INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2017 Cigna

Coverage Policy

Cigna covers apremilast (Otezla®) as medically necessary for the treatment of moderate to severe plaque psoriasis in an adult (18 years of age or older) when ALL of the following criteria are met:

- For Employer Group Benefit Plans: Standard and Performance Prescription Drug Lists, Value and Advantage Prescription Drug Lists
  - Body Surface Area (BSA) of greater than 5% OR BSA less than 5% and there is involvement with the face, genitals, hands and feet (for example, nail psoriasis, palmoplantar disease), scalp, or intertriginous areas
  - Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE of the following:
    - Systemic therapy (for example, methotrexate, cyclosporine, Soriatane)
    - Phototherapy (narrow or broad band ultraviolet B [UVB], or psoralen plus ultraviolet A [PUVA])
    - Topical therapy (for example, coal tar, keratolytics, corticosteroids, anthralin, Dovonex, Tazorac)

- For Individual & Family Benefit Plans:
  - Body Surface Area (BSA) of greater than 5% OR BSA less than 5% and there is involvement with the face, genitals, hands and feet (for example, nail psoriasis, palmoplantar disease), scalp, or intertriginous areas
  - Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate to ONE of the following:
    - Systemic therapy (for example, methotrexate, cyclosporine, Soriatane)
    - Phototherapy (narrow or broad band ultraviolet B [UVB], or psoralen plus ultraviolet A [PUVA])
Topical therapy (for example, coal tar, keratolytics, corticosteroids, anthralin, Dovonex, Tazorac)
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, unable to use, or not a candidate for adalimumab (Humira®) and etanercept (Enbrel®)

Cigna covers apremilast (Otezla®) as medically necessary for the treatment of psoriatic arthritis in an adult (18 years of age or older) when ALL of the following criteria are met:

**For Employer Group Benefit Plans: Standard and Performance Prescription Drug Lists, Value and Advantage Prescription Drug Lists**
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate to methotrexate
  o ONE of the following:
    ▪ Documented failure, inadequate response or intolerance to ONE preferred AntiTNF agent
    ▪ Contraindication per FDA label, unable to use, or not a candidate for AntiTNF therapy (for example, serious infection, invasive fungal infections, malignancies, demyelinating disease, heart failure, lupus-like syndromes)

**For Individual & Family Benefit Plans:**
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate to methotrexate
  o ONE of the following:
    ▪ Documented failure, inadequate response or intolerance to TWO preferred AntiTNF agents
    ▪ Contraindication per FDA label, unable to use, or not a candidate for AntiTNF therapy (for example, serious infection, invasive fungal infections, malignancies, demyelinating disease, heart failure, lupus-like syndromes)

*Please refer to the following table for the corresponding preferred biologic agents for the applicable Benefit Plan:*

<table>
<thead>
<tr>
<th>Benefit Plan Type</th>
<th>Drug Lists</th>
<th>Corresponding Preferred AntiTNF Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual &amp; Family Benefit Plans</td>
<td></td>
<td>adalimumab (Humira®) etanercept (Enbrel®) infliximab (Remicade®)</td>
</tr>
</tbody>
</table>

Cigna does not cover the use of apremilast (Otezla) for any other indication including the following because it is considered experimental, investigational or unproven (this list may not be all inclusive):

- Concomitant use with any other biologic including all non-tumor necrosis factor (TNF) biologics and anti-tumor necrosis factor (TNF) biologics

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to apremilast (Otezla).

*Note: Receipt of sample product does not satisfy any criteria requirements for coverage*

**FDA Approved Indication**

- **Psoriatic Arthritis**

  Otezla is indicated for the treatment of adult patients with active psoriatic arthritis.
• **Psoriasis**

Otezla is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

**FDA Recommended Dosing**

The recommended initial dosage titration of Otezla from Day 1 to Day 5 is shown in Table 1. Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

**Table 1: Dosage Titration Schedule**

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

**Drug Availability**

Otezla is available as 10 mg, 20 mg, and 30 mg tablets. Otezla is packaged as a 2-week starter pack (containing 4 tablets of 10 mg, 4 tablets of 20 mg, 5 tablets of 30 mg with an additional 14 tablets of 30 mg); a 28-count carton (containing 2 blister cards each containing 14 tablets of 30 mg); and bottles of 60 tablets of 30 mg.

**General Background**

**Pharmacology**

Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that decreases pro-inflammatory mediators and increases anti-inflammatory mediators.

**Guidelines**

**American Academy of Dermatology (AAD): Position Statement on Treatment of Psoriatic Patients** (AAD, 2013)

Therapeutic options in treating chronic plaque psoriasis should tailor the needs of the individual patient. Patients with moderate to severe plaque psoriasis are candidates for systemic therapy. The choice of treatment should be based on efficacy, potential adverse events, prior treatments used, medical risk factors, etc. Apremilast is not mentioned within this guideline.

**American Academy of Dermatology (AAD): Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis**

Patients with moderate to severe psoriasis are candidates for systemic therapy (i.e. phototherapy or systemic therapy including biologic therapy). The old paradigm of using a step-wise approach in ascending order is not required (i.e. first phototherapy, then oral systemic treatment, followed by biologic therapies). Treatment options in the treatment of chronic plaque psoriasis should be tailored to meet the individual needs of the patients.

Psoriasis severity is defined by both the extent of body surface area (BSA) involvement (<5% considered mild, ≥ 5% but <10% moderate, and ≥ 10% severe), and the involvement of the hands, feet, facial, or genital regions. The majority of psoriasis patients have involvement defined as less than 5% BSA and can effectively treated with topical agents. Psoriasis patients who are candidates for ultra-violet based or systemic therapy (which include oral and biologic agents) have more significant disease, defined as affecting more than 5% of the BSA, or may have less than 5% BSA affected but have psoriasis in vulnerable areas such as the face, genitals, hands and feet (palmoplantar disease), scalp, or intertriginous areas and have disease that adversely affects their quality of life.

Apremilast is not mentioned within this guideline.

**National Psoriasis Foundation**

Consensus Guidelines for the Management of Plaque Psoriasis (Hsu et al, 2012)

The focus of this guideline is on the management of moderate to severe plaque psoriasis. Apremilast is not mentioned within this guideline.
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) provides recommendations for the treatment of Plaque Psoriasis which includes the following: topical therapies, phototherapy, DMARDs, antiTNFs, IL-12/23 inhibitors, IL-17 inhibitors, and PDE-4 inhibitors. The GRAPPA recommendations for Psoriatic Arthritis vary based on the domain which is involved: peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nails. (Coates, 2016)

Treatment for psoriatic arthritis is based on peripheral or axial disease and prior therapies. Recommendations include DMARDs, NSAIDs, simple analgesics, antiTNFs, IL-12/23 inhibitors, or PDE-4 inhibitors. (Coates, 2016)

Treatment for nail disease in psoriatic arthritis is based on data from the psoriasis clinical studies. For mild disease, treatment options could include topical agents, corticosteroid injections or nonbiologic DMARDs. For moderate to severe nail psoriasis disease, GRAPPA recommends antiTNFs agents based on available data. In addition, GRAPPA further recommends that ustekinumab and IL-17 inhibitors should be considered alternative biologic therapy to antiTNFs. (Coates, 2016)

Clinical Efficacy

• Plaque Psoriasis

The ESTEEM trials (ESTEEM 1 and ESTEEM 2) established the safety and efficacy of apremilast 30 mg twice daily compared to placebo for 16 weeks in 1,257 patients with moderate to severe plaque psoriasis. The primary endpoint evaluated was the proportion of patients who achieved a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) score. In the ESTEEM 1 study, PASI 75 was achieved in 33.1% of apremilast patients compared to 5.3% for placebo. In the ESTEEM 2 study, PASI 75 was achieved in 28.8% of apremilast patients compared to 5.8% of placebo patients. (Papp, 2015) (Paul 2015)

Further analysis by Rich et al evaluated apremilast in patients with difficult to treat nail and scalp psoriasis. In the ESTEEM 1 and ESTEEM 2 trials, 66.1% and 64.7% had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis at baseline, respectively. At week 16, the Nail Psoriasis Severity Index (NAPSI) score demonstrated greater improvement with apremilast treatment compared to placebo. In addition, apremilast demonstrated greater NAPSI-50 response, which is defined as a 50% reduction from baseline in target nail NAPSI score. In addition, the Scalp Physician Global Assessment response was greater with apremilast compared to placebo. Over 52 weeks, improvements in outcomes were generally maintained in patients who experienced a PASI response at week 32 in the study. (Rich et al, 2016)

• Psoriatic Arthritis

Two published clinical trials evaluated the safety and efficacy of apremilast compared to placebo for psoriatic arthritis. (Kavanaugh, 2014; Schett, 2012) Apremilast was used alone or in combination with methotrexate, leflunomide, sulfasalazine, low-dose corticosteroids, or NSAIDs. There are no published trials directly comparing apremilast with other active psoriatic arthritis treatments. Apremilast resulted in significant benefit over placebo for the primary endpoint of 20% improvement in modified American College of Rheumatology response criteria (ACR20). At the labeled dose, 30 mg twice daily, ACR20 response was achieved in 38.1% of patients treated with apremilast compared with 19.4% in the placebo group (p=0.0001). (Kavanaugh, 2014)

Experimental, Investigational, and Unproven Uses

Ankylosing Spondylitis

Otezla is being studied for use in ankylosing spondylitis. At this time, however, there is insufficient published data in terms of safety and efficacy to support the use of Otezla for this indication. In a randomized controlled trial comparing apremilast 30 mg BID to placebo in 28 patients for 12 weeks, the primary endpoint, mean change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at week 12 compared to baseline was not significant.

Warnings and Precautions for Therapeutic Alternative Agents (this list may not be all-inclusive):

<table>
<thead>
<tr>
<th>Warnings and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Refer to FDA Product Information for complete information)</td>
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</tbody>
</table>

Warning, Precaution, and Analysis of Therapeutic Alternative Agents (this list may not be all-inclusive):
<table>
<thead>
<tr>
<th>AntiTNFs</th>
<th>Serious infection (for example, tuberculosis, bacterial sepsis), invasive fungal infections, malignancies, demyelinating disease, heart failure, lupus-like syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARDs</td>
<td>Embryo-fetal toxicity, reproduction effects</td>
</tr>
</tbody>
</table>

**Coding/Billing Information**

**Note:** Apremilast is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions; therefore, this section is not in use.

**References**

4. Gottlieb et al, 2008; Menter et al, 2008; Menter et al, 2009[a]; Menter et al, 2009[b]; Menter et al, 2010; Menter et al, 2011American Academy of Dermatology (AAD): Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 1, 2, 3, 4, 5 and 6
7. Pathan et al; Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis; Ann Rheum Dis 2013