PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Otezla® (apremilast tablets – Amgen)

DATE REVIEWED: 04/29/2020

OVERVIEW

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

1. Psoriatic arthritis (PsA) in adults; and
2. Plaque psoriasis, in moderate to severe disease in patients who are candidates for phototherapy or systemic therapy; and
3. Behcet's disease, in adults with oral ulcers.[1]

Disease Overview

PDE4 regulates immune and inflammatory processes through control of intracellular cAMP levels and downstream protein kinase A pathways. The production of a number of key inflammatory cytokines is affected by PDE4 including interferon (IFN)γ, tumor necrosis factor (TNF)α, interleukin (IL)-12, and IL-23, thus shaping the immune response.[2] Otezla is a targeted synthetic disease-modifying anti-rheumatic drug (DMARD) that specifically targets intracellular PDE4 and, therefore, has an inhibitory effect on multiple cytokines involved in the inflammatory process.[2-3]

Guidelines

Joint guidelines from the American Academy of Dermatology (AAD) and National Psoriasis Medical Board (2020) have been published for management of psoriasis with systemic nonbiologic 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 recommendations as methotrexate. Additionally, data support use of MTX 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] Guidelines from the American College of Rheumatology (ACR) [2019] recommend TNF inhibitors over other biologics and Otezla for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[6]

EULAR recommendations for the management of Behcet's disease (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 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.

Safety

Warnings/Precautions for Otezla include depression, weight decrease, and drug interactions with strong cytochrome P450 inducers. The most commonly observed adverse events (AEs) [incidence ≥ 5%] were diarrhea, nausea, and headache.[1] Of note, Otezla does not have Warnings regarding serious infection and malignancy, which are listed for the biologic DMARDs approved for PsA, nor does Otezla have warnings for organ toxicity and laboratory monitoring that are noted with methotrexate (MTX) and leflunomide.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Otezla. Because of the specialized skills required for evaluation and diagnosis of patients treated with Otezla as well as the monitoring required for AEs and long-term efficacy, initial approval requires Otezla to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Otezla is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Plaque Psoriasis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** The patient is an adult greater than or equal to 18 years of age; AND
     - **ii.** The patient meets ONE of the following conditions (a or b):
       - **a)** The patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant.
         Note: Examples of traditional systemic agents for psoriasis include methotrexate (MTX), cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for plaque psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis); OR
       - **b)** The patient has a contraindication to methotrexate (MTX), as determined by the prescriber; AND
     - **iii.** Otezla is prescribed by or in consultation with a dermatologist.
   - **B)** Patient is Currently Receiving Otezla. Approve for 3 years if the patient meets BOTH of the following conditions (i and ii):
     - **i.** The patient has already received at least 4 months of therapy with Otezla.
       Note: Patients who have received < 4 months of therapy or those who are restarting therapy with Otezla should be considered under criterion 1A (Plaque Psoriasis, initial therapy); AND
     - **ii.** The patient has had a response, as determined by the prescriber.
       Note: There may not be a full response by Month 4, but there should be some response.

2. **Psoriatic Arthritis (PsA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the BOTH of following (i and ii):
     - **i.** The patient is an adult greater than or equal to 18 years of age; AND
     - **ii.** Otezla is prescribed by or in consultation with a rheumatologist or a dermatologist.
   - **B)** Patient is Currently Receiving Otezla. Approve for 3 years if the patient meets BOTH of the following conditions (i and ii):
     - **i.** The patient has already received at least 4 months of therapy with Otezla.

Note: Patients who have received < 4 months of therapy or those who are restarting therapy with Otezla should be considered under criterion 2A [PsA, initial therapy]); AND

ii. The patient has had a response, as determined by the prescriber.
Note: Examples of a response to therapy include: less joint pain, morning stiffness, or fatigue; improved function or activities of daily living, decreased soft tissue swelling in joints or tendon sheaths, improvements in acute phase reactants [for example, C-reactive protein]).

3. **Behcet's Disease.** Approve for the duration noted if the patient meets the following criteria (A or B):
   A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
   i. The patient is an adult greater than or equal to 18 years of age; AND
   ii. The patient has oral ulcers or other mucocutaneous involvement; AND
   iii. The patient has tried at least ONE other systemic therapy.
   Note: Examples of systemic therapies include colchicine, systemic corticosteroids, azathioprine, thalidomide, interferon alpha, tumor necrosis factor inhibitors (e.g., adalimumab [Humira], etanercept [Enbrel], certolizumab pegol [Cimzia], golimumab [Simponi/Aria], or infliximab products [Inflectra, Remicade, Renflexis]); AND
   iv. Otezla is prescribed by or in consultation with a rheumatologist or dermatologist.
   B) Patient is Currently Receiving Otezla. Approve for 1 year if the patient is currently taking Otezla for ≥ 120 days and has responded to therapy, as determined by the prescriber.
   Note: Examples of a response to therapy include: a decrease in the number/frequency of oral and/or genital ulcers. Patients who have received < 4 months of therapy or those who are restarting therapy with Otezla should be considered under criterion 3A (Behcet's disease, initial therapy).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Otezla has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Ankylosing Spondylitis (AS).** Current evidence does not support use of Otezla in AS. 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 BID or placebo.[13] 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 (BASDAI, BASFI, BAS-G, or BASMI), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), or night pain scores.

2. **Concurrent Use with a Biologic or with a Targeted Synthetic DMARD.** Otezla is a small molecule that specifically targets intracellular PDE4 and has an inhibitory effect on multiple cytokines involved in the inflammatory process, including TNF, IFNγ, 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 evaluated. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Otezla.

3. **Rheumatoid Arthritis (RA).** 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 BID, Otezla 30 mg BID, or placebo.[14] All patients were required to take a stable

dose of MTX 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 BID 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 (MRI) evaluation; however, no significant difference in response rates was observed at Week 16. The study was terminated early; data were not analyzed at Year 2 as originally planned.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Otezla® tablets [prescribing information]. Summit, NJ: Celgene Corporation; April 2020.
2. Palfreeman AC, McNamee KE, McCann FE. New developments in the management of psoriasis and psoriatic arthritis: a focus on apremilast. *Drug Des Devel Ther*. 2013;7:201-210.
3. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol*. 2012;15;83(12):1583-1590.
4. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.
5. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris – Update 2015 – Short version – EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29(12):2277-2294.
6. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2019;71(1):2-29.
7. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis*. 2018;77(6):808-818.
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. Published online April 18, 2020. Available at: https://www.sciencedirect.com/science/article/pii/S019096222030284X. Accessed on April 23, 2020.

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.