VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Otezla® (apremilast tablets – Celgene Corporation)

TAC APPROVAL DATE: 07/17/2019; selected revision 07/31/2019

OVERVIEW

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

1. adult patients with psoriatic arthritis (PsA); and
2. patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy; and
3. adults with oral ulcers due to Behcet's disease.[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 (2019) have been published for management of psoriasis with biologics.[4] These guidelines list Siliq as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (EDF) [2015] recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara SC) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[5] Guidelines from the American College of Rheumatology (ACR) [2019] recommend TNF inhibitors over other biologics 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 <u>not</u> 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 an 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 (e.g., methotrexate [MTX], cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light [PUVA]) for at least 3 months, unless intolerant.
         Note: 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. Examples of biologics for plaque psoriasis include: an etanercept product (e.g., Enbrel®, Erelzi), a secukinumab product (Cosentyx), a certolizumab pegol product (Cimzia), an adalimumab product (Humira), a tildrakizumab product (Ilumya), an infliximab product (Remicade, Inflectra, Renflexis), a ustekinumab product (Stelara subcutaneous), a brodalumab product (Siliq), an ixekizumab product (Taltz), a risankizumab product (Skyrizi), or a guselkumab product (Tremfya). 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 prescribing physician; 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 ALL of 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 has tried or previously used at least one conventional synthetic DMARD (e.g., MTX, leflunomide, sulfasalazine) for at least 3 months, unless intolerant;

Note: If the patient has had a 3-month trial of a biologic, the patient is not required to try a conventional synthetic DMARD). Examples of biologics for psoriatic arthritis include: a certolizumab pegol product (Cimzia), a secukinumab product (Cosentyx), an etanercept product (Enbrel, Erelzi), an adalimumab product (Humira), an infliximab product (Remicade, Inflectra, Renflexis), an abatacept product (Orenica IV or SC), a golimumab product (Simponi SC or Aria), a ustekinumab product (Stelara SC), and an ixekizumab product (Taltz); AND

iii. 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.

iv. 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]); ANDOtezla 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; June 2017.
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 Feb 13. [Epub ahead of print].

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.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes.	05/24/2017
Selected revision	Add to the criteria for initial therapy for plaque psoriasis that the patient must be 18 years of age or greater.	10/18/2017
Annual revision	Throughout the policy, references to Humira, Enbrel, and Remicade were reworded as adalimumab, etanercept, and infliximab products, respectively, with the innovator names listed as examples of these products. Erelzi was added as an example of an etanercept product and Renflexis and Inflectra were added as examples of infliximab products. Ilumya, Siliq, Tremfya were added as examples of biologics that may have been previously tried for psoriasis. Simponi Aria and Taltz were added as examples of biologics that may have been previously tried for psoriatic arthritis. To align with updated EULAR guidelines for Behcet's disease, add that the requirement that the patient has mucocutaneous involvement. As a result of this change, update the criterion which requires a specialist to be involved in care (remove ophthalmologist, gastroenterologist, or neurologist and add obstetrician and gynecologist). To further align with guidelines, specify that a TNFi must have been previously tried (previously required any biologic). Since approval condition for Patients Established on Otezla for ≥ 120 days only applies to Behcet's disease, move directly under this condition. Shorten initial approval to 4 months (previously 1 year) and require a response to therapy for continuation of therapy.	06/27/2018
Annual revision	**Plaque Psoriasis and Psoriatic Arthritis:** When a response to therapy is required for patients continuing therapy, wording was changed to be according to the prescriber (previously worded as prescribing physician).	07/17/2019
Selected revision	**Behcet's disease:** Move to FDA-Approved Indications (previously listed under Other Use with Supportive Evidence). To align with the approval condition, revise criteria to include adults ≥ 18 years of age. Coverage criteria was expanded to specify for patients with oral ulcers or other mucocutaneous involvement (previously listed as mucocutaneous involvement without any age limitation). To align with the approval condition, remove obstetrician and gynecologist from the specialists who may be consulted prior to prescribing Otezla. To align with pivotal study population, change criteria to require previous use of another systemic agent (previously specifically required a TNFi, unless exception criteria were met). **Psoriatic Arthritis:** To align with the labeling, limit initial approval to adults ≥ 18 years of age with psoriatic arthritis.	07/31/2019

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TNF – Tumor necrosis factor; csDMARD – Conventional synthetic disease-modifying anti-rheumatic drug; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis.

APPENDIX

Brand (generic name)	Mechanism of Action
Cimzia® (certolizumab pegol for SC injection)	Inhibition of TNF
Enbrel® (etanercept for SC injection)	Inhibition of TNF
Erelzi™ (etanercept-szzs for SC injection)	Inhibition of TNF
Humira® (adalimumab for SC injection)	Inhibition of TNF
Amjevita® (adalimumab-atto for SC injection)	Inhibition of TNF

Cyltezo® (adalimumab-adbm for SC injection)	Inhibition of TNF
Simponi® (golimumab for SC injection)	Inhibition of TNF
Simponi® Aria™ (golimumab for IV infusion)	Inhibition of TNF
Remicade® (infliximab for IV infusion)	Inhibition of TNF
Inflectra™ (infliximab-dyyb for IV infusion)	Inhibition of TNF
Renflexis® (infliximab-abda for IV infusion)	Inhibition of TNF
Actemra® (tocilizumab for IV infusion)	Inhibition of IL-6
Actemra® (tocilizumab for SC injection)	Inhibition of IL-6
Kevzara® (sarilumab for SC injection)	Inhibition of IL-6
Orencia® (abatacept for IV infusion)	T-cell costimulation modulator
Orencia® (abatacept for SC injection)	T-cell costimulation modulator
Rituxan® (rituximab for IV infusion)	CD20-directed cytolytic antibody
Truxima® (rituximab-abbs IV injection)	CD20-directed cytolytic antibody
Kineret® (anakinra for subcutaneous SC injection)	Inhibition of IL-1
Stelara® (ustekinumab for SC injection)	Inhibition of IL-12/23
Stelara® (ustekinumab for IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab for SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab for SC injection)	Inhibition of IL-17A
Ilumya™ (tildrakizumab-asmn for SC injection)	Inhibition of IL-23
Skyrizi™ (risankizumab SC injection)	Inhibition of IL-23
Tremfya™ (guselkumab for SC injection)	Inhibition of IL-23
Otezla® (apremilast tablets)	Inhibition of PDE4
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathway
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase.