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Coverage Policy Number **IP0226**

Apremilast

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. 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.

Overview

This policy supports medical necessity review for apremilast (**Otezla®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Apremilast (Otezla) is considered medically necessary when ONE of the following is met:

1. **Behcet's Disease.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Has oral ulcers or other mucocutaneous involvement
   C. Documentation of **ONE** of the following:
      i. Failure to **ONE** conventional systemic therapy, unless contraindicated or intolerant

Examples of conventional systemic therapy: corticosteroids, other immunosuppressants, colchicine.

ii. Already tried a biologic for Behcet's Disease

D. Medication is prescribed by, or in consultation with, a rheumatologist, dermatologist, ophthalmologist, gastroenterologist or neurologist

2. **Plaque Psoriasis.** Individual meets **ALL** of the following criteria:
   A. 6 years of age or older
   B. Documentation of **ONE** of the following:
      i. Failure after at least 6 weeks to **ONE** of the following, unless contraindicated or intolerant to **ALL** of the following:
         a. Topical therapy (for example, topical corticosteroids, topical vitamin D analogs, Tazorac)
         b. Systemic therapy (for example, methotrexate, cyclosporine, Soriatane)
         c. Phototherapy
      ii. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Plaque Psoriasis
   C. Medication is prescribed by, or in consultation with, a dermatologist

3. **Psoriatic Arthritis.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Documentation of **ONE** of the following:
      i. For Non-axial disease, failure to **ONE** disease-modifying anti-rheumatic drug (DMARD), unless contraindicated or intolerant
      ii. For Axial disease, failure to **ONE** disease-modifying anti-rheumatic drug (DMARD), OR a nonsteroidal anti-inflammatory drug (NSAID), unless contraindicated or intolerant
      iii. Already tried a biologic or targeted synthetic DMARD (tsDMARD)
   C. Medication is prescribed by, or in consultation with, a rheumatologist or dermatologist

Coverage varies across plans and requires the use of Preferred Products. Refer to the customer's benefit plan document for coverage details.

Employer Group Plans	
Condition	
Plaque Psoriasis	**Preferred** [requires prior authorization]
Psoriatic Arthritis - Adult	

Individual and Family Plan	
Condition	
Plaque Psoriasis	**Preferred** [requires prior authorization]
Psoriatic Arthritis - Adult	**Preferred** [requires prior authorization]

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 therapy.

Reauthorization Criteria

Continuation of apremilast (Otezla) is considered medically necessary for **ALL** covered diagnoses when initial criteria are met AND beneficial response is demonstrated.

Authorization Duration

Initial approval duration is up to 12 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Alopecia areata.** Insufficient efficacy and safety data to support use in alopecia. Otezla is not indicated for this use.[1]

2. **Ankylosing Spondylitis.** Current evidence does not support use of Otezla in ankylosing spondylitis. In a published double-blind, placebo-controlled, Phase II study, patients (n = 38) were randomized in a 1:1 ratio to treatment with Otezla 30 mg twice daily or placebo.[9] At Week 12, there was not a statistically significant change from baseline compared with placebo in multiple endpoints, including the Bath Ankylosing Spondylitis Disease Activity Index, Functional Index, Global Score, or Metrology Index, the Functional Assessment of Chronic Illness Therapy-Fatigue, or night pain scores.

3. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drugs (tsDMARD).** Otezla is a small molecule that specifically targets intracellular PDE4 and has an inhibitory effect on multiple cytokines involved in the inflammatory process, including tumor necrosis factor, interferon gamma, interleukin (IL)-12, and IL-23.[2-3] **Co**-administration of Otezla with a biologic or another targeted synthetic DMARD (see Appendix for examples) has the risk of added immunosuppression and has not been adequately evaluated.

   This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Otezla.

4. **Rheumatoid Arthritis.** Current evidence does not support use of Otezla in RA. A multicenter, double-blind, Phase II study (n = 237) randomized patients in a 1:1:1 ratio to treatment with Otezla 20 mg twice daily, Otezla 30 mg twice daily, or placebo.[10] All patients were required to take a stable dose of methotrexate throughout the study. At Week 16, a similar proportion of patients in all treatment groups achieved an American College of Rheumatology (ACR) 20 response (28%, 34%, and 35%, respectively). At Week 16, patients who were non-responders, defined as patients with a swollen joint count and tender joint count that had not improved by at least 20%, were required to enter early escape (patients who were receiving placebo were transitioned to Otezla 20 mg twice daily and patients receiving Otezla continued on the assigned therapy for an additional year). At Week 24, all patients who received placebo were similarly transitioned to Otezla. At Weeks 24 and 52, both doses of Otezla were associated with generally similar changes versus placebo, including ACR 20, ACR 50, and ACR 70. A subset of patients underwent magnetic resonance imaging evaluation; however, no significant difference in response rate was observed at Week 16. The study was terminated early; data were not analyzed at Year 2 as originally planned.

5. **Vitiligo.** Insufficient efficacy and safety data to support use in vitiligo. Otezla is not indicated for this use.[1]

Background

OVERVIEW

Otezla, an oral phosphodiesterase 4 (PDE4) inhibitor, is indicated for the following indications:[1]

- **Behcet's disease**, in adults with oral ulcers.
- **Plaque psoriasis**, adults who are candidates for phototherapy or systemic therapy.
- **Plaque psoriasis**, in pediatric patients ≥ 6 years of age and ≥ 20 kg with moderate to severe disease who are candidates for phototherapy or systemic therapy.
- **Psoriatic arthritis**, in adults with active disease.

Guidelines

Otezla is addressed in guidelines for treatment of inflammatory conditions.

- **Behcet's Disease:** Recommendations for the management of Behcet's disease from the European League Against Rheumatism (2018) mention Otezla as a treatment option for Behcet's disease with mucocutaneous involvement.[7] Other options include topical steroids, colchicine, azathioprine, thalidomide, interferon alpha, and tumor necrosis factor inhibitors (TNFis). TNFis are also listed among the therapeutic options for patients who present with eye involvement, refractory venous thrombosis, arterial involvement, refractory/severe gastrointestinal involvement, nervous system involvement, and/or joint involvement.
- **Plaque Psoriasis:** Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2020) have been published for management of psoriasis with systemic non-biologic therapies.[8] These guidelines list Otezla as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. For treatment of moderate to severe psoriasis in adults, Otezla has a similar level of evidence and strength of recommendation as methotrexate. Additionally, data support use of methotrexate in combination with other systemic therapies for psoriasis,[4,8] whereas there is no strong evidence supporting combination use of Otezla with other systemic therapies or with phototherapy.[4] Pediatric guidelines were published by the American Academy of Dermatology and the National Psoriasis Foundation (NPF) [2020]. These guidelines list traditional systemic therapies (e.g., methotrexate, cyclosporine, acitretin) and biologics as options for treatment of moderate to severe plaque psoriasis. There was insufficient data in pediatric patients to make recommendations for Otezla.
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (2019) recommend TNFis over other biologics and Otezla for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[6]

References

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8. Mentor A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology – National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol*. 2020;82(6):1445-1486..
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10. Genovese MC, Jarosova K, Cieślak D, et al. Apremilast in patients with active rheumatoid arthritis: a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheumatol*. 2015;67(7):1703-1710.

11. Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol.* 2020 Jan;82(1):161-201.

APPENDIX

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	JIA	AS	nr-axSpA	PsA	PsO	CD	UC
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Adalimumab products (Humira, biosimilars)	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitors; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Crohn's Disease	Ulcerative Colitis
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	√	--
Skyrizi Intravenous	--	--	--	--	√[#]	--
Skyrizi Subcutaneous	--	--	√	√	√[^]	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√[^]	√[^]
Stelara Intravenous	--	--	--	--	√[#]	√[#]

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; [^] Maintenance dosing only; [#] Induction dosing only

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
Janus Kinases Inhibitors							
Olumiant	√	--	--	--	--	--	--
Rinvoq	√	--	√	√	√	--	√
Xeljanz tablets	√	√[#]	√	--	√	--	√
Xeljanz oral solution	--	√[#]	--	--	--	--	--
Xeljanz XR	√	--	√	--	√	--	√

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
Phosphodiesterase Type 4 Inhibitor							
Otezla	--	--	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator							
Zeposia	--	--	--	--	--	--	√
Tyrosine Kinase 2 Inhibitor							
Sotyktu	--	--	--	--	--	√	--

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; # Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology		
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Psoriatic Arthritis
Interleukin-6 Blockers			
Actemra Intravenous	√	√^	--
Actemra Subcutaneous	√	√^	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√#	√
Orencia Subcutaneous	√	√#	√
CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; # Indicated in polyarticular JIA.