



Louisiana

apremilast (Otezla®)

Policy # 00436

Original Effective Date: 07/16/2014

Current Effective Date: 07/13/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Psoriatic Arthritis

Based on review of available data, the Company may consider the use of apremilast (Otezla®)‡ for the treatment of adult patients with active psoriatic arthritis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for apremilast (Otezla) will be considered when all of the following criteria are met:

- Patient has a diagnosis of active psoriatic arthritis; AND
- Patient is 18 years of age or older; AND
- Requested drug is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as adalimumab (Humira®)‡ or etanercept (Enbrel®)‡ OR other drugs such as tofacitinib (Xeljanz/XR®)‡; AND
- Patient has failed treatment with one or more DMARDs unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient.

*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Plaque Psoriasis

Based on review of available data, the Company may consider the use of apremilast (Otezla) for the treatment of patients with plaque psoriasis to be **eligible for coverage.****

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Patient Selection Criteria

Coverage eligibility for apremilast (Otezla) will be considered when all of the following criteria are met:

- Patient has a diagnosis of moderate to severe plaque psoriasis; AND
- Patient is 18 years of age or older; AND
- Patient is a candidate for phototherapy or systemic therapy; AND
- Requested drug is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as adalimumab (Humira) or etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR); AND
- Patient has greater than 10% of body surface area (BSA) or less than or equal to 10% BSA with plaque psoriasis involving sensitive areas or areas that would significantly impact daily function (such as palms, soles of feet, head/neck or genitalia); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has failed to respond to an adequate trial of one of the following treatment modalities unless there is clinical evidence or patient history that suggests these treatments will be ineffective or cause an adverse reaction to the patient:
 - Ultraviolet B; or
 - Psoralen positive Ultraviolet A; or
 - Systemic therapy (i.e. methotrexate, cyclosporine, acitretin).

*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Oral Ulcers Associated with Behçet's Disease

Based on review of available data, the Company may consider the use of apremilast (Otezla) for the treatment of adult patients with oral ulcers associated with Behçet's Disease to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for apremilast (Otezla) will be considered when all of the following criteria are met:

- Patient has oral ulcers associated with Behçet's Disease; AND
- Patient is 18 years of age or older; AND

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- Patient has failed at least one other systemic therapy for the condition (e.g., colchicine, systemic corticosteroids, azathioprine, thalidomide, interferon alpha, etc.) unless there is clinical evidence or patient history that suggests these treatments will be ineffective or cause an adverse reaction to the patient.

*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of apremilast (Otezla) when any of the following criteria for the respective disease listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary****:

- For psoriatic arthritis:
 - Patient has failed treatment with one or more DMARDs
- For plaque psoriasis:
 - Patient has greater than 10% of BSA or less than or equal to 10% BSA with plaque psoriasis involving sensitive areas or areas that would significantly impact daily function (such as palms, soles of feet, head/neck or genitalia)
 - Patient has failed to respond to an adequate trial of one of the following treatment modalities:
 - Ultraviolet B; or
 - Psoralen positive Ultraviolet A; or
 - Systemic therapy (i.e. methotrexate, cyclosporine, acitretin).
- For oral ulcers associated with Behçet's Disease:
 - Patient has failed at least one other systemic therapy for the condition (e.g., colchicine, systemic corticosteroids, azathioprine, thalidomide, interferon alpha, etc.)

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of apremilast (Otezla) when patient selection criteria are not met to be **investigational*** (with the exception of those denoted above as **not medically necessary****).

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Based on review of available data, the Company considers the use of apremilast (Otezla) for indications other than those listed above to be **investigational**.*

Background/Overview

Otezla is an oral small molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP) and is indicated for the treatment of adult patients with active psoriatic arthritis, the treatment of adult patients with moderate to severe plaque psoriasis, and the treatment of adult patients with oral ulcers associated with Behçet's Disease. The inhibition of PDE4 results in increased intracellular cAMP. The mechanism by which Otezla works is not well defined. Otezla is provided as 10 mg, 20 mg, and 30 mg tablets. In order to reduce the risk of gastrointestinal symptoms, the dose should be titrated up to 30 mg twice daily. The titration schedule can be found in the prescribing information. Patients with severe renal impairment should be dosed at 30 mg once daily.

Psoriatic Arthritis

Psoriatic arthritis is an arthritis that is often associated with psoriasis of the skin. Typically first line treatments such as DMARDs are used to treat this condition. It should be noted that in the 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis, Otezla was classified as an oral small molecule (similarly categorized with drugs such as methotrexate and sulfasalazine). It should also be noted that the recommendations given in the guidelines for treatment naïve patients with psoriatic arthritis were conditional and based on mostly low to very low levels of evidence. Given the conditional recommendations and the level of evidence, traditional DMARDs, such as methotrexate, will continue to be required prior to the use of Otezla in this condition.

Plaque Psoriasis

Psoriasis is a common skin condition that is caused by an increase in production of skin cells. It is characterized by frequent episodes of redness, itching and thick, dry silvery scales on the skin. It is most commonly seen on the trunk, elbows, knees, scalp, skin folds and fingernails. This condition can appear suddenly or gradually and may affect people of any age; it most commonly begins between the ages of 15 and 35. Psoriasis is not contagious. It is an inherited disorder related to an inflammatory response in which the immune system produces too much tumor necrosis factor (TNF) alpha. It may be severe in immunosuppressed people or those who have other autoimmune disorders

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such as rheumatoid arthritis. Typical treatments for severe cases of plaque psoriasis include ultraviolet therapy or systemic therapies such as methotrexate or cyclosporine. Newer biologic therapies are also approved for the treatment of plaque psoriasis.

Disease-Modifying Anti-Rheumatic Drugs

Disease-modifying anti-rheumatic drugs are used for the treatment of conditions such as psoriatic arthritis and plaque psoriasis. These drugs slow the disease process by modifying the immune system.

- methotrexate
- cyclosporine
- sulfasalazine
- mercaptopurine
- gold compounds

Behçet's Disease

Behçet's Disease is characterized by recurrent aphthae and several systemic manifestations. These systemic manifestations include genital aphthae, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease, or arthritis. Most of these manifestations are believed to be due to vasculitis. The most common clinical feature is the presence of recurrent mucocutaneous ulcers, particularly oral ulcers. These ulcers can be painful and can often times limit eating. In particular, it should be noted that Otezla is specifically approved the treatment of oral ulcers associated with Behçet's Disease. Current treatment options for oral ulcers associated with Behçet's Disease are colchicine, systemic corticosteroids, azathioprine, thalidomide, interferon alpha. If the patient doesn't have an adequate response, then treatment should be escalated to include Otezla.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Otezla was approved in March of 2014 by the FDA for the treatment of adult patients with active psoriatic arthritis. In September of 2014, Otezla gained approval for the treatment of moderate to severe plaque psoriasis in patients that are candidates for phototherapy or systemic therapy. In July of 2019, Otezla was approved for the treatment of adult patients with oral ulcers associated with

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Behçet's Disease. In April of 2020, the package insert was updated to specify that Otezla is approved for adults with plaque psoriasis vs. prior when no age was listed.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Psoriatic Arthritis

The safety and efficacy of Otezla in patients with psoriatic arthritis was evaluated in 3 multi-center, randomized, double-blind, placebo-controlled trials of similar design. A total of 1493 adult patients with active psoriatic arthritis despite prior or current treatment with DMARD therapy were randomized. The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 responses at week 16. The proportion of patients achieving ACR 20 at week 16 in the placebo group in the three psoriatic arthritis trials was: 19%, 19%, and 18%, respectively. The proportion of patients achieving ACR 20 in the Otezla treatment group in the three psoriatic arthritis trials was 38%, 32%, and 41%, respectively (all of which reached statistical significance $p < 0.05$).

Plaque Psoriasis

The safety and efficacy of Otezla for plaque psoriasis was studied in two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2) and enrolled a total of 1257 subjects 18 years of age and older with moderate to severe plaque psoriasis. In both studies, subjects were randomized 2:1 to Otezla 30 mg BID or placebo for 16 weeks. Both studies assessed the proportion of subjects who achieved Psoriasis Area Severity Index-75 (PASI-75) at week 16 and the proportion of subjects who achieved a Physician Global Assessment (PGA) score of clear (0) or almost clear (1) at week 16. Across both studies, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.19% (median 21.0%), the mean baseline PASI score was 19.07 (median 16.80), and the proportion of subjects with a PGA score of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively. Approximately

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30% of all subjects had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of subjects had not received prior phototherapy, conventional systemic nor biologic therapy. A total of 18% of subjects had a history of psoriatic arthritis. In PSOR-1, 5.3% of subjects in the placebo group achieved PASI-75 vs. 33.1% in the Otezla group. In the placebo group, there were 3.9% of patients that achieved a PGA of clear or almost clear vs. 21.7% in the Otezla group. In PSOR-2, 5.8% of subjects in the placebo group achieved PASI-75 vs. 28.8% in the Otezla group. In the placebo group, there were 4.4% of patients that achieved a PGA of clear or almost clear vs. 20.4% in the Otezla group.

Oral Ulcers Associated with Behçet's Disease

The safety and efficacy of Otezla for the treatment of adult patients with oral ulcers associated with Behçet's Disease was evaluated in a multicenter, randomized, placebo-controlled trial that enrolled a total of 207 adult patients. Patients were previously treated with at least one nonbiologic Behçet's Disease medication and were candidates for systemic therapy. Patients met the International Study Group (ISG) Criteria for Behçet's Disease. Patients had at least 2 oral ulcers at screening and at least 2 oral ulcers at randomization and without currently active major organ involvement. Concomitant treatment for Behçet's Disease was not allowed. Patients were randomized 1:1 to receive either Otezla 30 mg twice daily (n=104) or placebo (n=103) for 12 weeks. After week 12, all patients received Otezla 30 mg twice daily. Efficacy was assessed based on the number and pain of oral ulcers. The level of pain was measured by the VAS (visual analog scale), which ranges from 0 (no pain)-100 (worst possible pain). At 12 weeks, the Otezla group experienced a 42.7 point reduction in pain vs. the placebo group, which experienced an 18.7 point reduction in pain. At week 12, 52.9% of the Otezla patients achieved a complete response (ulcer free) vs. 22.3% of patients in the placebo group.

References

1. Otezla [package insert]. Celgene Corporation: Summit, New Jersey. Updated April 2020.
2. Treatment of Behçet Syndrome. UpToDate. Accessed October 2019.
3. Sing JA, Guyatt G, Ogdie, A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis and Rheumatology*. 71:1, p. 5-32. DOI 10.1002/art.40726

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07/10/2014 Medical Policy Committee review

07/16/2014 Medical Policy Implementation Committee approval. New policy.

11/06/2014 Medical Policy Committee review

11/21/2014 Medical Policy Implementation Committee approval. Added a new indication for plaque psoriasis and made updates throughout to reflect the new indication (background, rationale, etc).

10/29/2015 Medical Policy Committee review

11/16/2015 Medical Policy Implementation Committee approval. No change to coverage eligibility.

11/03/2016 Medical Policy Committee review

11/16/2016 Medical Policy Implementation Committee approval. No change to coverage eligibility.

12/07/2017 Medical Policy Committee review

12/20/2017 Medical Policy Implementation Committee approval. Removed requirement for Humira and Enbrel prior to Otezla for plaque psoriasis. Changed to fail one of the following for psoriatic arthritis: Humira, Enbrel, Stelara, or Cosentyx.

12/06/2018 Medical Policy Committee review

12/19/2018 Medical Policy Implementation Committee approval. Added Xeljanz/XR as an option for use in psoriatic arthritis

11/07/2019 Medical Policy Committee review

11/13/2019 Medical Policy Implementation Committee approval. Updated to include the most recent FDA approval for oral ulcers associated with Behçet's Disease.

06/04/2020 Medical Policy Committee review

06/10/2020 Medical Policy Implementation Committee approval. Removed the requirement for a trial and failure of a preferred biologic before Otezla in psoriatic arthritis. Updated the age for use in plaque psoriasis to 18 years and older to correspond with the FDA package insert update. Updated Background information.

Next Scheduled Review Date: 06/2021

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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