other anti-VEGF agents. The studies by Finger, 2008; Finger, 2016; and Manabe, 2015 are summarized above.

### Definitions

**Age-related macular degeneration (AMD):** A slowly progressive, painless disease affecting the macula that blurs the sharp, central vision needed for "straight-ahead" activities such as reading, sewing, and driving.

**Branch retinal vein occlusion:** An occlusion near the retina in a branch retinal vein.

**Central retinal vein occlusion:** An occlusion of the central retinal vein where it enters the eye.

**Choroid:** Sponge like membrane in the eye located between the sclera and the retina.

**Diabetic macular edema:** The leakage of fluid from retinal blood vessels which in turn causes the macula to swell.

**Diabetic retinopathy:** The progressive damage to the blood vessels in the back of the eye.

**Neovascular (wet) AMD:** A subset of AMD representing approximately 10% of all cases but accounting for 90% of the severe vision loss. AMD occurs when abnormal blood vessels behind the retina start to grow under the macula. These new blood vessels tend to be very fragile and often leak blood and fluid which thickens the macula and damages the photoreceptors. Damage to the macula can occur rapidly, resulting in sudden loss of central vision. Wet AMD is considered to be advanced AMD and more severe than the dry form.

**Neovascular glaucoma:** A severe form of glaucoma with devastating visual outcome caused by the growth of new blood vessels which obstruct aqueous humor outflow.

**Neovascularization:** The formation of abnormal new blood vessels.

**Pseudoxanthoma elasticum:** An inherited disorder of the connective tissue in the skin, eyes, gastrointestinal and cardiovascular system.

**Retinal vein occlusion:** A blockage in the blood supply from the retina.

**Retinopathy:** Damage to the retina.

**Vascular endothelial growth factor:** A chemical signal produced by the body’s cells that stimulates growth of new blood vessels.
References

Peer Reviewed Publications:


**Government Agency, Medical Society, and Other Authoritative Publications:**


Aflibercept
Age-Related Macular Degeneration
AMD
Avastin
Bevacizumab
Branch retinal vein occlusion
Central retinal vein occlusion
Choroidal Neovascularization
Diabetic macular edema
Diabetic retinopathy
Eylea
Lucentis
Macugen
Macular degeneration
Neovascular glaucoma
Pegaptanib
Ranibizumab
Retinopathy of prematurity

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

### History

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<td>Updated Coding section with 01/01/2019 HCPCS updates; added Q5107.</td>
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<td>Updated the Description section with a Note which cross-references CG-DRUG-64 FDA-Approved Biosimilar Products. Updated Coding section with HCPS J3490. Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Initial document development. Moved content of DRUG.00028 Intravitreal Treatment for Retinal Vascular Conditions to new clinical utilization management guideline document with the same title.</td>
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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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This document addresses the following intravitreal corticosteroid implants:

- Dexamethasone intravitreal implant (Ozurdex®, Allergan Inc., Irvine, CA)
- Fluocinolone acetonide intravitreal implant (Iluvien®, Alimera Sciences, Inc., Alpharetta, GA; Retisert®, Bausch & Lomb Inc., Rochester, NY)

An intravitreal corticosteroid implant is a drug delivery system, surgically implanted in the vitreous of the eye, for sustained release of a corticosteroid.

**Clinical Indications**

**I. Fluocinolone acetonide intravitreal implant (Iluvien)**

**Medically Necessary:**

Fluocinolone acetonide intravitreal implant (Iluvien) is considered **medically necessary** for the treatment of diabetic macular edema.

**Not Medically Necessary:**

All other uses of fluocinolone acetonide intravitreal implant (Iluvien) are considered **not medically necessary**.

**II. Fluocinolone acetonide intravitreal implant (Retisert)**

**Medically Necessary:**

Fluocinolone acetonide intravitreal implant (Retisert) is considered **medically necessary** to treat chronic (duration of 1 year or more) non-infectious uveitis affecting the posterior segment of the eye.

**Not Medically Necessary:**
All other uses of fluocinolone acetonide intravitreal implant (Retisert) are considered not medically necessary, including, but not limited to, the treatment of diabetic macular edema.

**III. Dexamethasone intravitreal implant (Ozurdex)**

**Medically Necessary:**

Dexamethasone intravitreal implant (Ozurdex) is considered medically necessary for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO); or

Dexamethasone intravitreal implant (Ozurdex) is considered medically necessary for the treatment of chronic (duration of 1 year or more) non-infectious uveitis affecting the posterior segment of the eye; or

Dexamethasone intravitreal implant (Ozurdex) is considered medically necessary for the treatment of diabetic macular edema.

**Not Medically Necessary:**

All other uses of dexamethasone intravitreal implant (Ozurdex) are considered not medically necessary.

**NOTE:** Please refer to Discussion/General Information section below for contraindications of Iluvien, Retisert and Ozurdex.

**Coding**

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

*Fluocinolone acetonide implant [Retisert]*

CPT

67027  Implantation of intravitreal drug delivery system (eg, ganciclovir implant), includes concomitant removal of vitreous [when specified as fluocinolone acetonide implant Retisert]

HCPCS

J7311  Fluocinolone acetonide, intravitreal implant [Retisert]

ICD-10 Procedure

08H033Z  Insertion of infusion device into right eye, percutaneous approach [when specified as Retisert implantation]

08H133Z  Insertion of infusion device into left eye, percutaneous approach [when specified as Retisert implantation]

ICD-10 Diagnosis

H30.001-H30.049  Focal chorioretinal inflammation

H30.101-H30.149  Disseminated chorioretinal inflammation

H30.90-H30.93  Unspecified chorioretinal inflammation

*Fluocinolone acetonide implant [Iluvien]*

CPT

67028  Intravitreal injection of a pharmacologic agent [when specified as fluocinolone acetonide implant Iluvien]
**HCPCS**

J7313  
Injection, fluocinolone acetonide intravitreal implant, 0.01 mg [Iluvien]

**ICD-10 Diagnosis**

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**Dexamethasone implant [Ozurdex]**

**CPT**

67028  
Intravitreal injection of a pharmacologic agent [when specified as intravitreal injection of dexamethasone implant Ozurdex]

**HCPCS**

J7312  
Injection, dexamethasone intravitreal implant, 0.1 mg [Ozurdex]

**ICD-10 Diagnosis**

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**Discussion/General Information**

- Fluocinolone acetonide intravitreal implant (Iluvien)
Diabetic macular edema is defined as retinal thickening within 2 disc diameters of the center of the macula, and results from retinal microvascular changes that compromise the blood-retinal barrier, causing leakage of plasma constituents into the surrounding retina and, consequently, retinal edema (Albert, 2000). Diabetes is a leading cause of new blindness in the United States, with clinically significant macular edema greatly contributing to this vision loss.

Iluvien is a small, nonbiodegradable cylindrical tube with a central drug-polymer matrix that releases 0.19 mg of fluocinolone acetonide into the vitreous cavity. It is inserted intravitreally via a 25-gauge needle in the same manner as in intravitreal injection and can be done in the office setting. It releases small doses of fluocinolone acetonide for at least 3 years.

In September 2014, the U.S. Food and Drug Administration (FDA) approved Iluvien (fluocinolone acetonide implant) to treat diabetic macular edema in individuals who received previous treatment with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. The safety and efficacy of Iluvien was studied in two multi-center, randomized, sham-controlled, masked trials, the FAME (Fluocinolone Acetonide for Diabetic Macular Edema) A and B studies (Campochiaro, 2011; Campochiaro, 2012) in which individuals with diabetic macular edema were randomized to one of two Iluvien insert groups (low-dose insert [n=375], or high-dose insert [n=393]) or a sham group (n=185). The primary efficacy endpoint in both trials was the proportion of persons in whom vision had improved by 15 letters or more from baseline after 24 months. In each of the insert groups, 28% of subjects achieved this goal vs. 16% in the sham group. Mean change from baseline best corrected visual acuity (BCVA) was also significantly higher in the insert groups compared to sham. There was a drop in visual acuity between months 9 and 18 in the insertion group due to the development of cataracts which later improved with surgery.

Warnings and precautions (Iluvien product information, 2016):

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection.
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.
- The implant may migrate into the anterior chamber if the posterior lens capsule is not intact.

Contraindications for Iluvien placement (Iluvien product information, 2016) are:

- active or suspected ocular or periocular infections
- glaucoma with cup to disc ratios of greater than 0.8
- known hypersensitivity to any components of this product

Fluocinolone acetonide intravitreal implant (Retisert)

Uveitis is a broad term referring to a number of conditions that produce inflammation of the uvea, the vascular layer of the eye sandwiched between the sclera and the retina. Uveitis may affect any part of the uvea, including the anterior (iritis), intermediate (pars planitis), posterior (choroiditis), or the entire uvea (pan-uveitis). Uveitis may affect one or both eyes. Potential causes of uveitis are autoimmune disorders including sarcoidosis, infection, or exposure to toxins. However, the cause remains unknown in most individuals.

Posterior uveitis primarily involves the choroid. If the adjacent retina is also affected it is called chorioretinitis. Posterior uveitis may follow a systemic infection or occur in association with an autoimmune disease. Symptoms may include redness of the eye, blurred vision, sensitivity to light, dark floating spots in the vision, and eye pain. The inflammation may lead to areas of scarring on the choroid and retina with corresponding areas of vision loss. For systemic infectious diseases, corticosteroids are often used along with antibiotic and anti-viral therapies. For autoimmune diseases, various forms of suppression of the immune system may be required. Chronic non-infectious uveitis may require long term corticosteroid therapy.

The Retisert implant is an alternative to systemic corticosteroid therapy, providing high concentrations of steroid in close proximity to the involved choroids. The implant contains a 0.59 mg pellet of fluocinolone acetonide in a nonbiodegradable/polyvinyl acetate/silicone laminate and continuously delivers fluocinolone acetonide to the posterior segment of the eye for approximately 30 months. Under local anesthesia (retrobulbar or peribulbar block) in an operating room, Retisert is surgically implanted into the posterior segment of the involved eye. The implant is
implant (n = 66) or standard of care (SOC; n = 74) with either systemic prednisolone or equivalent corticosteroid as

Retisert use has been associated with significant complications, which may include cataract formation, choroidal detachment, temporary decrease in visual acuity, endophthalmitis, increased intraocular pressure, retinal detachment, vitreous hemorrhage, and wound dehiscence. In clinical trials, approximately 60% of participants required medication to lower intraocular pressure, 40% required surgery to treat glaucoma, and 93% underwent cataract extraction. Corticosteroids should be used with caution in those with glaucoma, and individuals should be monitored for elevated IOP.

On April 11, 2005, the U.S. Food and Drug Administration (FDA) approved Retisert (fluocinolone acetonide implant) as an orphan drug for the single indication of chronic non-infectious uveitis affecting the posterior segment of the eye. FDA approval of Retisert was based in part on the results of two randomized double-masked multicenter clinical trials including 224 individuals with chronic (persisting for at least 1 year) non-infectious uveitis affecting the posterior segment of one or both eyes. The primary efficacy endpoint in both trials was the rate of recurrence of uveitis affecting the posterior segment of the study eye in the 34-week period post implantation compared to the rate of recurrence in the 34-week period pre implantation. The rates of recurrence ranged from approximately 7% to 14% for the 34-week period post implantation as compared to approximately 40-54% for the 34-week period pre implantation. Current evidence supporting the safety and efficacy of the fluocinolone acetonide intravitreal implant for this indication includes the results of several multicenter, randomized, controlled clinical trials (Callanan, 2008; Pavesio, 2010).

Callanan and colleagues (2008) reported the safety and efficacy results of a 3-year study designed to evaluate the fluocinolone acetonide implant in individuals with non-infectious posterior uveitis. This prospective, dose-masked, dose-randomized, historically controlled, multicenter trial was completed in September 2005. A total of 278 individuals were randomized to receive the implant in one eye while the other eye was not implanted and left as a control. One hundred and ten subjects received the 0.59 mg dose (low dose) implant and 168 received the 2.1 mg dose (high dose) implant. The fluocinolone acetonide implant reduced the rate of recurrence from 62% in the year preceding implantation to 20% and 41% post implantation in the study eyes receiving the low and high dose implant, respectively. The authors also reported that 23% and 18% of high and low dose eyes improved their visual acuity significantly when compared to the respective nonimplanted eyes (p<0.01). In contrast to these findings, there was no significant difference found for the proportion of eyes with deteriorating visual acuity. The percentage of eyes requiring adjunctive systemic medications decreased significantly, with nearly 80% reduction, regardless of dose or study visit. The number of individuals requiring periocular injections decreased by approximately 95% in the first year, and this trend continued through the rest of the study period (p<0.01). The proportion of subjects requiring topical corticosteroids decreased by 50% in the first year of the study (p<0.01), but subsequently increased to pre-implant levels during years 2-3. It should be noted that the proportion of subjects requiring intracocular injections and topical steroids increased throughout the study period for nonimplanted eyes. The proportion of individuals with a reduction in the area of cystoid macular edema (CME) declined significantly in the treated eyes. For low-dose subjects, the reduction was 73% at 3 years, compared to 28% reduction in nonimplanted eyes. For the high-dose group, reduction was reported as 45% at 3 years, compared to 22% in the nonimplanted eyes (p<0.01). Use of intraocular pressure (IOP) lowering eye drops and surgical interventions related to IOP significantly increased for implanted eyes compared to nonimplanted eyes. Over the course of 3 years, the rate of eye drop use increased 78% for all dose groups, compared to 36% for nonimplanted eyes (p<0.01). Similarly, 40% of all dose subjects required IOP-lowering surgery, compared to 2% of nonimplanted eyes (p<0.01). Overall, six implants were removed due to IOP-related complications. The authors reported significant increase in the incidence of cataracts in the implantation groups, with 67% of implanted eyes vs. 18% of nonimplanted eyes reporting increased cataract progression. Furthermore, 93% of implanted eyes underwent cataract surgery compared to 20% of nonimplanted eyes. Finally, the authors reported a significant number of adverse events (AEs), aside from increased IOP and cataracts. In the low- and high-dose eye groups, the most common AEs included eye pain (52% and 60% respectively), conjunctival hyperemia (31% and 38% respectively), conjunctival hemorrhage (29% and 34% respectively), and blurred vision (30% and 33% respectively). The evaluators concluded the fluocinolone acetonide implant effectively reduced uveitis recurrences, improved or stabilized visual acuity in eyes with noninfectious posterior uveitis. In addition, Jaffe (2006) reported on a 34-week interim report describing this study which reported similar conclusions.

Pavesio and colleagues (2010) evaluated the safety and efficacy of fluocinolone acetonide implant compared with standard therapy in individuals with unilateral or bilateral noninfectious posterior uveitis in a randomized, open-label, controlled, phase 2b/3, multicenter superiority trial. The study was conducted from April 2002 through August 2005 at 37 centers across 10 countries. A total of 140 individuals received either a 0.59 mg fluocinolone acetonide intravitreal implant (n=66) or standard of care (SOC; n=74) with either systemic prednisolone or equivalent corticosteroid as
monotherapy or, if deemed necessary by the evaluator, combination therapy with an immunosuppressive agent and a lower dose of prednisolone or equivalent corticosteroid. The main outcome measure was time to first recurrence of uveitis. Eyes that received the fluocinolone acetonide intravitreal implant had delayed onset of observed recurrence of uveitis (p<0.01) and a lower rate of recurrence of uveitis (18.2% vs. 63.5%; p≤0.01) compared with the SOC study eyes. Adverse events commonly observed in the implanted eyes included cataracts requiring extraction (occurring in 87.8% of phakic implanted eyes) and increased IOP requiring IOP-lowering surgery (occurring in 21.2% of implanted eyes). There were no treatment-related nonocular adverse events observed in the implant group while such events occurred in 25.7% of subjects in the SOC group. The authors concluded that based on the results of this study, the fluocinolone acetonide intravitreal implant seemed to be more effective than SOC therapy in controlling the intraocular inflammation in those with posterior uveitis. It was also noted that although increased rates of cataract development and elevated IOP were observed with the fluocinolone acetonide implant, these events were well managed by conventional surgical or medical treatment.

In a follow-up of a randomized cohort, Tomkins-Netzer and colleagues (2015) evaluated the 2-year outcomes of uveitic macular edema of 148 eyes (117 subjects) enrolled in the Multicenter Uveitis Steroid Treatment (MUST) Trial. A total of 134 eyes (108 subjects) completed a 2-year follow-up. Eyes were randomized to either systemic immunosuppression or intravitreal fluocinolone acetonide implant therapy. Randomization was stratified on the basis of the class of uveitis: intermediate uveitis and posterior or panuveitis. By year 2 of follow-up, 62% and 25% of eyes in the systemic and implant groups, respectively, received at least one supplemental regional corticosteroid injection. By year 2 follow-up, macular edema had resolved in 71% of eyes and resolved in 60%. There were no differences between treatment groups in the percentage of eyes with macular edema improving and resolving. However, eyes randomized to implant had more improvement in macular thickness. Eyes with baseline fluorescein angiographic leakage were more likely to improve than those without. Overall, there was a mean 5-letter (1 line) improvement in BCVA at 2 years. Mean changes in BCVA from baseline at 2 years by macular edema response status were: resolution, +10 letters; improvement without resolution, +10 letters (P=0.92); little to no change, 6 letters (P=0.19); and worsening, -16 letters (worsening acuity; P=0.0003).

Warnings and precautions (Retisert product information, 2012):

- Cataract formation: Nearly all phakic patients are expected to develop cataracts and require cataract surgery.
- Endophthalmitis: Late onset endophthalmitis has been observed.
- Increase in intraocular pressure: Use of corticosteroids may result in elevated IOP and/or glaucoma. IOP lowering medications were required in > 75% of patients; filtering surgeries were required in > 35% of patients.
- Separation of implant components: Physicians should periodically monitor the integrity of the implant by visual inspection.

Contraindications for Retisert placement (Retisert product information, 2012) are active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also active bacterial, mycobacterial or fungal infections of the eye.

Currently, the Retisert implant is not FDA approved for the treatment of diabetic macular edema. However, Iluvien, another brand of fluocinolone acetonide is now approved for this use. Although several randomized trials (Pearson, 2011; Campochiaro, 2011) suggest potential promise for the treatment of diabetic macular edema with fluocinolone acetonide intravitreal implant therapy, significant complications related to the use of this implant for diabetic macular edema have been reported. Associated complications include cataract formation, increased intraocular pressure (IOP), and surgery to lower IOP (Messenger, 2013). To date, there is a lack of sufficient evidence in the peer-reviewed medical literature to support the use of Retisert intravitreal implant for diabetic macular edema or any other off-label indication. Significant differences between Retisert and Iluvien include: different dosages of the drug being delivered to different areas of the eye. Retisert is a 0.59 mg sterile implant designed to release fluocinolone acetate to the posterior segment of the eye over approximately 30 months, while Iluvien is a 0.19 mg sterile implant in a 36-month drug delivery system injected directly into the vitreous.

_Dexamethasone intravitreal implant (Ozurdex)_

Retinal vein occlusion is a common vascular disorder of the retina and is one of the most common causes of vision loss after diabetic retinopathy. It is classified according to where the occlusion is located. Obstruction at a branch of
the retinal vein is referred to as BRVO and obstruction of the retinal vein at the optic nerve is referred to as CRVO. BRVO is the most common form of retinal vein occlusion, whereas CRVO is less common.

The Ozurdex implant uses a solid polymer delivery system, in which biodegradable material is combined with dexamethasone to form a small rod-shaped implant which is injected into the vitreous using a specially designed injector (Taylor, 2010). It can be inserted as an office based procedure, in contrast to Retisert. Dexamethasone is released over approximately 6 months, after which the implant dissolves, leaving no residue.

The most common adverse reactions to dexamethasone intravitreal implant reported in clinical studies have been increased intraocular pressure and conjunctival hemorrhage.

On June 17, 2009, the U.S. FDA approved Ozurdex (dexamethasone 0.7 mg intravitreal implant) for the treatment of macular edema after BRVO or CRVO. Subsequently, on September 24, 2010 the FDA also approved Ozurdex (dexamethasone 0.7 mg intravitreal implant) for the treatment of non-infectious ocular inflammation, or uveitis, affecting the posterior segment of the eye. The treatment of diabetic macular edema in persons who are pseudophakic or are phakic and scheduled for cataract surgery was added as an FDA approved indication in June 2014, and in September 2014 this indication was changed to diabetic macular edema without any additional qualifications. However, the 2014 prescribing information warns:

- Intravitreal injections, including those with Ozurdex, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.
- Patients should be monitored regularly following the injection.
- Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, and glaucoma.
- Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

According to 2014 prescribing information, Ozurdex is contraindicated in individuals with the following conditions:

- Glaucoma with cup to disc ratios of greater than 0.8;
- Active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases;
- Posterior lens capsule is torn or ruptured. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for use;
- Known hypersensitivity to any components of the product.

The safety and efficacy of dexamethasone intravitreal implant for the treatment of macular edema (ME) after BRVO or CRVO was studied in two identical, multicenter, masked, randomized, 6-month sham-controlled clinical trials. Haller and colleagues (2010) reported on the “Global Evaluation of implaNTable dExamethasone in retinal Vein occlusion with macular edema” (GENEVA) trials which evaluated a total of 1267 individuals at least 18 years of age with vision loss due to ME associated with either BRVO or CRVO. Participants were randomized to a single treatment with dexamethasone intravitreal implant (DEX implant) 0.7 mg (n=427), DEX implant 0.35 mg (n=414), or sham (n=426). The primary outcome measure for the combined data from the two studies was time to achieve a greater than or equal to 15-letter improvement in BCVA. Central retinal thickness, BCVA and safety were the secondary endpoints. After the single treatment, the time to achieve a greater than or equal to 15-letter improvement in BCVA was substantially less in both DEX implant groups compared to the sham group. The percentage of eyes with a greater than or equal to 15-letter loss in BCVA was substantially lower in the DEX implant 0.7 mg group compared with sham at all follow-up visits. Both DEX implant groups demonstrated an improvement in mean BCVA compared with sham at all follow-up visits. Improvements were seen in BCVA with DEX implant in participants with BRVO and in those with CRVO; however, response patterns differed. The IOP of DEX implant-treated eyes (both doses) peaked at day 60, but was not different from the sham by day 180. The authors concluded that the results of this study demonstrated that DEX implant can increase the chance of visual acuity improvement and reduce the risk of additional vision loss in eyes with BRVO or CRVO. Study results also demonstrated that if eyes with retinal vein occlusion remain untreated, a significant number will either experience further visual acuity loss or fail to improve. The implant appeared to be well tolerated with transient, manageable IOP increases noted in less than 16% of eyes.
Haller and colleagues (2011) reported on a 6-month open-label extension of the GENEVA trials. A total of 1267 subjects who had clinically detectable macular edema associated with either CRVO or BRVO were enrolled. The mean visual acuity at baseline was approximately 54 letters (20/80) and the mean central retinal thickness was approximately 550 microns. About 75% of the subjects had macular edema for a duration of more than 3 months. Individuals were randomized to a single treatment with a 0.7 mg dexamethasone implant (n=427), 0.35 mg dexamethasone implant (n=414), or sham control (n=426). Individuals in both the implant and sham-control groups who completed the 6-month double-masked phase could receive a 0.7 mg dexamethasone implant if BCVA was less than 84 letters or retinal thickness was greater than 250 microns. At day 180, a total of 997 subjects received a dexamethasone implant, of which 349 received a second implant. Another 199 subjects entered into the open-label phase of the study for follow-up without receiving further treatment. The primary outcome at 12 months was safety, and results were analyzed according to the treatment received. Cataract progression over the 12 months occurred in 90 of 302 phakic eyes (29.8%) that received two implants in comparison with 31 of 296 eyes (10.5%) that received a single implant and 5 of 88 sham-treated phakic eyes (5.7%). Increases in IOP tended to be transient but increased to 35 mm Hg or more in about 15% of eyes at 60 days after implantation. A 15-letter or more improvement in BCVA was found in 30% of subjects at 60 days after the first implant and 32% of subjects at 60 days after the second dexamethasone implant. With the exception of cataract progression, the efficacy and safety of receiving two implants was similar to the efficacy and safety of one dexamethasone implant.

In 2013, Sadda and colleagues performed a post hoc analysis of pooled data from the GENEVA trials. Subjects with 6 or more week's duration of vision loss as a result of ME after BRVO or CRVO for whom angiographic data were available (n=329 eyes) were included in this study. Fluorescein angiography (FA) results were assessed by certified, masked graders using standardized protocols. The primary outcome measure in the parent studies was change from baseline in best-corrected visual acuity. Prospectively defined secondary outcomes included FA measurements (to assess macular capillary leakage, neovascularization, and nonperfusion) and optical coherence tomography results (to assess central retinal thickness [CRT]). A total of 42% of eyes in the DEX implant group and 38% of eyes in the sham group had unreadable baseline assessments due to hemorrhage. Significantly fewer DEX implant-treated eyes (2%) than sham-treated eyes (9%) had unreadable assessments because of hemorrhage at day 180. The incidence of nonperfusion remained fairly steady from baseline to day 180 among eyes with gradable assessments. The proportion of eyes with active neovascularization increased from baseline to day 180 in the sham group, but stayed fairly constant in the DEX implant group (p=0.026 for DEX vs. sham). The mean area of overall nonperfusion and the mean area of macular capillary nonperfusion increased from baseline to day 180 in both treatment groups with no statistically significant difference between groups. There was a statistically significant positive correlation between changes in macular leakage and changes in CRT in both the DEX implant group (r=0.22; 95% confidence interval [CI], 0.03-0.40; p=0.023) and the sham group (r=0.29; 95% CI, 0.10-0.46; p=0.003). The authors concluded that clinical improvements observed with the DEX implant were accompanied by significant improvements in vascular parameters. Also suggested was that treatment with the DEX implant may be associated with some clinically significant improvements in angiographic findings, specifically active neovascularization.

The safety and efficacy of the dexamethasone intravitreal implant for the treatment of non-infectious uveitis affecting the posterior segment of the eye was studied in a single, multicenter, masked, randomized 26-week trial. Lowder and colleagues (2011) reported on the study which included 229 participants from 18 countries and 46 study sites randomized to receive a single treatment with a 0.35 mg DEX implant (n=76), 0.7 mg DEX implant (n=77) or a sham procedure (n=76). The mean duration of uveitis prior to the trial was 50.5 months in the 0.7 mg DEX, 43.9 months in the 0.35 mg DEX, and 61.2 months in the sham cohorts. A primary outcome measure was the percentage of eyes with a vitreous haze score of 0, which represents no inflammation, at week 8 of the trial. The percentage of eyes with a vitreous haze score of 0 at week 8 was 36% for the 0.35 mg DEX implant, 47% for the 0.7 mg DEX implant, and 12% for the sham. There were also significantly more eyes with improved visual acuity in the DEX implant groups than the sham group. The authors concluded that in this study a single dose of the DEX implant was well tolerated and produced significant improvements in intraocular inflammation and visual acuity that persisted for 6 months. In addition, it was noted that the 0.7 mg DEX implant demonstrated greater efficacy than the 0.35 implant, with similar safety.

Boyer and colleagues (2014), for the Ozurdex MEAD study group, evaluated the safety and efficacy of dexamethasone intravitreal implant (Ozurdex, DEX implant) 0.7 and 0.35 mg for the treatment of diabetic macular edema (DME) in two randomized, multicenter, masked, sham-controlled, phase III clinical trials with identical protocols. A total of 1048 subjects with DME, best-corrected visual acuity (BCVA) of 20/50 to 20/200 (Snellen equivalent), and central retinal thickness (CRT) of ≥ 300 µm by optical coherence tomography were randomized in a 1:1:1 ratio to study treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or sham procedure and followed for 3 years (or 39 months for subjects treated at month 36) at 40 or fewer scheduled visits. Individuals who met retreatment eligibility criteria could be retreated no more than every 6 months. The predefined primary efficacy endpoint was achievement of 15-letter improvement in BCVA from baseline at study end. Safety measures included
adverse events and intraocular pressure (IOP). The mean number of treatments received over 3 years was 4.1, 4.4, and 3.3 with DEX implant 0.7 mg, DEX implant 0.35 mg, and sham, respectively. The percentage of subjects with a 15-letter improvement in CRT from baseline at study end was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12.0%). Mean average reduction in CRT from baseline was greater with DEX implant 0.7 mg and DEX implant 0.35 mg than sham. Rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively. Increases in IOP were usually controlled with medication or no therapy; only 2 subjects (0.6%) in the DEX implant 0.7 mg group and 1 (0.3%) in the DEX implant 0.35 mg group required glaucoma incisional surgery. The authors concluded that the DEX implant 0.7 mg and 0.35 mg met the primary efficacy endpoint for improvement in BCVA with an acceptable safety profile.

Multiple authors have further analyzed the MEAD study (Bower, 2014) and reported benefits of the DEX implant. In a 2014 post hoc data analysis, Kupperman and colleagues (2014) evaluated the onset and duration of improvement in best-corrected visual acuity (BCVA) in eyes treated with sustained-delivery 0.7 mg DEX implant for macular edema after branch or central retinal vein occlusion. Subjects received a single DEX implant (n=427) or sham procedure (n=426) in the study eye. The baseline mean BCVA was 20/80. At day 7, 10.3% of DEX implant treated eyes vs. 4.0% of sham treated eyes had at least a 15-letter improvement in the BCVA, and 27.2% of DEX implant-treated eyes vs. 10.6% of sham-treated eyes had at least a 10-letter improvement. The mean improvement at day 7 was 5.3 letters (branch retinal vein occlusion, 5.1; and central retinal vein occlusion, 5.8) with DEX implant and 1.6 letters (branch retinal vein occlusion, 2.3; and central retinal vein occlusion, 0.1) with sham. The mean time from initial observation of the 15-letter or greater BCVA gain to the last observation of 15-letter or greater BCVA gain was 70 days.

A subgroup analysis (Augustin, 2015) used pooled data from the MEAD study with identical protocols that evaluated the safety and efficacy of DEX implant for treatment of DME. Adults with diabetes mellitus and vision loss secondary to fovea-involved macular edema associated with diabetic retinopathy were enrolled. The subset analysis included individuals that had been previously treated with laser and/or medical therapy. Baseline characteristics of previously treated DEX 0.7 (n=247) and sham (n=261) adults were similar. In the previously treated subgroup, mean number of treatments over 3 years was 4.1 for DEX 0.7 and 3.2 for sham. A total of 21.5% of DEX 0.7 subjects vs. 11.1% of those in the sham group had at least a 15-letter BCVA gain from baseline at study end (P=0.002). Cataract-related adverse events occurred in 70.3% of baseline phakic subjects in the previously treated DEX 0.7 subgroup and vision gains were restored following cataract surgery. The authors concluded that this subgroup analysis has shown “beneficial effects of DEX implant 0.7 mg treatment on visual and anatomic outcomes in patients with previously treated DME.”

Maturi and colleagues (2016) evaluated IOP increases in individuals with DME treated with DEX implant in the MEAD study. In the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively, ≥ 10 mmHg IOP increases from baseline occurred in 27.7%, 24.8%, and 3.7% of subjects. IOP-lowering medication was used by 41.5%, 37.6%, and 9.1% of subjects. Among the individuals treated with the DEX implant 0.7 mg with and without a ≥ 10 mmHg IOP increase, 21.9% (21 of 96) and 22.4% (57 of 255), respectively, achieved ≥ 15 letter BCVA gain at the end of the study. Mean average change in central retinal thickness from baseline was -127 μm and -106 μm, respectively. The authors concluded that the DEX implant demonstrated a clear benefit in improving outcomes in those who have increases in IOP, as well as in those without IOP increases.

In 2018, Li and colleagues published a 6-month, randomized, double-blind, sham-controlled, multicenter, phase III clinical trial with a 2-month open-label study extension that evaluated the safety and efficacy of DEX implant for treatment of ME associated with BRVO or CRVO. Subjects were randomized into either a treatment group with DEX 0.7 mg (n=129) or a sham procedure group (n=130). There was a significant difference (p<0.001) between the DEX group and the sham group in improvement in the time to ≥15-letter BCVA (primary endpoint). In addition, DEX also met the secondary outcome measures with significant differences from the sham procedure group. Study eye mean BCVA change from baseline was +10.6 letters in the DEX group and +1.7 letters in the sham procedure group (p<0.001). The percentage of subjects with ≥15-letter improvement in BCVA from baseline in the DEX group was 35% and in the sham procedure group was 12% (p<0.001). The mean CRT change from baseline on optical coherence tomography was -407 μm in the DEX group and -62 μm in the sham procedure group (p<0.001). It was noted that the treatment-emergent adverse events reported were expected with DEX and no subject required incisional glaucoma surgery. The authors concluded that DEX showed significant benefits in the treatment of ME associated with BRVO or CRVO while maintaining a good safety profile.

Definitions
Aphakia: The absence of the natural crystalline lens.

Diabetic macular edema: The leakage of fluid from retinal blood vessels which in turn causes the macula to swell; is common in diabetics.

Glaucoma: A disease characterized by destruction of the nerve fiber layer of the optic disc.

Intravitreal or intravitreous: In the vitreous, the clear, jelly-like substance that fills the posterior segment of the eye.

Phakic: An eye containing the natural lens.

Pseudophakic: An eye in which a natural lens is replaced with an artificial lens implant.

Vitreous body: A transparent jellylike substance that fills the posterior segment of the eye, delimited by the hyaloid membrane.

References

Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:


Websites for Additional Information


Index

Dexamethasone Intravitreal Implant
Fluocinolone Acetonide
Iluvien
Intravitreal Corticosteroid Implant
Ozurdex
Retisert

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

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<th>Status</th>
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Medical Policy & Technology Assessment Committee (MPTAC) review. Initial
document development. Moved content of DRUG.00032 Intravitreal Corticosteroid
Implants to new clinical utilization management guideline document with the same
title.

Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM
Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines
approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or
lines of business for consistent review of the medical necessity of services related to the clinical guideline when the
plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose
whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline,
please contact the customer service number on the member’s card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline
to review services generally across all providers delivering services to Plan’s or line of business’s members may
instead use the clinical guideline for provider education and/or to review the medical necessity of services for any
provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or
claims that are not consistent with other providers, in terms of frequency or in some other manner.

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Clinical UM Guideline

**Subject:** Belatacept (Nulojix®)

**Guideline #:** CG-DRUG-95  **Publish Date:** 06/28/2018

**Status:** New  **Last Review Date:** 05/03/2018

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**Description**

This document addresses the use of belatacept (Nulojix) (Bristol-Myers Squibb, Princeton, New Jersey). Belatacept is an intravenous drug that is a selective T-cell co-stimulation blocker indicated for the prophylaxis of organ rejection in Epstein-Barr virus (EBV) seropositive adults receiving a kidney transplant.

**Note:** Please see the following related document for additional information:

- [CG-TRANS-02 Kidney Transplantation](#)

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**Clinical Indications**

**Medically Necessary:**

Belatacept is considered **medically necessary** for prevention of organ rejection in adults receiving a kidney transplant who are Epstein-Barr virus (EBV) seropositive.

**Not Medically Necessary:**

Belatacept is considered **not medically necessary** when the above criteria are not met.

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**Coding**

*The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

**HCPCS**

- J0485  
  Injection, belatacept, 1 mg [Nulojix]

**ICD-10 Diagnosis**

- N18.6  
  End stage renal disease
- Z48.22  
  Encounter for aftercare following kidney transplant
Kidney transplant status

Discussion/General Information

A serious complication of kidney transplantation is rejection of the donated kidney. Immunosuppressant drugs are used to help prevent the organ recipient from rejecting the donor kidney. The U.S. Food and Drug Administration (FDA) approved belatacept (Nulojix) on June 15, 2011 for prophylaxis of organ rejection in combination with other immunosuppressants (specifically basiliximab, mycophenolate mofetil, and corticosteroids) in adults receiving a kidney transplant who are EBV seropositive. Belatacept is used during an initial phase beginning on the day of kidney transplantation prior to implantation and also for a maintenance phase post kidney transplantation (Nulojix PI, 2017). Use of this drug has not been established for the prophylaxis of organ rejection in transplanted organs other than the kidney. The FDA approval of belatacept was based on two open-label, randomized, multicenter phase III trials using cyclosporine as a comparator (Durrbach, 2010; Vincenti, 2010). All groups in both trials received basiliximab induction, mycophenolate mofetil, and corticosteroids. Both trials evaluated two dosing regimens consisting of a more intensive (MI) or less intensive (LI) regimen of belatacept versus (vs.) cyclosporine.

The 2017 FDA Product Information label includes the following information related to adverse reactions, black boxed warnings and other warnings / precautions:

**Adverse Reactions:**

The most common adverse events seen in 20% or more of subjects in clinical trials treated with the recommended dose and frequency of belatacept were anemia, diarrhea, urinary tract infection, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, nausea, vomiting, headache, hypokalemia, hyperkalemia, and leukopenia. Spontaneous reports during the postmarketing experience included a case of anaphylaxis, which was observed in a kidney transplant recipient whose belatacept therapy had been interrupted for 2 months during treatment of a systemic varicella infection (Nulojix PI, 2017).

**Black Boxed Warnings:**

- Post-Transplant Lymphoproliferative Disorder, Other Malignancies, and Serious Infections
  - Increased risk for developing PTLD, predominantly involving the CNS. Recipients without immunity to EBV are at a particularly increased risk; therefore use in EBV seropositive individuals only. Do not use this drug in transplant recipients who are EBV seronegative or who have unknown serostatus.
  - Only physicians experienced in immunosuppressive therapy and management of kidney transplants should prescribe Nulojix.
  - Increased susceptibility to infection and the possible development of malignancies may result from immunosuppression.
  - Use in those receiving a liver transplant is not recommended due to an increased risk of graft loss and death.

**Other Warnings and Precautions:**

- Acute Rejection and Graft Loss with Corticosteroid Minimization: corticosteroid utilization should be consistent with the Nulojix clinical trial experience.
- Avoid prolonged exposure to ultraviolet light and sunlight.
- Increased risk of PML.
- Risk for other serious infections: increased risk of bacterial, viral, fungal, and protozoal infections, including opportunistic infections, and tuberculosis. Some infections were fatal. Polyoma virus-associated nephropathy can lead to kidney graft loss; consider reduction in immunosuppression. Evaluate for tuberculosis and initiate treatment for latent infection prior to Nulojix use. Cytomegalovirus and pneumocystis prophylaxis are recommended after transplantation.
- Use of live vaccines during treatment should be avoided.

Vincenti and colleagues (2010), in the phase III Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT Study), randomized 686 adults age 18 and older of whom 666 were recipients of living donor or standard criteria deceased donor kidneys. A total of 527 recipients completed the initial 12-month
treatment phase. The co-primary endpoints at 12 months were recipient/graft survival, a composite renal impairment endpoint (percent with a measured glomerular filtration rate [mGFR] < 60 mL/min/1.73 m² at month 12 or a decrease in mGFR > or =10 mL/min/1.73 m² month 3-month 12) and the incidence of acute rejection. At 12 months, both belatacept regimens had similar recipient/graft survival vs. cyclosporine (MI: 95%, LI: 97% and cyclosporine: 93%), and were associated with superior renal function as measured by the composite renal impairment endpoint (MI: 59%; LI: 54% and cyclosporine: 78%; p < or =0.001 MI or LI vs. cyclosporine) and by the mGFR (65, 63 and 50 mL/min for MI, LI and cyclosporine; p < or =0.001 MI or LI vs. cyclosporine). Safety was similar between groups, but posttransplant lymphoproliferative disorder (PTLD) was more common in the belatacept groups. Belatacept was associated with superior renal function and similar recipient/graft survival vs. cyclosporine at 1 year post-transplant, despite a higher rate of early acute rejection.

In 2012, Vincenti and colleagues further evaluated outcomes of the BENEFIT Study to determine if the previously reported results were sustained at 3 years. A total of 471 of the original kidney transplant recipients (n=158 MI; n=170 LI; n=143 cyclosporine) completed at least 3 years of study therapy. A total of 92% (MI), 92% (LI), and 89% (cyclosporine) recipients survived with a functioning graft. The mean calculated GFR (cGFR) was ∼21 mL/min/1.73 m² higher in the belatacept groups vs. cyclosporine at year 3. From month 3 to year 3, the mean cGFR increased in the belatacept groups by +1.0 mL/min/1.73 m²/year (MI) and +1.2 mL/min/1.73 m²/year (LI) vs. a decline of -2.0 mL/min/1.73 m²/year (cyclosporine). A single cyclosporine-treated individual experienced acute rejection between year 2 and year 3. There were no new safety signals and no new cases of PTLD after 18 months. The authors concluded that 3-year results confirmed the persistence of renal function benefits of belatacept over time. These benefits appeared to balance the early risks associated with belatacept in the study subjects, namely increased occurrence of acute rejection and PTLD.

Durbach and colleagues (2010), in the Extended Criteria Trial (BENEFIT-EXT Study), randomized 578 adults, of whom 543 were age 18 and older, and were transplanted with extended criteria donor (ECD) kidneys. ECD was defined as all deceased donors age 60 years and older and donors age 50 years and older with any two of the following criteria: hypertension, cerebrovascular cause of brain death, or pre-retrieval serum creatinine (SCr) level >1.5 mg/dL. The co-primary endpoints at 12 months were composite recipient/grant survival and a composite renal impairment endpoint. Recipient/grant survival with belatacept was similar to cyclosporine (86% MI, 89% LI, 85% cyclosporine) at 12 months. Fewer individuals in the belatacept group reached the composite renal impairment endpoint vs. cyclosporine (71% MI, 77% LI, 85% cyclosporine; p=0.002 MI vs. cyclosporine; p=0.06 LI vs. cyclosporine). The mean measured glomerular filtration rate was 4-7 mL/min higher on belatacept vs. cyclosporine (p=0.008 MI vs. cyclosporine; p=0.1039 LI vs. cyclosporine), and the overall cardiovascular/metabolic profile was better on belatacept vs. cyclosporine. Acute rejection, rates of infection and malignancy were similar between groups, but more cases of PTLD occurred in the central nervous system (CNS) of those on belatacept. ECD kidney transplant recipients treated with belatacept-based immunosuppression achieved similar recipient/grant survival, improved renal function, had an increased incidence of PTLD, and exhibited improvement in the cardiovascular/metabolic risk profile as compared to those treated with cyclosporine.

Vanrenterghem and colleagues (2011) evaluated the cardiovascular and metabolic endpoints from the BENEFIT and the BENEFIT-EXT studies. Cardiovascular disease, one of the most common causes of death in kidney transplant recipients with a functioning graft, can be exacerbated by immunosuppressive drugs. The authors reported that from the individuals randomized and transplanted across the two studies, at month 12, the belatacept regimen was associated with better cardiovascular and metabolic risk profiles, with better serum lipids and lower blood pressure and less new onset diabetes after transplant vs. cyclosporine. The overall profile of belatacept continues to be assessed.

In 2012, Pestana and colleagues evaluated 3-year outcomes of the BENEFIT-EXT Study. A total of 323 kidney transplant recipients completed treatment by year 3. Individual survival with a functioning graft was comparable between groups (80% in MI, 82% in LI, 80% in cyclosporine). Mean calculated GFR (cGFR) was 11 mL/min higher in the belatacept-treated group vs. those treated with cyclosporine (42.7 in MI, 42.2 in LI, 31.5 mL/min in cyclosporine). More cyclosporine-treated recipients (44%) progressed to GFR < 30 mL/min (chronic kidney disease stage 4/5) than those treated with belatacept (27-30%). Rates of acute rejection were similar between groups. PTLD occurrence was higher in belatacept-treated recipients (2 in MI, 3 in LI), most of which occurred during the first 18 months. Tuberculosis was reported in 2 MI, 4 LI and no cyclosporine recipients. The authors concluded that the 3-year study results demonstrated similar individual and graft survival, sustained improvements in renal function over time, with no new safety issues identified in those receiving belatacept. As previously reported, PTLD and tuberculosis were the principal safety findings associated with belatacept in this study population.
Grinyo and colleagues (2012), in a long-term extension of a phase II trial, addressed whether improvement continued at 2 years. Individuals receiving cyclosporine or tacrolimus were randomized to switch to belatacept or continue calcineurin inhibitor (CNI). Of 173 randomized subjects, 162 completed the 12-month main study and entered into the long-term extension (LTE) of this phase II, randomized multi-center clinical trial. The study subjects were adult recipients of a renal allograft from a deceased or living donor at least 6 months, but no more than 36 months prior to enrollment. Only 2 subjects (n=1 each group) had graft loss between the first and second years. At year 2, mean cGFR was 62.0 ml/min (belatacept) vs. 55.4 ml/min (CNI). The mean change in cGFR from baseline was +8.8 ml/min (belatacept) and +0.3 ml/min (CNI). Higher cGFR was reported in those switched from either cyclosporine (+7.8 ml/min) or tacrolimus (+8.9 ml/min). The frequency of acute rejection in the LTE cohort was comparable between the belatacept and CNI groups by year 2. All acute rejection episodes occurred during year 1 in the belatacept group and during year 2 in the CNI group. There were more non-serious mucocutaneous fungal infections in the belatacept group. The authors concluded that results of this study suggest that switching from either cyclosporine or tacrolimus based therapy to belatacept may result in improved renal function. However, they further noted that these results should be confirmed in a Phase III study.

A Cochrane review by Masson and colleagues (2014) analyzed five studies that compared belatacept and CNI in 1535 kidney transplant recipients. At up to 3 years post kidney transplant, both belatacept and CNI-treated recipients were found to have similar risks of acute rejection, death, and loss of transplant and returning to dialysis. Recipients treated with belatacept were 28% less likely to have chronic kidney scarring and also had better graft function than those treated with CNI. Additionally, those treated with belatacept had lower blood pressure and a decreased incidence of new-onset diabetes. The risk of PTLD was similar in both belatacept and CNI-treated recipients. However, the authors noted a lack of clarity regarding whether the short-term advantages of belatacept could be maintained over the medium to long term or translate into better cardiovascular outcomes or longer kidney transplant survival.

In 2016, Vincenti and colleagues reported 7-year results of the phase III BENEFIT study of belatacept-based immunosuppression compared to cyclosporine-based immunosuppression. Of the 660 treated kidney transplant recipients the following were monitored for the entire 7 year (84 month) period: 153 of the 219 subjects treated with the more-intensive belatacept regimen, 163 of the 226 treated with the less-intensive belatacept regimen, and 131 of the 215 treated with the cyclosporine regimen. Previous significant improvements in renal function that had been observed with belatacept as compared to cyclosporine were sustained at 7 years. Subjects randomized to either the more or less intensive belatacept regimen had a 43% reduction in the risk of death or graft loss as compared to those randomized to the cyclosporine regimen. The mean estimated glomerular filtration rate (eGFR) increased over the 7-year period with both belatacept regimens but decreased with the cyclosporine regimen. The cumulative frequencies of serious adverse events at final follow-up were similar across treatment groups. The authors concluded that in their study the risk of death or graft loss at year 7 was significantly lower for the belatacept-treated group than for the cyclosporine-treated group and the survival benefit emerged as early as 5 years after transplantation.

In 2017, a retrospective study (Bertrand, 2017) and a phase II randomized trial (Grinyo, 2017) were published to report evaluations of converting from CNI to belatacept. Bertrand and colleagues evaluated the difference in eGFR variation from baseline to month 6 and from baseline to month 12 in a CNI-to-belatacept switch group (n=17) and CNI control group (n=18). The authors found that when compared to the control group, subjects in the switch group had significantly improved graft function at 6 months from baseline (p=0.03) and at 12 months from baseline (p=0.01). Grinyo and colleagues assessed the safety of belatacept by evaluating serious adverse events in a CNI-to-belatacept switch group (n=84) and CNI control group (n=89). Results showed the total frequency of serious adverse events was similar for the switch group (33 of 84 [39%]) and the control group (36 of 89 [40%]). The authors concluded that further evaluation is needed.

Three retrospective studies individually analyzed the change in eGFR after conversion from tacrolimus to belatacept (Abdelwahab Elhamahmi, 2018; Schulte, 2017; Wojciechowski, 2017). Abdelwahab Elhamahmi and colleagues studied 30 subjects in the conversion group and 30 subjects in the control group, and found the change in eGFR at 4 months postconversion was 11.0 (12.9) ml/min per 1.73 m^2 in the conversion group and 4.8 (10.5) ml/min per 1.73 m^2 in the control group (p=0.045). Schulte and colleagues evaluated 20 subjects who all participated in the belatacept conversion. There was no control group. Results showed eGFR before conversion was 22.2 ± 9.4 ml/min and improved significantly to 28.3 ± 10.1 ml/min at 4 weeks and to 32.1 ± 12.6 ml/min at 12 months after conversion (p<0.001). Wojciechowski and colleagues studied 20 subjects who converted to belatacept, but did not include a control group. The authors found a mean eGFR increase from 16 ml/min/1.73 m^2 at baseline to 54.2 ml/min/1.73 m^2 at 1 year postconversion. Limitations include small sample size for all three studies and no control group for two studies (Schulte, 2017; Wojciechowski, 2017).
In clinical trials belatacept was found to be associated with risks including PTLD and progressive multifocal leukoencephalopathy (PML). The risk of PTLD was higher in EBV seronegative individuals as compared to those who were EBV seropositive. Due to risks involved, the FDA did not approve belatacept for individuals who are EBV seronegative. The FDA has issued black boxed warnings regarding the increased risk for developing PTLD, predominantly involving the CNS and warns that “recipients without immunity to EBV are at a particularly increased risk; therefore use in EBV seropositive individuals only.”

Definitions

Immunosuppressant: Drugs used to control or reduce the immune system response.

References

Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:

Belatacept
Nulojix

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

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<tr>
<td>New</td>
<td>05/03/2018</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Initial document development. Moved content of DRUG.00049 Belatacept (Nulojix®) to new clinical utilization management guideline document with the same title.</td>
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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member’s card.

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Subject: Abaloparatide (Tymlos™) Injection

Guideline #: CG-DRUG-112  Publish Date: 09/20/2018
Status: New  Last Review Date: 07/26/2018

Description

This document addresses the use of abaloparatide (Tymlos™) injection manufactured by Radius Health, Inc. (Waltham, MA), which is a novel synthetic 34 amino acid peptide, intended for subcutaneous use. Abaloparatide is an analog of human parathyroid hormone related peptide, PTHrP (1-34) that selectively activates the parathyroid hormone type 1 receptor for the treatment of postmenopausal osteoporosis in a select population of women considered at high risk for fractures.

Note: Please see the following related document for additional information:

- CG-DRUG-73 Denosumab (Prolia®, Xgeva®)

Clinical Indications

Medically Necessary:

Abaloparatide (Tymlos) injection is considered medically necessary for the treatment of osteoporosis to increase bone mass when all the following criteria are met (A through F):

A. Individual is a postmenopausal female with one of the following (1 or 2):
   1. A diagnosis of osteoporosis defined as a bone mineral density (BMD) T-score in the spine, femoral neck, total hip or distal 1/3 of the radius of less than or equal to -2.5 as compared to a young-adult reference population; or
   2. A diagnosis of osteoporosis based on history of an osteoporotic low trauma fracture (fragility fracture) and considered at high risk for additional fractures;

and

B. The individual meets one of the following (1 or 2):
   1. Has been refractory to a prior trial of an oral bisphosphonate; or
   2. Is intolerant of, or has a contraindication to, oral bisphosphonate therapy as defined by one of the following (a through e):
      a. Hypersensitivity to TWO oral bisphosphonates (one of which must be generic alendronate); or
      b. Inability to stand or sit upright for at least 30 minutes; or
c. A pre-existing gastrointestinal disorder (for example, Barrett's esophagus, hypersecretory disorders, delayed esophageal emptying, etc.); or
d. Uncorrected hypocalcemia; or
e. Severe renal insufficiency as defined by creatinine clearance less than 35 mL/min for alendronate agents or creatinine clearance less than 30 mL/min for risedronate and ibandronate;

and

C. The individual has sustained an osteoporotic low trauma fracture (fragility fracture) while on an oral bisphosphonate or has been refractory to, intolerant of, or has a contraindication to one of the following drugs (1 or 2):
   1. Prolia (denosumab); or
   2. Reclast (zoledronic acid);

and

D. The individual has been refractory to, or intolerant of, or has a contraindication to Forteo (teriparatide);

and

E. The individual is not using abaloparatide injection in combination with any of the following drugs (1 through 6):
   1. Prolia (denosumab); or
   2. Bisphosphonates; or
   3. Evista (raloxifene); or
   4. Miacalcin/Fortical (calcitonin nasal spray); or
   5. Reclast (zoledronic acid); or
   6. Forteo (teriparatide);

and

F. The individual has utilized abaloparatide injection AND parathyroid hormone analogs (for example, teriparatide [Forteo®]) for a combined total duration of less than 24 months in the individual's lifetime.

**Not Medically Necessary:**

Abaloparatide (Tymlos) injection is considered not medically necessary for any of the following (A, B, or C):

A. When abaloparatide (Tymlos) injection has been used for more than a total lifetime duration of 2 years; or
B. If a parathyroid hormone analog (for example, teriparatide [Forteo]) has been used for more than a total lifetime duration of 2 years' time; or
C. If abaloparatide and a parathyroid hormone analog (for example, teriparatide [Forteo]) have been used for a combined total lifetime duration of 2 years or longer.

**Note:** Cumulative use of Tymlos and parathyroid hormone analogs (for example, teriparatide [Forteo]) for more than 2 years during an individual's lifetime is not recommended (FDA Black Box Warning, 2017).

Abaloparatide (Tymlos) injection is considered not medically necessary in males and when the criteria are not met and for all other indications.

**Coding**

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member
coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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Discussion/General Information

According to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (2016), more than 53 million people in the United States today either have osteoporosis or are at high risk for the disease, as a result of low bone mass. Osteoporosis is a disease in which the bones become weak and are more likely to break. The disease is 4 times more likely to occur in women than in men. It is estimated that a total of 1.5 million fractures occurring annually, (that is, 1 out of every 2 women over age 50) are due to osteoporosis. These fractures are most common at the hip, spine, and wrist and can result in serious morbidity, including death. As the U.S. population ages, the incidence of osteoporosis in the U.S. is expected to increase significantly in the future.

On April 28, 2017 the U.S. Food and Drug Administration (FDA) approved abaloparatide (Tymlos) injection, which is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. This decision was based on the studies described below. Abaloparatide is intended for daily subcutaneous injection and is supplied in a pre-assembled disposable pen for self-injection use for up to 30 days. Notably, the FDA issued a Black Box Warning for risk of osteosarcoma as follows:

- It is unknown whether TYMLOS will cause osteosarcoma in humans.
- The use of TYMLOS is not recommended in patients at increased risk of osteosarcoma including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton.
- Cumulative use of TYMLOS and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient’s lifetime is not recommended.

Additionally, Tymlos is not indicated for use in females of reproductive potential (FDA, 2017). For additional warnings, precautions, and possible adverse reactions, see the FDA prescribing information.

Clinical trials of abaloparatide have consisted of a phase II dose ranging study (Leder, 2015) and one phase III double-blinded randomized controlled trial, the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), which published results in 2016. From March 2011 to October 2014, 28 sites in 10 countries recruited postmenopausal women with bone mineral density (BMD) T-scores of less than or equal to -2.5 and greater than -5.0 at the lumbar spine or femoral neck, and radiological evidence of greater than or equal to 2 mild or 1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years. For 18 months, blinded, daily subcutaneous injections of placebo (n=821); abaloparatide, 80 μg (n=824); or open-label teriparatide, 20 μg (n=818) were administered. The primary endpoint was the percentage of participants with new vertebral fracture in the abaloparatide vs. placebo groups. Sample size was set to detect a 4% difference (57% risk reduction) between treatment groups. Secondary endpoints included change in BMD at total hip, femoral neck, and lumbar spine in abaloparatide-treated vs. placebo participants and time to first incident of nonvertebral fracture. Hypercalcemia was a prespecified safety endpoint in the abaloparatide-treated vs. teriparatide participants.

Results showed that, among 2463 women (mean age, 69 years [range, 49-86]), 1901 completed the study. New morphometric vertebral fractures occurred less frequently in the active treatment groups vs. placebo. The Kaplan-Meier estimated event rate for nonvertebral fracture was lower with abaloparatide vs. placebo. BMD increases were greater with abaloparatide than placebo (all p<0.001). The incidence of hypercalcemia was lower with the abaloparatide group (3.4%) vs. the teriparatide group (6.4%) (risk difference [RD], -2.96; 95% confidence interval [CI], -5.12 to -0.87; p=0.006). The authors concluded that among postmenopausal women with osteoporosis, the use of subcutaneous abaloparatide, compared with placebo, reduced the risk of new vertebral and nonvertebral fractures over 18 months. However, further research is needed to understand the clinical importance of the difference in risk
(RD), the risks and benefits of abaloparatide treatment, and the efficacy of abaloparatide vs. other osteoporosis treatment options (Miller, 2016).

Results of the ACTIVE trial and of an extension of the ACTIVE, the ACTIVEExtend trial, showed that there were no clinically meaningful interactions between any of the baseline risk factors and the treatment effect of abaloparatide-SC on new morphometric vertebral fractures, nonvertebral fractures, or BMD increases. The authors concluded that abaloparatide provides protection against fractures consistently across a wide variety of ages and baseline risks, including those with and without prior fractures, and it has potential utility for a broad group of postmenopausal women with osteoporosis (Bone, 2018; Cosman, 2017a; Cosman, 2017b; Moreira, 2017).

Abaloparatide most closely compares with Forteo (teriparatide), which is a recombinant human parathyroid hormone that stimulates bone formation. Abaloparatide is indicated for treatment of postmenopausal women with osteoporosis who are determined to be at higher-than-average risk for nonvertebral fractures. Both Forteo and abaloparatide are for daily subcutaneous injections. According to the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis (updated 2016), Forteo has a 2 year lifetime maximum limitation of use (Grade A, BEL: 1), due to the lack of long-term safety data, and an FDA Black Box warning for possible risk of osteosarcoma. The FDA labeling for abaloparatide (Tymlos) injection contains this same 2 year limitation of use due to possible risk for osteosarcoma.

**Definitions**

Osteopenia: A condition of bone in which decreased calcification, decreased density, or reduced mass occurs (defined as a BMD T-score between -1.0 and -2.5 SD).

Osteoporosis: Loss of normal bone density, mass and strength, leading to increased porousness and vulnerability to fracture (defined as a BMD T-score of -2.5 or less).

Refractory (to treatment for osteoporosis): This term refers to ineffectual clinical results of medical therapy which, regarding osteoporosis, results in conditions, such as continued loss of bone mass or occurrence of low-trauma fractures, despite compliance with prescribed treatment doses of medications, such as oral bisphosphonates.

**References**

**Peer Reviewed Publications:**

Government Agency, Medical Society, and Other Authoritative Publications:


Websites for Additional Information


Index

Abaloparatide
Osteoporosis
Tymlos

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

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Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member’s card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan’s or line of business’s members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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Subject: Ziconotide Intrathecal Infusion (Prialt®) for Severe Chronic Pain

Document #: DRUG.00027  Publish Date: 02/27/2019
Status: Reviewed  Last Review Date: 01/24/2019

Description/Scope

This document addresses ziconotide (Prialt, TerSera™ Therapeutics LLC, Lake Forest, IL), a non-opioid analgesic drug that reduces pain and is used to treat individuals with severe chronic pain. Ziconotide is infused into the intrathecal space, a fluid-filled space between the thin layers of tissue that cover the brain and spinal cord.

Position Statement

Medically Necessary:

Ziconotide intrathecal infusion is considered medically necessary for the management of severe chronic pain in those individuals for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine.

Investigational and Not Medically Necessary:

All other uses of ziconotide intrathecal infusion, including but not limited to treatment of post-operative pain, acute brain injury, and spasticity associated with spinal cord trauma are considered investigational and not medically necessary.

Rationale

On December 28, 2004, the U.S. Food and Drug Administration (FDA) approved ziconotide intrathecal infusion (Prialt) for the management of severe chronic pain in individuals for whom IT therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine. FDA approval of Prialt was based on the treatment of more than 1200 participants and three phase III clinical trials, which evaluated the efficacy and safety of IT ziconotide infusion in those with severe chronic pain that was not adequately managed despite a regimen of systemic and/or IT analgesic and other drugs.

Three published double-blind placebo-controlled randomized controlled trials (RCTs) have evaluated the safety and efficacy of IT ziconotide infusion in individuals with severe chronic pain refractory to treatment with other medications. Staats and colleagues (2004) used a high-dose IT ziconotide, fast titration method. This trial involved 111 participants with refractory pain due to acquired immune deficiency syndrome (AIDS) or cancer and a mean Visual Analog Scale of Pain Intensity (VASPI) score of 50 mm or greater. Subjects were randomized 2:1 to receive ziconotide or placebo, respectively. A mean change in VASPI score from baseline to the end of the titration period...
was the main outcome measure of the study. IT medications were discontinued in those who were already receiving IT therapy and those who were not yet receiving IT therapy received implantation of an intrathecal catheter with an external infusion pump system. All participants continued to receive systemic and oral analgesics during the study period. Subjects underwent a 5-day titration period and “responders” (defined as those with a 30% or greater decrease in VASPI with no concomitant increase in opioid use or change in opioid class) were continued on a 5-day maintenance phase; all drug responders could opt to enroll in a long-term open-label study of the drug. Nonresponders were allowed to cross over to the opposite group for 5 or 6 days. The main efficacy results reported by the study were: mean VASPI scores improved 53.1% (95% confidence interval [CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group (p<0.001), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of those in the ziconotide group compared with 17.5% in the placebo group (p<0.001). Five participants receiving ziconotide achieved complete pain relief, and 50.0% of those receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo (p=0.001). Twelve subjects in the ziconotide group had to discontinue therapy because of adverse events, compared with 4 in the placebo group. During the titration phase, 4 placebo participants (10%) and 22 ziconotide participants (30.6%) reported 31 serious adverse events and, of these, 14 involving the nervous system (5 moderate, 9 severe) were considered to be related to ziconotide therapy. The most common serious adverse events experienced by ziconotide subjects during the initial titration phase were confusion, somnolence and urinary retention.

Rauck and colleagues (2006), was a phase III trial conducted in response to the FDA’s request for additional data using lower doses and a slower titration. This randomized, double-blind, placebo-controlled study was conducted at 39 sites in the U.S. and included 220 adults with opioid-resistant, severe chronic pain. Most of the subjects had neuropathic pain. All subjects had programmable IT infusion systems and were randomized to receive IT ziconotide (n=112) or placebo (n=108). At baseline, the mean VASPI score, for both placebo and ziconotide groups was 80.7 mm (VASPI score of 0 mm = no pain; 100 mm = worst possible pain). Treatment was initiated at 2.4 mcg/day (0.1 mcg/hour) and was increased by less than or equal to 2.4 mcg/day (less than or equal to 0.1 mcg/hour), no more than 2 to 3 times a week for 3 weeks. The primary efficacy measure was mean percent change in the VASPI score at week 3, which showed statistically significant improvement in those receiving ziconotide IT infusion versus placebo (p=0.036). Improvement in VASPI score was seen as early as week 1. The mean dose at week 3 was 6.9 mcg/day (0.29 mcg/hour). The majority of secondary efficacy endpoints also showed statistically significant improvement in those receiving ziconotide IT infusion. Adverse events were mild or moderate for a majority of the participants. The four most frequently reported adverse events in this clinical trial were dizziness, ataxia (unsteady walking), confusion, and abnormal gait (difficulty walking). Study discontinuation amongst the ziconotide group due to adverse events was comparable with that for placebo (5.4% and 4.6%, respectively).

The third RCT, a fast titration trial by Wallace and colleagues (2006), included adults with severe non-malignant chronic pain (VASPI score ≥ 50 mm) refractory to other treatments. Individuals were randomized in a 2:1 ratio to receive IT ziconotide (n=169) or placebo (n=86) using an implanted infusion pump. Participants underwent an initial 6-day titration period and treatment responders, defined as at least a 30% improvement in the VASPI and stable or decreased opioid use, continued receiving medications in a 5-day maintenance phase. The primary efficacy endpoint was the mean percent change in VASPI score from baseline to the end of the titration period. At this time, there was significantly greater improvement in VASPI score in the ziconotide group (mean: 31.2%) than the placebo group (mean: 6%), p<0.001. The proportion of treatment responders was significantly higher in the ziconotide group (33.7%) than the placebo group (12.8%), p<0.001. Overall, 57 serious adverse events (SAEs) were reported by 39 individuals in the ziconotide group compared with 3 SAEs in the placebo group.

The 3 RCTs described above are included in a meta-analysis published by Brookes and colleagues in 2017. A pooled analysis of the primary outcome in all of the studies, VASPI, found a statistically significant benefit of ziconotide compared with placebo (Odds ratio [OR]: 2.77, 95% CI: 1.37 to 5.59).

There are also a number of uncontrolled observational studies evaluating IT ziconotide for treating chronic pain (Alicnio, 2012; Deer, 2017; Mohammed, 2013; Wallace, 2008; Webster, 2009). One of the larger studies with longer-term follow-up was Wallace and colleagues (2008). The authors reported on 644 participants who received ziconotide titration followed by long-term infusion. Of this group, 119 participants received ziconotide for greater than or equal to 360 days with a median duration of therapy of 67.5 days (range, 1.2-1215.5 days). The mean dose at last infusion was 8.4 mcg/d (range, 0.048-240.0 mcg/d). Median VASPI scores at baseline, 1 month, and the last available observation up to 2 months were 76 mm (range, 4-100 mm), 68 mm (range, 0-100 mm), and 73 mm (range, 0-100 mm), respectively. Most participants (99.7%) experienced one or more adverse events. Most adverse events were of mild (43.5%) or moderate (42.3%) severity and 58.6% of adverse events were considered unrelated to ziconotide. The most common adverse events reported included nausea, dizziness, headache, confusion, pain, somnolence and memory impairment. Clinically significant abnormalities in creatine kinase levels were reported in
of serious neurological or psychiatric signs or symptoms. The risk of addiction, and therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in potential advantages of ziconotide IT infusion for treating chronic pain is that the mediator of neurotransmitter release from primary nociceptive afferents term labeling. Direction of a physician experienced in the technique of IT administration and who is familiar with the drug and device transmission of pain signals. Ziconotide does not bind to opioid receptors and opioid antagonists do not block the pharmacological effects of ziconotide. Ziconotide should be administered intrathecally using a programmable implanted variable-rate microinfusion device or an external microinfusion device and catheter, by or under the direction of a physician experienced in the technique of IT administration and who is familiar with the drug and device labeling. Ziconotide is not intended for intravenous administration. Ziconotide produces analgesia by blocking neurotransmitter release from primary nociceptive afferents terminating in the superficial layers of the spinal cord dorsal horn. The combination of ziconotide with IT opiates is not recommended (Product Information Label, 2013).

Potential advantages of ziconotide IT infusion for treating chronic pain is that the medication is not associated with the risk of addiction, and therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.
**Adverse Events and Warnings**

Black box warnings and recommendations from the Product Information Label (2018) include the following:

**WARNING: Neuropsychiatric Adverse Reactions.** PRIALT is contraindicated in patients with a preexisting history of psychosis. Severe psychiatric symptoms and neurological impairment may occur during treatment with PRIALT. Monitor all patients frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. Discontinue PRIALT therapy in the event of serious neurological or psychiatric signs or symptoms.

Additional information and recommendations from the Product Information Label (2018) include the following:

The following medically important adverse reactions occurred in less than 2% of patients were assessed by the clinical investigators as related to PRIALT: acute renal failure, atrial fibrillation, cerebrovascular accident, sepsis, meningitis, psychotic disorder, suicidal ideation, respiratory distress, rhabdomyolysis, electrocardiogram abnormal, stupor, loss of consciousness, clonic convulsion and grand mal convulsion. Fatal aspiration pneumonia and suicide attempt were reported in less than 1% of patients.

**Definitions**

Afferent: Carrying inward to a central organ or section, as nerves that conduct impulses from the periphery of the body to the brain or spinal cord.

Intrathecal space: The space between the spinal cord and the surrounding membrane, which is filled with cerebrospinal fluid.

Neuropathic pain: Pain resulting from actual damage to the nervous system.

Nystagmus: Fast, uncontrollable movements of the eye.

**Coding**

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**When services may be Medically Necessary when criteria are met:**

**HCPCS**

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**ICD-10 Diagnosis**

All diagnoses

**When services are Investigational and Not Medically Necessary:**

For the procedure code listed above when criteria are not met, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.
Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:


Websites for Additional Information


Index

Prialt
Ziconotide

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

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<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review.</td>
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<td></td>
<td></td>
<td>Description/Scope, Rationale and References sections updated.</td>
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</table>
Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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The document addresses the indications for interleukin-17A (IL-17A) monoclonal antibody drugs used in the treatment of adults with active ankylosing spondylitis, moderate to severe plaque psoriasis, or active psoriatic arthritis.

The U.S. Food and Drug Administration (FDA) has approved the following IL-17A receptor antagonists for use in specific indications:

- Brodalumab (Siliq™, Valeant Pharmaceuticals North America, LLC, Inc., Bridgewater, NJ)
- Ixekizumab (Taltz®, Eli Lilly and Company, Indianapolis, IN)
- Secukinumab (Cosentyx®, Novartis Pharmaceuticals Corporation, East Hanover, NJ)

Note: Please see the following related documents for additional information:

- CG-DRUG-65 Tumor Necrosis Factor Antagonists
- CG-DRUG-69 Ustekinumab (Stelara®)

Note: For additional information on review of clinically equivalent cost effective criteria for products addressed in DRUG.00077, please refer to CG-ADMIN-02 Clinically Equivalent Cost Effective Services - Targeted Immune Modulators.

Position Statement

I. Brodalumab

Medically Necessary:

Brodalumab is considered medically necessary for the treatment of plaque psoriasis when each of the following criteria are met:

1. Individual is 18 years of age or older with moderate to severe plaque psoriasis with either of the following:
   a. Plaque psoriasis involving greater than 5% body surface area (BSA); or
   b. Plaque psoriasis involving less than or equal to 5% BSA involving sensitive areas or areas that significantly impact daily function (such as, palms, soles of feet, head, neck, or genitalia); and
2. Agent is used for any of the following reasons:
   a. To reduce signs or symptoms; or
   b. To induce or maintain clinical response; and
3. Individual has failed to respond to, is intolerant of, or has a medical contraindication to phototherapy or other systemic therapy (such as acitretin, cyclosporine, or methotrexate).

**Not Medically Necessary:**

Brodalumab is considered **not medically necessary** for an individual with any of the following:

1. Use of brodalumab in combination with other immunosuppressive therapy or phototherapy; or
2. Use of brodalumab in combination with other biologic drugs (such as adalimumab, certolizumab pegol, etanercept, infliximab, ixekizumab, secukinumab, or ustekinumab); or
3. Tuberculosis, invasive fungal infection, other active serious infections, or a history of recurrent infections; or
4. Individual has not had a tuberculin skin test (TST) or a Centers for Disease Control and Prevention (CDC)-recommended equivalent test to evaluate for latent tuberculosis prior to initiating brodalumab.

**Investigational and Not Medically Necessary:**

Brodalumab is considered **investigational and not medically necessary** when the criteria above are not met and for all other conditions including, but not limited to:

1. Asthma; or
2. Crohn’s disease; or
3. Psoriatic arthritis; or
4. Rheumatoid arthritis.

**II. Ixekizumab**

**Medically Necessary:**

A. Ixekizumab is considered **medically necessary** for the treatment of plaque psoriasis when each of the following criteria are met:
   1. Individual is 18 years of age or older with moderate to severe plaque psoriasis with either of the following:
      a. Plaque psoriasis involving greater than 5% BSA; or
      b. Plaque psoriasis involving less than or equal to 5% BSA involving sensitive areas or areas that significantly impact daily function (such as, palms, soles of feet, head, neck, or genitalia); and
   2. Agent is used for any of the following reasons:
      a. To reduce signs or symptoms; or
      b. To induce or maintain clinical response; and
   3. Individual has failed to respond to, is intolerant of, or has a medical contraindication to phototherapy or other systemic therapy (such as acitretin, cyclosporine, or methotrexate).

B. Ixekizumab is considered **medically necessary** for the treatment of psoriatic arthritis when the following criteria are met:
   1. Individual is 18 years of age or older with active psoriatic arthritis; and
   2. Agent is used for any of the following reasons:
      a. To reduce signs or symptoms; or
      b. To induce or maintain clinical response; and
   3. Individual has failed to respond to, is intolerant of, or has a medical contraindication to conventional drug therapy including disease-modifying antirheumatic drugs or a tumor necrosis factor antagonist.

**Not Medically Necessary:**
Ixekizumab is considered **not medically necessary** for an individual with any of the following:

1. Use of ixekizumab in combination with other immunosuppressive therapy or phototherapy; or
2. Use of ixekizumab in combination with other biologic drugs (such as adalimumab, brodalumab, certolizumab pegol, etanercept, infliximab, secukinumab, or ustekinumab); or
3. Tuberculosis, invasive fungal infection, other active serious infections, or a history of recurrent infections; or
4. Individual has not had a TST or a CDC-recommended equivalent test to evaluate for latent tuberculosis prior to initiating ixekizumab.

**Investigational and Not Medically Necessary:**

Ixekizumab is considered **investigational and not medically necessary** when the criteria above are not met and for all other conditions including, but not limited to:

1. Rheumatoid arthritis; or
2. Uveitis.

**III. Secukinumab**

**Medically Necessary:**

A. Secukinumab is considered **medically necessary** for the treatment of ankylosing spondylitis when the following criteria are met:
   1. Individual is 18 years of age or older with active ankylosing spondylitis; and
   2. Agent is used for any of the following reasons:
      a. To reduce signs or symptoms; or
      b. To induce or maintain clinical response; and
   3. Individual has failed to respond to, is intolerant of, or has a medical contraindication to conventional drug therapy including a tumor necrosis factor antagonist.

B. Secukinumab is considered **medically necessary** for the treatment of plaque psoriasis when each of the following criteria are met:
   1. Individual is 18 years of age or older with moderate to severe plaque psoriasis with either of the following:
      a. Plaque psoriasis involving greater than 5% BSA; or
      b. Plaque psoriasis involving less than or equal to 5% BSA involving sensitive areas or areas that significantly impact daily function (such as, palms, soles of feet, head, neck, or genitalia); and
   2. Agent is used for any of the following reasons:
      a. To reduce signs or symptoms; or
      b. To induce or maintain clinical response; and
   3. Individual has failed to respond to, is intolerant of, or has a medical contraindication to phototherapy or other systemic therapy (such as acitretin, cyclosporine, or methotrexate).

C. Secukinumab is considered **medically necessary** for the treatment of psoriatic arthritis when the following criteria are met:
   1. Individual is 18 years of age or older with active psoriatic arthritis; and
   2. Agent is used for any of the following reasons:
      a. To reduce signs or symptoms; or
      b. To induce or maintain clinical response; and
   3. Individual has failed to respond to, is intolerant of, or has a medical contraindication to conventional drug therapy including disease-modifying antirheumatic drugs or a tumor necrosis factor antagonist.

**Not Medically Necessary:**

Secukinumab is considered **not medically necessary** for an individual with any of the following:
1. Use of secukinumab in combination with other immunosuppressive therapy or phototherapy; or
2. Use of secukinumab in combination with other biologic drugs (such as adalimumab, brodalumab, certolizumab pegol, etanercept, infliximab, ixekizumab, or ustekinumab); or
3. Tuberculosis, invasive fungal infection, other active serious infections, or a history of recurrent infections; or
4. Individual has not had a TST or a CDC-recommended equivalent test to evaluate for latent tuberculosis prior to initiating secukinumab.

Investigational and Not Medically Necessary:

Secukinumab is considered investigational and not medically necessary when the criteria above are not met and for all other conditions including, but not limited to:

1. Rheumatoid arthritis; or
2. Uveitis.

Rationale

Brodalumab

Brodalumab for Moderate to Severe Plaque Psoriasis

Brodalumab is a human immunoglobulin G2 (IgG2) IL-17A monoclonal antibody that selectively binds and blocks signaling to the interleukin 17 receptor A (IL-17RA). On February 15, 2017, the FDA approved brodalumab for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies (Siliq Product Information [PI] Label, 2017). Labeling for brodalumab includes a Boxed Warning for suicidal ideation and behavior and the drug is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Siliq REMS Program. Brodalumab is a 210 milligram (mg) subcutaneous injection administered at weeks 0, 1, and 2 followed by 210 mg every 2 weeks thereafter.

AMAGINE-1 Clinical Trial

The safety and efficacy of brodalumab was evaluated in three multicenter, prospective, double-blind, placebo and comparator controlled phase III clinical trials (AMAGINE-1, AMAGINE-2, AMAGINE-3) of adults 18-75 years of age with stable moderate to severe plaque psoriasis ≥ 6 months, ≥ 10% BSA involvement, a Psoriasis Area and Severity Index (PASI) ≥ 12 and static Physician’s Global Assessment (sPGA) ≥ 3, and no known history of active tuberculosis and were negative for tuberculosis during screening (or received prophylactic treatment). Individuals with a history of psychiatric disorders were not specifically excluded from the trials. AMAGINE-1 (Papp, 2016) was a 12-week placebo controlled study and included an induction period followed by a withdrawal and retreatment period up to 52 weeks. Participants who responded at week 12 were re-randomized to receive placebo or to continue their induction dose in a blinded manner. AMAGINE-2 and AMAGINE-3 (Lebwohl, 2015) were identical in study design and included both a placebo and an active control (ustekinumab [Stelara], Janssen Biotech, Inc, Horsham, PA). Participants originally randomized to receive brodalumab during the induction phase were re-randomized at week 12 to receive one of four maintenance regimens of brodalumab. The sPGA success (0 or 1) and the PASI 75 at week 12 were co-primary efficacy endpoints in all three phase III studies for brodalumab and placebo comparisons. PASI 100 was a coprimary endpoint for comparison of brodalumab 210 mg every 2 weeks to ustekinumab at week 12. At week 52, the maintenance endpoint across all three studies was sPGA success (0 or 1) for brodalumab versus placebo in AMAGINE-1, and comparison of the four maintenance regimens for AMAGINE-2 and AMAGINE-3.

During the induction phase of AMAGINE-1 (Papp, 2016), 661 participants were randomized to receive brodalumab 210 mg (n=222), brodalumab 140 mg (n=219), or placebo (n=220) every 2 weeks, with an additional dose at week 1. During the withdrawal phase, participants originally randomized to brodalumab 210 or 140 mg every 2 weeks with sPGA score 0 or 1 (sPGA success) at week 12 were re-randomized to receive induction doses of brodalumab or placebo. Beginning at week 16, re-randomized participants who experienced return of disease (sPGA ≥ 3) were eligible for retreatment with sPGA score 0 or 1 (sPGA success) at week 12 were re-randomized to receive induction doses of brodalumab or placebo. Beginning at week 16, re-randomized participants who experienced return of disease (sPGA ≥ 3) were eligible for retreatment and received induction doses of brodalumab. After at least 12 weeks of retreatment with inadequate response (sPGA 2 over at least a 4-week period or sPGA ≥ 3), participants qualified for rescue therapy and received open-label brodalumab 210 mg every 2 weeks. At week 12, participants originally randomized to
brodalumab with sPGA ≥ 2 or placebo received brodalumab 210 mg every 2 weeks. The coprimary endpoints were the percentage of participants with ≥ 75% improvement in PASI 75 and sPGA success at week 12. At week 12, 132 (60.3%) and 185 (83.3%) participants in the brodalumab 140 mg and 210 mg arms, respectively versus 6 (2.7%) participants in the placebo group achieved PASI 75. A total of 118 (53.9%) and 168 (75.7%) participants in the brodalumab 140 mg and 210 mg arms, respectively, versus 3 (1.4%) participants in the placebo group achieved sPGA success (p<0.001 between both brodalumab arms and placebo). Participants who achieved sPGA success at week 12 were re-randomized to their induction doses of brodalumab or placebo during the withdrawal phase (12-52 weeks). At week 52, the percentages of participants randomized to 210 mg in the induction phase with sPGA success were 83% and 0% for the re-randomized 210 mg and placebo groups, respectively. The percentages of participants randomized to 140 mg in the induction phase with sPGA success were 70% and 5% for the re-randomized 140 mg and placebo groups, respectively (p<0.001 for both brodalumab doses). The percentages of participants with PASI 90 and PASI 100 were maintained through week 52 among responders at week 12 who were re-randomized to their induction dose of brodalumab. Participants who experienced return of disease (sPGA ≥ 3 after week 16) during the withdrawal phase were eligible for retreatment with their induction dose of brodalumab. Among those participants evaluable after 12 weeks of retreatment, 97% (31 participants) and 84% (16 participants) receiving 210 mg and 140 mg brodalumab, respectively, regained sPGA success after 12 weeks of retreatment; 84% (27 participants) and 68% (13 participants) in the 210 mg and 140 mg arms, respectively achieved sPGA 0. The median time to regain sPGA success for both 210 mg and 140 mg was 4 weeks.

At least one adverse event reported during the induction phase occurred in 59%, 58%, and 51% of participants in the 210 mg, 140 mg, and placebo groups, respectively. Serious adverse events were reported in 1.8%, 2.7% and 1.4% in the 210 mg, 140 mg, and placebo groups, respectively. The most frequent adverse events (≥ 5% in any group) were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. Depression was reported in 3 participants (1 in each group), neutropenia in 1 participant (140 mg) and suspected Candida infection in 9 participants (3 in placebo, 1 in 140 mg and 5 in 210 mg). There were no major adverse cardiac events (MACE) or fatal adverse events. However, four fatal adverse events occurred through week 52: sudden death in a participant receiving constant 210 mg brodalumab; an intentional illicit drug overdose considered by the coroner to be suicide in a participant receiving placebo (induction phase) and 210 mg (withdrawal phase); esophageal varices hemorrhage in a participant with a history of cirrhosis receiving constant 210 mg brodalumab; and, cerebrovascular accident in a participant receiving 210 mg brodalumab (induction phase), placebo (withdrawal phase) and 210 mg brodalumab (retreatment phase). There was one additional suicide after week 52 (day 415) during the uncontrolled open-label extension in a participant receiving 210 mg brodalumab (induction phase), placebo (withdrawal phase) and 210 mg brodalumab (retreatment phase) (Papp, 2016).

AMAGINE-2 and AMAGINE-3 Clinical Trials

Study participants in AMAGINE-2 (n=1831) and AMAGINE-3 (n=1881) (Lebwohl, 2015) were randomly assigned to receive brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for participants with a body weight ≤ 100 kg and 90 mg for those > 100 kg), or placebo. At week 12, participants receiving brodalumab were randomly assigned again to receive a brodalumab maintenance dose of 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks, or every 8 weeks; participants receiving ustekinumab continued to receive ustekinumab every 12 weeks, and participants receiving placebo received 210 mg of brodalumab every 2 weeks. Response rates were statistically higher comparing brodalumab to placebo and to ustekinumab with respect to the primary endpoints in both studies. At week 12, the primary co-endpoint for PASI 75 response rates was higher with brodalumab at the 210 mg and 140 mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively, vs. 6% [AMAGINE-3]; p<0.001). The rates of sPGA scores of 0 or 1 were also higher with brodalumab (p<0.001). The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3]; p<0.001). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (p=0.08 for the comparison with ustekinumab) and 27% in AMAGINE-3 (p=0.007). Other secondary endpoints and efficacy response rates were significantly higher in the brodalumab groups than with use of ustekinumab, with the exception of 210 mg of brodalumab use in AMAGINE-2 (p=0.08). The median time to a response in both studies was significantly shorter with either brodalumab dose than with ustekinumab (p<0.001). In the maintenance phase of AMAGINE-2, 1174 participants were assigned in the re-randomization process to receive brodalumab, and 297 switched from placebo; 1331 participants (90%) remained in the study at week 52. In AMAGINE-3 study, 1200 participants were assigned in the re-randomization process to receive brodalumab, and 298 participants switched from placebo, with 1370 participants (91%) remaining in the study at week 52. A total of 55 of 300 participants in the AMAGINE-2 study who were assigned to receive ustekinumab were given rescue therapy with brodalumab at week 16; 69 of 313 participants (22%) received rescue therapy in the AMAGINE-3 study. The proportion of participants with an sPGA score of 0 or 1 at week 52 was significantly higher among those who had received 210 mg or 140 mg of brodalumab every 2 weeks than among those who had received the other brodalumab maintenance regimens (p<0.001). Most participants who were given rescue therapy
with brodalumab after ustekinumab treatment had PASI 75 and sPGA 0 or 1 responses, and more than 40% had PASI 100 responses.

Specific safety concerns with use of brodalumab were identified, including infections, malignancy, neutropenia, worsening of Crohn’s disease, immunogenicity (anti-brodalumab antibodies), suicide ideation and behavior (SIB), and cardiac disorders (including MACE). Rates of neutropenia were higher and mild or moderate candida infections were more frequent with brodalumab and with ustekinumab than with placebo. Serious adverse events overall occurred with similar frequency in the placebo, ustekinumab and brodalumab groups by 12 weeks, including cellulitis, appendicitis, gastroenteritis, and acute pancreatitis. By week 52, serious adverse events occurred with similar rates in the brodalumab and ustekinumab groups, including cellulitis, myocardial infarction, and cholelithiasis. The rates of serious adverse events per 100 patient-years through week 52 were 8.3 with brodalumab and 13.0 with ustekinumab in the AMAGINE-2 study and 7.9 and 4.0, respectively in the AMAGINE-3 study. One case of Crohn’s disease occurred during the maintenance phase. In the AMAGINE-2 study, one death from stroke occurred during the induction phase in the 210 mg brodalumab group, 20 days after the last dose. Five deaths occurred through week 52 in both studies: three deaths from cardiac arrest in brodalumab-treated participants, one death from pancreatic carcinoma in a ustekinumab-treated participant, and one accidental death in a motor vehicle accident. Three deaths occurred after exposure to brodalumab, including one suicide (27 days after the last dose of brodalumab in the AMAGINE-2 study). In the AMAGINE-3 study, one death occurred from hematophagic histiocytosis syndrome and one death from cardiomyopathy. There was one additional suicide after week 52 during the open-label extension of the AMAGINE-2 study (Lebwohl, 2015).

**Summary of Safety Information for Brodalumab**

From the clinical trials data, the known adverse events with use of brodalumab include exacerbation of existing Crohn’s disease, infections, and neutropenia. Through the end of the clinical trials, the long term rate of fatal events occurring during or after use of brodalumab was reported as 23 deaths: 12 cardiovascular, 4 completed suicides, 2 accidental deaths, and 4 other single events. There were insufficient numbers of MACE events in the studies for meaningful comparison to placebo. While the MACE rate was highest in brodalumab-treated participants, MACE rates were similar with use of other biologic drugs for the treatment of moderate to severe plaque psoriasis. In addition, it is uncertain from the study data if there is a potential relationship between brodalumab and completed suicide, and other SIB and adverse events; therefore, no conclusions can be drawn whether or not these serious adverse events were drug-related. According to the FDA (2017),

> …brodalumab users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior compared to users without this history. A causal association between treatment with Siliq and increased risk of suicidal ideation and behavior has not been established.

Because of the observed risk of suicidal ideation and behavior, the FDA is requiring additional labeling for brodalumab including a Boxed Warning and availability of the drug only through the restricted Siliq REMS Program.

**Other Proposed Uses of Brodalumab**

Brodalumab has been investigated for use in the treatment of asthma, Crohn’s disease, generalized pustular psoriasis and psoriatic erythroderma, psoriatic arthritis, and rheumatoid arthritis. To date, the FDA has not approved the use of brodalumab for any of these indications.

**Asthma**

Busse and colleagues (2013) attempted to determine the efficacy and safety of brodalumab in a randomized, double-blind, placebo-controlled study of 302 individuals with inadequately controlled moderate to severe asthma taking regular inhaled corticosteroids. Subjects were randomized to brodalumab (140 mg, 210 mg, or 280 mg) or placebo. The primary endpoint was change in Asthma Control Questionnaire (ACQ) score from baseline to week 12. For the overall study population, no treatment differences were observed. Nine prespecified subgroups were examined without corrections for multiple testing. A change of nominal significance was only observed in the ACQ score in the high-reversibility subgroup (post-bronchodilator forced expiratory volume [FEV1] improvement ≥ 20%; n=112). ACQ responses were nominally significant in the 210 mg brodalumab group (estimated treatment difference, 0.53) but not significant in the higher 280 mg brodalumab group (estimated treatment difference, 0.38). The investigators
concluded that brodalumab did not produce a treatment effect in subjects with asthma and the results of the high-reversibility subgroup analysis were of uncertain significance.

Crohn’s Disease

Targan and colleagues (2016) performed a randomized, double-blind, placebo-controlled, phase II dose-ranging study in individuals with moderate to severe Crohn’s disease and evidence of active inflammation. Participants were randomized to receive brodalumab (210 mg, 350 mg, or 700 mg at baseline and week 4) or placebo. The primary endpoint was the proportion of participants achieving Crohn’s disease activity index (CDAI) remission ($\leq 150$) at week 6. According to the study authors, “the study was terminated early based on an imbalance in worsening CD in active treatment groups.”

Generalized Pustular Psoriasis and Psoriatic Erythroderma

Yamasaki and colleagues (2017) evaluated the efficacy and safety of brodalumab in a 52-week, open-label, multicenter, phase III study in individuals with rare and severe types of psoriasis including generalized pustular psoriasis (n=12) and psoriatic erythroderma (n=18). Participants received brodalumab 140 mg at day 1 and weeks 1 and 2, and then every 2 weeks until week 52. The primary endpoint was the Clinical Global Impression of Improvement (CGI). Evaluation of safety included treatment-emergent adverse events and changes in laboratory parameters. A total of 26 participants completed the study at week 52: 10 and 16 participants in the generalized pustular psoriasis and psoriatic erythroderma groups, respectively. CGI remission or improvement was achieved in 11 and 18 participants with generalized pustular psoriasis and psoriatic erythroderma, respectively. The most commonly reported adverse event was nasopharyngitis (33.3%). Five serious adverse events occurred during the study; however, none was considered treatment-related.

Psoriatic Arthritis

Mease and colleagues (2014) evaluated the efficacy and safety of brodalumab in a phase II, randomized, double-blind, placebo-controlled study involving individuals with psoriatic arthritis. Participants with active psoriatic arthritis were randomly assigned to receive brodalumab (140 mg or 280 mg) or placebo on day 1 and at weeks 1, 2, 4, 6, 8, and 10. At week 12, those who had not discontinued study participation were offered open-label brodalumab (280 mg) every 2 weeks. The primary endpoint was American College of Rheumatology (ACR) response (ACR20) improvement at week 12. A total of 159 of the 168 subjects who underwent randomization (57 in the brodalumab 140 mg group, 56 in the brodalumab 280 mg group, and 55 in the placebo group), completed the double-blind phase and 134 completed 40 weeks of the open-label extension. At week 12, the brodalumab 140 mg and 280 mg groups had higher rates of ACR20 response than the placebo group (37% [p=0.03] and 39% [p=0.02], respectively, vs. 18%); higher rates of 50% improvement (ACR50) were also reported (14% [p=0.05] and 14% [p=0.05] vs. 4%). Rates of 70% improvement were not significantly higher in the brodalumab groups. Similar degrees of improvement were noted among subjects who were previously treated with biologic therapy and those who had not received such therapy. At week 24, ACR20 response rates in the brodalumab 140 mg and 280 mg groups were 51% and 64%, respectively, compared with 44% among subjects who switched from placebo to open-label brodalumab; responses were sustained through week 52. At week 12, serious adverse events occurred in 3% of subjects in the brodalumab groups and in 2% of those in the placebo group. Additional study of larger populations and longer duration are necessary to determine the clinical efficacy and safety of brodalumab in the treatment of individuals with active psoriatic arthritis.

Rheumatoid Arthritis

In a randomized, double-blind, phase Ib multiple ascending dose study, Martin and colleagues (2014) evaluated the safety, pharmacokinetics, and early clinical response of brodalumab in methotrexate-resistant rheumatoid arthritis, with moderate to severe rheumatoid arthritis. Subjects with moderate to severe disease (≥ 6 of 66 swollen and ≥ 8 of 68 tender joints) were randomized 3:1 to receive brodalumab (50 mg, 140 mg, or 210 mg subcutaneously every 2 weeks for six doses per group; or 420 mg or 700 mg intravenously every 4 weeks for two doses per group) or placebo. The study was not designed to assess efficacy. The primary endpoints included incidence of adverse events and pharmacokinetics. A total of 40 subjects were randomized to brodalumab; 1 subject in the placebo group discontinued treatment due to worsening of rheumatoid arthritis-related symptoms. Adverse events were reported by 70% (7 of 10) of placebo subjects and 77% (22 of 30) of brodalumab subjects. Three serious adverse events were reported in 2 subjects; there were no opportunistic infections. No treatment effects were observed with individual measures of rheumatoid arthritis disease activity. On day 85 (week 13) 37% (11 of 30) of brodalumab subjects and
22% (2 of 9) of placebo subjects achieved ACR20; 7% (2 of 30) of brodalumab subjects and 11% (1 of 9) of placebo subjects achieved ACR50; and 0% (0 of 30) of brodalumab subjects and 0% (0 of 9) of placebo subjects achieved ACR70. Although multiple dose administration of brodalumab was tolerated in the study subjects, there was no evidence of a clinical response to brodalumab-treated subjects with moderate to severe rheumatoid arthritis.

Pavelka and colleagues (2015) evaluated the safety, tolerability, and efficacy of brodalumab in subjects with rheumatoid arthritis who had an inadequate response to methotrexate. A total of 252 subjects were randomized to receive subcutaneous injections of brodalumab (70 mg, 140 mg, or 210 mg) or placebo. The primary endpoint was ACR50 response at week 12. At week 12, nonsignificant responses were observed in all subjects in the evaluation of ACR50 response (16% [70 mg], 16% [140 mg], 10% [210 mg], and 13% [placebo]). No significant treatment effects were observed for the secondary endpoints, including ACR20, ACR70, and Disease Activity Score (DAS) in 28 joints. Incidences of all adverse events, including serious adverse events, were similar across treatment groups. A total of 7 subjects reported serious adverse events during the study (2 in the placebo group and 5 in the brodalumab groups), none of which was treatment related. There was one death (cardiopulmonary failure) approximately 1 week after the last dose in the 140 mg group. The investigators conclude that the study “…failed to find evidence of meaningful clinical efficacy with brodalumab treatment” in individuals with rheumatoid arthritis who had an inadequate response to methotrexate. “These preliminary results do not support further evaluation of brodalumab as a treatment for rheumatoid arthritis [RA].”

**Ixezumab**

**Ixekizumab for Moderate to Severe Plaque Psoriasis**

Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) anti-IL-17A monoclonal antibody with neutralizing activity against IL-17A, a naturally occurring cytokine involved in normal inflammatory and immune responses and found in high concentration in skin affected by plaque psoriasis. On March 22, 2016, the FDA approved ixekizumab subcutaneous injection for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Ixekizumab is administered by subcutaneous injection at a recommended dose of 160 mg (two 80 mg injections given via a single-dose prefilled autoinjector or prefilled syringe) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. Ixekizumab is intended for use under the guidance and supervision of a physician. Persons may self-inject only after trained in subcutaneous injection technique using an autoinjector or prefilled syringe (Taltz PI Label, 2017).

The FDA approval of ixekizumab was based on findings from three multicenter, double-blind, placebo-controlled and/or biologic-active phase III clinical studies (UNCOVER-1, UNCOVER-2, UNCOVER-3) that enrolled a total of 3866 individuals, 18 years of age or older, with moderate to severe plaque psoriasis (Gordon, 2014; Griffiths, 2015; Gordon, 2016). Participants had a minimum BSA involvement of 10%, a sPGA score of ≥ 3 in the overall assessment of psoriasis (on a severity scale of “0” to “5”), a PASI score of ≥ 12, and were candidates for phototherapy or systemic therapy. All three studies evaluated different dosing regimens of ixekizumab, administered at 80 milligram (mg) every 2 to 4 weeks following a 160 mg starting dose, compared to placebo after 12 weeks. UNCOVER-2 and UNCOVER-3 included an additional comparator arm in which participants received etanercept (Enbrel®, Immunex Corporation, Thousand Oaks, CA) 50 mg twice a week for 12 weeks. In UNCOVER-1 and UNCOVER-2, the safety and efficacy of ixekizumab was further evaluated through 60 weeks.

The primary efficacy endpoints at 12 weeks were a 75% improvement in the composite PASI score and sPGA score of 0 or 1 and at least a 2-point improvement from baseline. In all three studies at week 12, 87% to 90% of ixekizumab-treated participants experienced significant improvement in their psoriasis plaques. A total of 81% to 83% of ixekizumab-treated participants achieved a sPGA score of 0 or 1. The majority of ixekizumab-treated participants (68% to 71%) achieved virtually clear skin (PASI 90) and 35% to 42% saw complete resolution of their psoriasis plaques (PASI 100, sPGA 0) when compared to minimal improvement in placebo-treated participants. In UNCOVER-1 and UNCOVER-2, 75% of participants who responded to ixekizumab (sPGA 0 or 1 and at least a 2-point improvement from baseline) at 12 weeks consistently maintained that response at the 60-week endpoint.

The most common (≥ 1%) adverse events in the studies were reported as injection site reactions (ISRs), upper respiratory tract infections, nausea, and fungal infections. Serious adverse events were reported in 14 (1.9%) of 734 participants given ixekizumab every 2 weeks, 14 (1.9%) of 729 participants given ixekizumab every 4 weeks, 7 (1.9) of 360 participants given placebo, and 14 (1.9%) of 739 participants given etanercept.
Blauvelt and colleagues (2017) performed a post-hoc analysis of the UNCOVER-2 and UNCOVER-3 phase III trials to assess response to ixekizumab in those participants with moderate to severe plaque psoriasis who had an inadequate response to etanercept. In this subanalysis, non-response was defined by either failure to have an sPGA of 0/1 in UNCOVER-2 or failure to have at least 75% improvement in PASI 75 in UNCOVER-3 at week 12 of each study. Non-responders treated with twice-weekly etanercept 50 mg in the first 12 weeks received two injections of placebo at week 12 (4-week wash-out period), followed by ixekizumab every 4 weeks for weeks 16-60. Non-responders to placebo in the first 12 weeks were administered ixekizumab 160 mg at week 12, followed by ixekizumab every 4 weeks for weeks 16-60. After switching to an ixekizumab subcutaneous injection every 4 weeks, a substantial proportion of participants who were unresponsive to etanercept experienced rapid and sustained improvement in all efficacy evaluations. Among sPGA 0/1 (UNCOVER-2) and PASI 75 (UNCOVER-3) non-responders to etanercept, 73.0% achieved sPGA 0/1 and 78.2% achieved PASI 75, respectively, after 12 weeks of ixekizumab treatment. Safety profiles in participants who switched from etanercept to ixekizumab were similar to those in participants who switched from placebo to ixekizumab. A limitation of this analysis is that the original studies were not designed to directly compare outcomes in etanercept non-responders versus placebo non-responders who switched to every 4-week ixekizumab. In addition, while participants and investigators in UNCOVER-2 remained blinded through week 60, participants and investigators in UNCOVER-3 were not blinded after the first 12 weeks of treatment, potentially resulting in higher responses after week 12 in that trial. Another potential limitation cited by the investigators is that some persons may require more than 12 weeks to achieve sPGA 0/1 or PASI 75 in response to etanercept; “therefore, it is conceivable that with longer exposure to etanercept, some of the non-responders might have become responders.”

A 2018 study by Shear and colleagues analyzed ISRs in UNCOVER-1, UNCOVER-2 and UNCOVER 3. During the first 12 weeks of those three studies, which included a total of 3858 participants, the overall frequency of ISRs with twice weekly ixekizumab was 16.8%. The rate is similar to that reported for twice weekly etanercept (16.4%), but higher than placebo (3.3%). A single ISR was most common.

**Psoriatic Arthritis**

On December 1, 2017, the FDA approved ixekizumab subcutaneous injection for the treatment of active psoriatic arthritis in adults. The recommended dose for this use is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks. For adults with psoriatic arthritis with coexistent moderate to severe plaque psoriasis, the dosing regimen used is that for plaque psoriasis. Ixekizumab may be administered alone or in combination with a conventional disease-modifying antirheumatic drug (DMARD) (for example, methotrexate) (Taltz PI Label, 2017).

Mease and colleagues (2017) evaluated the efficacy and safety of ixekizumab in the treatment of biologic-naive individuals with active psoriatic arthritis in a 24-week randomized, double-blind, placebo-controlled and active (adalimumab)-controlled period phase III clinical trial (SPIRIT-P1). Participants were randomized to subcutaneous injections of placebo (n=106), adalimumab 40 mg once every 2 weeks (active reference; n=101), ixekizumab 80 mg once every 2 weeks (IXEQ2W) (n=103), or ixekizumab 80 mg once every 4 weeks (IXEQ4W) (n=107). Participants randomized to IXEQ4W or IXEQ2W were administered a starting dose of 160 mg given as two injections at week 0. Because the different randomized treatments used distinct schedules and distinguishable prefilled syringes, a double-dummy design with every 2-week dosing was used to conceal treatment allocation. The study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab.

The primary objective was to assess the superiority of IXEQ2W or IXEQ4W versus placebo as measured by the proportion of participants who achieved an ACR20 response at week 24. Efficacy analyses were conducted on the intent-to-treat population (all randomized participants). The adalimumab 40 mg every 2-week treatment arm acted as active reference for comparison with placebo.

The primary efficacy endpoint of ACR20 response at week 24 was met with both IXEQ4W (57.9%) and IXEQ2W (62.1%); response rates in both ixekizumab groups were significantly greater than in the placebo group (30.2%) (p≤0.001). The adalimumab group (active reference) also had a significantly greater ACR20 response at week 24 (57.4%) compared with placebo (p≤0.001). Disease activity and functional disability were significantly improved with both ixekizumab doses versus placebo at week 12. In addition, there was significantly less progression of structural damage at week 24 as measured by changes from baseline in mTSS (that is, the van der Heijde modified total Sharp score) in both ixekizumab groups (IXEQ4W, 0.17; IXEQ2W, 0.08) and adalimumab (0.10) groups compared with the placebo group (0.49) (p≤0.01). Among participants with psoriasis at baseline affecting ≥ 3% BSA, a significantly greater percentage of participants achieved PASI 75 at week 12 for the IXEQ4W (75.3%), IXEQ2W (69.5%) and adalimumab (33.8%) groups compared with the placebo group (7.5%) (p<0.001). A greater percentage of participants
receiving ixekizumab (66%) and adalimumab (64%) reported at least one treatment-emergent adverse event compared with participants receiving placebo (47.2%) (p<0.05). Adverse events were mostly mild or moderate, and the most common were injection site reaction, injection site erythema and nasopharyngitis. The safety profile of ixekizumab for use in active psoriatic arthritis was consistent with the safety profile in the studies of moderate to severe plaque psoriasis.

Nash and colleagues (2017) evaluated the efficacy and safety of ixekizumab in individuals with active psoriatic arthritis who had an inadequate response to prior tumor necrosis factor (TNF) antagonist drugs. In this double-blind, multicenter, randomized, placebo-controlled, phase III clinical trial (SPIRIT-P2), participants (n=363) ages 18 years or older with a confirmed diagnosis of psoriatic arthritis for at least 6 months, and a previous inadequate response (that is, refractory to therapy or had loss of efficacy, or were intolerant) to TNF antagonists were randomly assigned to receive 80 mg subcutaneous ixekizumab every 4 weeks (n=122) or every 2 weeks (n=123) after a 160 mg starting dose, or placebo (n=118). The primary endpoint was the proportion of participants who attained at least an ACR20 response at week 24. At week 24, a higher proportion of participants achieved an ACR20 response with ixekizumab every 4 weeks (n=65 [53%] participants; effect size vs. placebo 33.8% [95% CI, 22.4-45.2]; p<0.0001) and ixekizumab every 2 weeks (n=59 [48%] participants; 28.5% [17.1-39.8]; p<0.0001) than did participants with placebo (n=23 [20%] participants). Up to week 24, serious adverse events were reported in 3 (3%) participants with ixekizumab every 4 weeks, 8 (7%) participants with ixekizumab every 2 weeks, and 4 (3%) placebo-treated participants; no deaths were reported. Infections were reported in 47 (39%) participants with ixekizumab every 4 weeks, 47 (38%) participants with ixekizumab every 2 weeks, and 35 (30%) placebo-treated participants. A total of 3 (2%) serious infections were reported in participants in the ixekizumab every 2 weeks group. This safety profile is consistent with previous studies investigating the use of ixekizumab.

Other Proposed Uses of Ixekizumab

Ixekizumab has been studied in a phase III clinical trial for use in moderate to severe plaque psoriasis in individuals naive to systemic treatment. Additional data in the peer-reviewed published medical literature suggests a potential treatment benefit of ixekizumab in individuals with rheumatoid arthritis who are naive to biologic agents or experienced an inadequate response to TNF antagonists (Genovese, 2014; Genovese, 2016). To date, the FDA has not approved ixekizumab for use in the treatment of any of these conditions.

Secukinumab

Secukinumab is a fully human immunoglobulin (Ig)-G1k monoclonal antibody that selectively binds to IL-17A cytokine and inhibits its interaction with the IL-17 receptor. The FDA has approved secukinumab for use in the treatment of adults with active ankylosing spondylitis, moderate to severe plaque psoriasis, and active psoriatic arthritis (Cosentyx PL Label, 2018).

Secukinumab for Active Ankylosing Spondylitis

On January 15, 2016, the FDA approved secukinumab subcutaneous injection for the treatment of adults with active ankylosing spondylitis. The clinical efficacy and safety of secukinumab for this indication was evaluated in two phase III, double-blind, randomized controlled trials (MEASURE 1, n=371; MEASURE 2, n=219) (Baeten, 2013; Baeten, 2015). MEASURE 1 is a 2-year study followed by a 3-year extension study; and, MEASURE 2 is a 5-year study.

In the MEASURE 1 study, 371 participants were randomly assigned to receive an intravenous loading dose of secukinumab (10 mg per kilogram) followed by subcutaneous secukinumab at a dose of 150 mg (n=125), an intravenous loading dose of secukinumab (10 mg per kilogram) followed by subcutaneous secukinumab at a dose of 75 mg (n=124), or placebo (n=122). At week 16, 351 (95%) participants remained in the study; 20 participants discontinued study protocol, with 10 participants from the placebo arm and 10 participants total from the two intervention arms (placebo, n=5, total intervention, n=3, due to adverse events).

A total of 219 participants in the MEASURE 2 trial received subcutaneous secukinumab at a dose of 150 mg (n=72), subcutaneous secukinumab at a dose of 75 mg (n=73), or matched placebo (n=74) at baseline and at weeks 1, 2, 3, and every 4 weeks starting at week 4. At week 16, 200 participants (91%) remained in the study; 19 participants discontinued the study, with 8 participants from the placebo arm and 11 participants total from the two intervention arms (placebo, n=4, total intervention, n=7, adverse events). At week 16, participants in the placebo group were randomly reassigned to subcutaneous secukinumab at a dose of 150 mg or 75 mg.
The primary endpoint, the proportion of participants with at least 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) response criteria at week 16, was met in both secukinumab groups in MEASURE 1, and in the group that received 150 mg of secukinumab subcutaneously in MEASURE 2 (61% vs. 29%, MEASURE 1; 61% vs. 28%, MEASURE 2). ASAS40 response was also significant with secukinumab 150 mg in both studies as compared to placebo (42% vs. 13%; 36% vs. 11%). The response rates were maintained in a 52-week follow-up analysis and similar in participants regardless of concomitant therapies. Participants treated with secukinumab showed improvement compared to placebo-treated participants in health-related quality of life assessed by the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) at week 16.

During the 16-week placebo controlled period of the trials, the overall proportion of participants with adverse events was higher in the secukinumab groups than the placebo groups (66% and 59%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the secukinumab groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, nausea, and upper respiratory tract infection. The safety profile of secukinumab was consistent with that in prior studies of its use for ankylosing spondylitis and moderate to severe plaque psoriasis. The incidence of infection was higher in secukinumab-treated participants than with placebo (30% vs. 12% in MEASURE 1; 32% vs. 27% in MEASURE 2). There were 8 cases of inflammatory bowel disease (IBD) during the entire treatment period (n=5, Crohn’s disease; n=3, ulcerative colitis). Other adverse events included grade 3 or 4 neutropenia and candida infections.

Braun and colleagues (2016) reported 2-year follow-up in individuals with ankylosing spondylitis who participated in the phase III MEASURE 1 study. Clinical efficacy assessments included ASAS20 response rates through week 104. Radiographic changes at week 104 were assessed using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Of the 371 participants originally randomized to treatment, a total of 97 of 125 (77.6%) and 103 of 124 (83.1%) participants in the intravenous 150 mg and intravenous 75 mg groups, respectively, completed week 104. No placebo treatment was given beyond week 24. Adverse events (6.4%), lack of efficacy (4.4%) and patient/ guardian decision (5.8%) were the primary reasons from discontinuation among secukinumab-treated participants. In the full intent-to-treat analysis set, ASAS20 response rates at week 104 were 73.7% and 68.0% in the intravenous 150 mg and intravenous 75 mg groups, respectively. Among participants with evaluable x-rays who were originally randomized to secukinumab (n=168), mean change in mSASSS from baseline to week 104 was 0.30 ± 2.53. Serious adverse events were reported in 12.2% and 13.4% of participants in the 150 mg and 75 mg groups, respectively. Limitations of this analysis include the lack of comparator group beyond week 16 and as noted by the investigators, even though there was “…use of accepted statistical methods to account for missing data during the continuation period of the study, there remains a possible bias from the fact that patients who stay on study are those who do well on study treatment.”

In 2018, Baraliakos and colleagues reported on 3-year efficacy and safety results from the MEASURE 1 trial. Of the 274 individuals who enrolled in the 3-year extension study, 260 (95%) completed the total 156 week (3 year) period. (A total of 371 individuals were initially randomized in MEASURE 1, so 70% of these completed the extension study). At week 156, ASAS20/40 response rates were 80.2%/61.6% per protocol and 79.5%/60.9% in the intention-to-treat analysis. The authors noted that improvements in other major efficacy endpoints were sustained as well. There was a low rate of serious adverse events. Two deaths were reported during the study, one of which occurred earlier in the trial and the other was due to a stroke in a participant with multiple risk factors (including hypertension and smoking).

Other Considerations

In September 2015, the ACR, in conjunction with the Spondylitis Association of America and the Spondyloarthritis Research and Treatment Network (Ward, 2015), released recommendations for both pharmacologic and non-pharmacologic treatment of AS and non-radiographic axial spondyloarthritis (SpA). The recommendations include treatment of individuals with active or stable ankylosing spondylitis (pharmacologic and rehabilitation) and treatment of those with ankylosing spondylitis and specific impairments or comorbidities (for example, acute iritis, advanced hip arthritis, severe kyphosis, and IBD). The recommendations also address the treatment of individuals with non-radiographic axial SpA and education and preventive care recommendations for ankylosing spondylitis and SpA. For treatment of an individual with active ankylosing spondylitis, strong recommendations include use of non-steroidal anti-inflammatory drugs (NSAIDs), TNF antagonists when activity persists despite NSAID treatment, and no use of systemic glucocorticoids; non-pharmacologic treatments include use of physical therapy and hip arthroplasty in individuals with advanced hip arthritis.

Secukinumab for Moderate to Severe Plaque Psoriasis
On January 23, 2015, the FDA approved secukinumab subcutaneous injection for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The clinical efficacy and safety of secukinumab was evaluated in two phase III, double-blind, 52-week trials, ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) (Langley, 2014). The proportion of participants who met the criterion for PASI reduction of at least 75% (PASI75) at week 12 was higher with each secukinumab dose than with placebo or etanercept. The proportion of participants with a response of 0 or 1 on the modified Investigator’s Global Assessment (mIGA) at week 12 was higher with each secukinumab dose than with placebo or etanercept. Changes in the Dermatology Quality of Life Index (DLQI) at week 12 were greater in secukinumab-treated participants than in placebo- or etanercept-treated participants. The proportions of participants meeting other secondary endpoints were also higher in the secukinumab-treated arms of the trials. The rates of infection were higher with secukinumab than with placebo in both studies and were similar to those with etanercept in FIXTURE. Serious adverse events were low in both trials and there were no treatment-related deaths. Discontinuations due to adverse events were slightly more frequent in the etanercept group than in either secukinumab group in the FIXTURE study. The most common adverse events in the secukinumab groups during induction and the entire treatment period were nasopharyngitis, headache, and diarrhea.

The route of administration of secukinumab was evaluated in two additional phase III studies (FEATURE: JUNCTURE) using a prefilled syringe and autoinjector/pen dosage forms for self-administration (Blauvelt, 2015; Paul, 2014). The recommended dose for secukinumab is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some individuals, a dose of 150 mg may be acceptable (Cosentyx PI Label, 2017).

**Secukinumab for Active Psoriatic Arthritis**

On January 15, 2016, the FDA approved secukinumab subcutaneous injection for the treatment of adults with active psoriatic arthritis. The clinical efficacy and safety of secukinumab for this indication was evaluated in two phase III, double-blind, randomized, placebo-controlled trials (FUTURE 1, n=606; FUTURE 2, n=397) (Mease, 2015; McInnes, 2015) of 1003 individuals, 18 years of age or older, with active psoriatic arthritis (> three swollen and > three tender joints) despite NSAID, corticosteroid, or DMARD therapy.

In FUTURE 1, 606 participants were randomized 1:1:1 to receive intravenous secukinumab 10 mg/kg at weeks 0, 2, and 4, followed by subcutaneous secukinumab at a dose of either 75 mg or 150 mg, or placebo every 4 weeks. Participants receiving placebo were re-randomized to receive secukinumab (either 75 mg or 150 mg every 4 weeks) at week 16 or week 24 based on responder status. The primary endpoint was the proportion of participants achieving ACR20 response rates at week 24. Results for the intervention groups were significantly higher than in the placebo group with 50.0% achieving ACR20 at the 75 mg dose compared to 17.3% at ACR20 for the placebo group (p<0.001 for both comparisons with placebo). While there were no major adverse events in the placebo group, two myocardial infarcts and four strokes occurred in the treatment groups. The authors report that these findings are consistent with previous studies.

In FUTURE 2, 397 participants were randomized 1:1:1:1 to receive subcutaneous secukinumab at 75 mg (n=99), 150 mg (n=100), 300 mg (n=100), or placebo (n=98) once a week from baseline and then every 4 weeks from week 4. Participants receiving placebo were re-randomized to receive secukinumab (either 150 mg or 300 mg every 4 weeks) at week 16 or week 24 based on responder status. The primary endpoint was the percentage of participants achieving at least 20% improvement in the ACR20 response criteria at week 24. In FUTURE 2, a significantly higher proportion of participants achieved ACR20 response at week 24 with secukinumab 300 mg (n=54, 54%), 150 mg (n=51, 51%), and 75 mg (n=29, 29%) versus placebo (n=15, 15%) (p<0.0001). Additionally, the proportion of participants receiving secukinumab 300 mg and 150 mg significantly improved with at least a 75% and 90% participants respectively achieving improvement on the PASI 75 and PASI 90 score, a change from baseline in the 28-point DAS using C-reactive protein (DAS28-CRP), and the Medical Outcomes Study 36-item Short Form Health Survey Physical Component Summary (SF36-PCS) score. At week 16 in FUTURE 2, the estimated mean change from baseline function as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) was -0.23 in the placebo group compared with -0.45 in the secukinumab 150 mg group and -0.55 in the secukinumab 300 mg group. During the 16-week placebo-controlled period of the trials, the overall proportion of participants with adverse events was similar in the secukinumab and placebo-treatment groups (59% and 58%, respectively); in addition, adverse events that occurred at a proportion of at least 2% and at a higher proportion in the secukinumab groups than the placebo groups were nasopharyngitis, upper respiratory tract infection, headache, nausea, and hypercholesterolemia. There were an increased proportion of participants with infections in the secukinumab groups (29%) compared to the placebo group (26%).
Kavanaugh and colleagues (2017) assessed the long-term efficacy and safety of secukinumab at 2-year follow-up in individuals with active psoriatic arthritis who participated in the phase III FUTURE 1 study. A total of 476 (78.5%) participants completed 104 weeks of treatment. Exploratory analysis of all primary and secondary endpoints continued to week 104 on an intent-to-treat basis. Secukinumab showed sustained efficacy in control of disease activity, quality of life, physical function, skin symptoms, dactylitis, and enthesitis. ACR20 response rates were 66.8% with secukinumab 150 mg and 58.6% with secukinumab 75 mg at week 104; PASI 75 improvement response rates were 74.6% and 63.0%, respectively. Based on observed data, 84.3% of participants in the secukinumab 150 mg group and 83.8% in the secukinumab 75 mg group showed no radiographic disease progression. No new or unexpected adverse events were reported during 2 years of treatment.

McInnes and colleagues (2017) assessed the long-term efficacy and safety of secukinumab at 2-year follow-up in individuals with active psoriatic arthritis who participated in the phase III FUTURE 2 study. A total of 86 of 100 (86%), 76 of 100 (76%), and 65 of 99 (66%) participants in the secukinumab 300 mg, 150 mg, and 75 mg groups, respectively, completed 104 weeks. At week 104, ACR20 response rates in the 300 mg, 150 mg, and 75 mg groups were 69.4%, 64.4%, and 50.3%, respectively. Sustained improvements were observed through week 104 with secukinumab across other clinically important domains of PsA (such as quality of life, physical function, and skin symptoms). Responses were sustained through week 104 regardless of prior TNF antagonist use. The incidence, type and severity of adverse events were consistent with those reported previously over the entire treatment period.

**Other Proposed Uses of Secukinumab**

Secukinumab is being studied in ongoing phase III trials for use in other skin disorders including moderate to severe palmoplantar psoriasis (GESTURE trial; Gottlieb, 2017), moderate to severe nail psoriasis, and palmoplantar pustulosis. Additional data in the peer-reviewed published medical literature suggests a potential treatment benefit for the use of secukinumab for non-infectious uveitis (Dick, 2013; Letko, 2015), and rheumatoid arthritis (Blanco, 2017; Genovese, 2013; Genovese, 2014). In a proof-of-concept trial, Hueber and colleagues (2013) found that use of secukinumab was ineffective in the treatment of Crohn's disease and higher rates of adverse events were noted compared with placebo. Other ongoing clinical trials are posted in the ClinicalTrials.gov database. To date, the FDA has not approved secukinumab for use in the treatment of any of these conditions.

**Background/Overview**

**Ankylosing Spondylitis and Spondyloarthropathy**

Spondyloarthritis (SpA) is a family of inflammatory rheumatic diseases that can affect the spine and peripheral joints, ligaments, and tendons. There are two main types of clinical presentation of SpA: axial (axSpA) (symptoms predominantly related to the spine) and peripheral SpA (symptoms predominantly related to the peripheral joints). Ankylosing spondylitis is the most familiar and severe form of SpA, classified with a group of spondyloarthritides comprised of Reiter’s syndrome, reactive arthritis, and psoriatic arthritis. Ankylosing spondylitis is characterized not by the inflammation of the synovium, as seen in rheumatoid arthritis, but inflammation of the enthesis, the site where ligaments, tendons, and joint capsules insert into bone. Inflammation around the spine/vertebrae, joints and feet can lead to fibrosis, ossification, deformity, and ankylosis. It can also cause inflammation in or injury to other organs, such as the eyes, heart, lungs, and kidneys. The disease most often begins between ages 20 and 40, but it may begin before age 10. It affects more males than females. Conventional therapy for ankylosing spondylitis consists primarily of NSAIDs, corticosteroids, and nonbiologic DMARDs, including methotrexate and sulfasalazine.

**Plaque Psoriasis and Psoriatic Arthritis**

According to the American Academy of Dermatology (AAD, 2008) plaque psoriasis is a multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. The major manifestation of plaque psoriasis is chronic inflammation of the skin, characterized by "disfiguring, scaling, and erythematous plaques that may be painful or often severely pruritic and may cause significant quality of life issues." Treatments available to help manage the symptoms of plaque psoriasis include topical therapy, phototherapy, systemic therapy, and biologic DMARDs.
The AAD has published a set of evidence-based guidelines, *Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis* (AAD, 2008), intended to assist physicians in managing the complexities of the treatment of individuals with plaque psoriasis. The first guideline, *Section 1: Overview of Psoriasis and Guidelines of Care for the Treatment of Psoriasis with Biologics* (AAD, 2008) provides an overview of psoriasis classification, co-morbidities, assessment tools, and the use of biologics to treat psoriasis. The work group states that approximately 80% of individuals affected with psoriasis have mild to moderate disease, with 20% having moderate to severe psoriasis, defining the extent of BSA involvement as:

...affecting more than 5% of the BSA or affecting crucial body areas such as the hands, feet, face, or genitals...The areas of involvement and types of psoriasis should be considered in evaluating severity of disease because the impact of these types of psoriasis may be quite substantial.

Individuals with more than 5% to 10% BSA affected are typically candidates for systemic or biologic therapy. Treatment planning for use of ixekizumab or secukinumab (and other FDA-approved biologic agents) for moderate to severe plaque psoriasis considers this definition of the extent of BSA involvement. In addition, for individuals with plaque psoriasis involving sensitive areas or areas that would significantly impact daily function (for example, palms, soles of feet, head, neck, or genitalia), ≤ 5% BSA involvement is considered as moderate to severe disease.

Psoriatic arthritis is condition associated with plaque psoriasis. Psoriatic arthritis is characterized by stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons. Symptoms of psoriatic arthritis can range from mild to very severe. Approximately 15% of people with plaque psoriasis develop psoriatic arthritis (National Psoriasis Foundation [NPF], 2017).

**Contraindications, Precautions, and Warnings with Use of Brodalumab, Ixekizumab and Secukinumab**

The FDA PI label for brodalumab (Siliq, 2017) includes the following Boxed Warning:

**WARNING: SUICIDAL IDEATION AND BEHAVIOR**

- Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. Prior to prescribing Siliq, weigh the potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. Patients with new or worsening suicidal ideation and behavior should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes.
- Because of the observed suicidal behavior in subjects treated with Siliq, Siliq is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Siliq REMS Program.

The FDA PI labels for brodalumab (Siliq, 2017), ixekizumab (Taltz, 2018), and secukinumab (Cosentyx, 2018) include the following Contraindications, Warnings and Precautions:

**Contraindications**

- Cosentyx and Taltz: Contraindicated for use in individuals with serious hypersensitivity reaction to ixekizumab or secukinumab or any of the excipients.
- Siliq: Contraindicated for use in individuals with Crohn’s disease because brodalumab may cause worsening of the disease. Exacerbation of Crohn’s disease was observed in some of the clinical trials with brodalumab use.

**Warnings and Precautions for Cosentyx and Taltz**

- Hypersensitivity Reactions: If an anaphylactic reaction or other serious allergic reaction occurs, discontinue ixekizumab or secukinumab immediately and initiate appropriate therapy.
- Inflammatory bowel disease (IBD) (including Crohn's disease and ulcerative colitis):
Crohn’s disease and ulcerative colitis, including exacerbations, occurred during the clinical trials of ixekizumab.

Exacerbations of IBD, some serious cases, were observed in the clinical trials of secukinumab.

Caution should be exercised when prescribing ixekizumab or secukinumab to individuals with IBD.

Warnings and Precautions for Cosentyx, Siliq, and Taltz

- Infections: Serious infections have occurred. Caution should be exercised when considering the use of brodalumab, ixekizumab, or secukinumab in individuals with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue brodalumab, ixekizumab or secukinumab until the infection resolves.
- Tuberculosis (TB): Prior to initiating treatment with brodalumab, ixekizumab or secukinumab, evaluate for TB. Do not administer brodalumab, ixekizumab or secukinumab to individuals with active TB infection. Initiate treatment of latent TB prior to administering brodalumab, ixekizumab or secukinumab. Consider anti-TB therapy prior to initiation of brodalumab, ixekizumab or secukinumab in individuals with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Individuals receiving brodalumab, ixekizumab or secukinumab should be monitored closely for signs and symptoms of active TB during and after treatment.
- Vaccinations: Prior to initiating therapy with brodalumab, ixekizumab, or secukinumab, consider completion of all age appropriate immunizations according to current immunization guidelines. Individuals treated with ixekizumab or secukinumab should not receive live vaccines.
- Pediatric Use: Safety and effectiveness of brodalumab, ixekizumab or secukinumab in the pediatric population have not been evaluated.

Definitions

Biologic disease-modifying antirheumatic drugs (DMARDs): A class of drugs thought to work by targeting components of the immune system by blocking specific immune cytokines, blocking other cytokines, binding with cytokines or chemokines suppressing IL-1α, IL-1β, IL-6, IL-12, IL-17A, and/or IL-23, or by directly suppressing lymphocytes.

Conventional therapy: Treatments that are widely accepted and practiced by the medical community.

Immunosuppressant drugs: A class of immunomodulatory drugs including 6-mercaptopurine (6-MP), azathioprine, cyclophosphamide, cyclosporine, methotrexate, and tacrolimus that reduce inflammation by affecting the immune system.

Interferon gamma (IFN-γ) release assay (IGRA): A test that aids in detecting Mycobacterium tuberculosis infection, both latent infection and infection manifesting as active tuberculosis that may be used for surveillance purposes and to identify persons likely to benefit from treatment. FDA-approved IGRAAs include the 1) QuantiFERON-TB Gold test (GFT-G), 2) QuantiFERON-TB Gold In-Tube test (QFT-GIT), and the 3) T-SPOT.TB test (T-Spot).

Monoclonal antibody: A laboratory-produced substance that can locate and bind to specific cells wherever they are in the body. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to their target cell.

Nonbiologic disease-modifying antirheumatic drugs (DMARDs): A class of drugs, also referred to as synthetic DMARDs, thought to work by altering the immune system function to halt the underlying processes that cause certain forms of inflammatory conditions, although their exact mechanisms of action are unknown; includes azathioprine, hydroxychloroquine, leflunomide, methotrexate, minocycline, organic gold compounds, penicillamine, and sulfasalazine.

Nonsteroidal anti-inflammatory drugs (NSAIDs): A class of drugs used to treat pain, redness, swelling, and inflammation from conditions including different types of arthritis; includes over-the-counter (OTC) and prescription medicines, such as celecoxib, diclofenac, ibuprofen, indomethacin, meloxicam, naproxen, sulindac, tolmetin, and valdecoxib.
The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

**HCPCS**
- J3490: Unclassified drug [when specified as brodalumab (Siliq), ixekizumab (Taltz), or secukinumab (Cosentyx)]
- J3590: Unclassified biologics [when specified as brodalumab (Siliq), ixekizumab (Taltz), or secukinumab (Cosentyx)]

**ICD-10 Diagnosis**
- L40.0: Psoriasis vulgaris (plaque psoriasis)
- L40.50-L40.59: Arthropathic psoriasis [secukinumab (Cosentyx) or ixekizumab (Taltz) only]
- L40.8-L40.9: Other, unspecified psoriasis
- M45.0-M45.9: Ankylosing spondylitis [secukinumab (Cosentyx) only]

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above for the indications listed in the Position Statement section as not medically necessary.

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

**References**

Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:


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QuantiFERON-TB Gold Test (GFT-G)
QuantiFERON-TB Gold In-Tube Test (QFT-GIT)
T-SPOT.TB test (T-Spot)

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

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<thead>
<tr>
<th>Status</th>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewed</td>
<td>11/08/2018</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Rationale and References sections updated.</td>
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<tr>
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<td>MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Added MN statement for use of ixekizumab in active psoriatic arthritis in adults when criteria are met. Removed psoriatic arthritis from the INV and NMN statement for ixekizumab. Updated Description, Rationale, Background, Coding, References, and Websites for Additional Information sections.</td>
</tr>
<tr>
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<td>MPTAC review. Added Note to Description section regarding CG-ADMIN-02. Updated Rationale, References, and Websites for Additional Information sections.</td>
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<td>MPTAC review. Added psoriatic arthritis to the INV and NMN statement for ixekizumab. Updated Rationale, Background, References, and Websites for Additional Information sections.</td>
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<td>03/01/2017</td>
<td>MPTAC review. Updated formatting in Position Statement section. Added MN statement for FDA approval of brodalumab (Siliq) for moderate to severe plaque psoriasis when criteria are met. Added NMN and INV and NMN statements for brodalumab when criteria are not met. Separated MN, NMN, and INV and NMN statements into sections specific to ixekizumab and secukinumab. Revised NMN statement for use of ixekizumab in combination with other biologic drugs (added brodalumab and secukinumab). Revised NMN statement for use of secukinumab in combination with other biologic drugs (added brodalumab and ixekizumab). Updated Description, Rationale, Background, Definitions, Coding, References, and Websites for Additional Information sections.</td>
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<tr>
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<td>MPTAC review. Added MN criteria for the FDA approval of ixekizumab (Taltz) for moderate to severe plaque psoriasis in individuals 18 years of age or older when criteria are met. Updated NMN and INV and NMN statements to include ixekizumab when criteria are not met. Updated Subject (title), Description, Rationale, Background, Coding, References, and Websites for Additional Information sections.</td>
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<tr>
<td>Revised</td>
<td>02/04/2016</td>
<td>MPTAC review. Revised medically necessary criteria to include FDA approval of secukinumab for the treatment of active ankylosing spondylitis or active psoriatic arthritis in individuals 18 years or age or older when criteria are met. Revised investigational and not medically necessary statement, removing ankylosing spondylitis and psoriatic arthritis. Updated Subject (title), Description, Rationale, Background, Definitions, Coding, References, and Websites for Additional Information sections. Removed ICD-9 codes from Coding section.</td>
</tr>
<tr>
<td>New</td>
<td>08/06/2015</td>
<td>MPTAC review. Initial document development.</td>
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