ozanimod (Zeposia®)

Policy # 00733
Original Effective Date: 03/08/2021
Current Effective Date: 08/09/2021

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.*

Multiple Sclerosis

Based on review of available data, the Company may consider ozanimod (Zeposia®)‡ for the treatment of relapsing forms of multiple sclerosis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ozanimod (Zeposia) will be considered when the following criteria are met:

- Patient has a relapsing form of multiple sclerosis (including clinically isolated syndrome, relapsing-remitting disease, active secondary progressive disease); AND
- Patient is greater than or equal to 18 years of age.

Ulcerative Colitis

Based on review of available data, the Company may consider ozanimod (Zeposia) for the treatment of ulcerative colitis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ozanimod (Zeposia) will be considered when the following criteria are met:

- Patient has a diagnosis of moderately to severely active ulcerative colitis; AND
- Patient is greater than or equal to 18 years of age; AND
- Patient has failed treatment with conventional therapies such as corticosteroids, azathioprine, or 6-mercaptopurine 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; 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 treatment with adalimumab (Humira®)‡ and ustekinumab (Stelara®)‡ after at least TWO months of therapy with each product 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; 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)*
- Requested drug is NOT being used in combination with biologic DMARDs for the treatment of ulcerative colitis, such as adalimumab (Humira) or ustekinumab (Stelara).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of ozanimod (Zeposia) for the treatment of ulcerative colitis when the patient has not failed the pre-requisite medications listed in the patient selection criteria to be **not medically necessary.****

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 ozanimod (Zeposia) when patient selection criteria are not met (except those criteria denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Zeposia is a sphingosine 1 (S1P) receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis including clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults as well as for the treatment of moderately to severely active ulcerative colitis in adults. It works by binding to S1P receptors 1 and 5 to prevent lymphocytes from leaving lymph nodes and reduces the number of lymphocytes in the peripheral blood. It is the third drug for the treatment of multiple sclerosis to be approved with this mechanism, but the first drug for ulcerative colitis to work via this mechanism. Gilenya®‡ (fingolimod) and Mayzent®‡

(siponimod) are also S1P receptor modulators, but have various advantages and disadvantages compared to Zeposia. Gilenya is indicated in patients as young as 10 years of age and binds to S1P receptors 1, 3, 4, and 5. All patients being treated with Gilenya must be monitored for at least 6 hours after receiving their first dose to assess for bradycardia. Mayzent binds to S1P receptors 1 and 5 and is indicated in adults. It does not require first-dose monitoring but does require genetic testing for the CYP2C9 variants prior to treatment. Both Mayzent and Zeposia require titration to the target dose. The target dose of Zeposia is 0.92 mg taken orally once daily for both multiple sclerosis and ulcerative colitis.

Multiple Sclerosis

Multiple sclerosis is believed to have an immunologic mechanism that is characterized by demyelination in the brain and spinal cord. This is often expressed by symptoms such as visual and oculomotor abnormalities, weakness, urinary dysfunction, and mild cognitive impairment. In the most common forms of MS, patients experience remissions and exacerbations. Treatment includes corticosteroids for acute exacerbations and immunomodulatory (disease modifying) drugs to prevent exacerbations. Disease modifying drugs include oral products such as fingolimod (Gilenya), dimethyl fumarate (Tecfidera®)‡, teriflunomide (Aubagio®)‡, cladribine (Mavenclad®)‡, and siponimod (Mayzent®)‡; subcutaneous and intramuscular injectable products such as glatiramer acetate (Copaxone®, Glatopa®)‡, interferon beta-1a (Avonex®, Rebif®)‡, interferon beta-1b (Extavia®, Betaseron®)‡, peginterferon beta-1a (Plegridy®)‡, and ofatumumab (Kesimpta®)‡; and intravenous infusions such as ocrelizumab (Ocrevus®)‡, natalizumab (Tysabri®)‡, and alemtuzumab (Lemtrada®)‡.

Ulcerative Colitis

Ulcerative colitis is a chronic, episodic, inflammatory disease of the large intestine and rectum characterized by bloody diarrhea. This disease usually begins in the rectal area and may eventually extend through the entire large intestine. Repeated episodes of inflammation lead to thickening of the wall of the intestine and rectum with scar tissue. Death of colon tissue or sepsis may occur with severe disease. The goals of treatment are to control the acute attacks, prevent recurrent attacks and promote healing of the colon. Hospitalization is often required for severe attacks. Typically, first line treatments such as corticosteroids, 6-mercaptopurine and azathioprine are used to treat this condition. Treatment options after the more traditional medications include adalimumab (Humira), ustekinumab (Stelara), tofacitinib (Xeljanz/XR®)‡, golimumab (Simponi®)‡, infliximab (Remicade®‡, biosimilars), and vedolizumab (Entyvio®)‡.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Zeposia was approved in early 2020 for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. In June of 2021, Zeposia was approved for the treatment of moderately to severely active ulcerative colitis in adults

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.

Multiple Sclerosis

The efficacy of Zeposia was demonstrated in 2 randomized, double-blind, double-dummy, parallel-group, active comparator-controlled clinical trials of similar design in patients with relapsing forms of MS (SUNBEAM and RADIANCE). Patients in SUNBEAM were treated until the last enrolled patient completed 1 year of treatment. Patients in RADIANCE were treated for 24 months. Both studies included patients who had experienced at least 1 relapse within the prior year, or 1 relapse within the prior 2 years with evidence of at least a gadolinium-enhancing (GdE) lesion in the prior year, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5 at baseline. Patients with primary progressive MS were excluded. In both studies, patients were randomized to receive either Zeposia 0.92 mg by mouth once daily beginning with a dose titration or interferon beta-1a, 30 mcg given intramuscularly once weekly. The primary endpoint of both studies was the annualized relapse rate (ARR) over the treatment period.

In SUNBEAM, a total of 895 patients were randomized to receive Zeposia (n=447) or interferon beta-1a (n=448). At baseline, the mean number of relapses in the prior year was 1.3 and 48% of patients had one or more T1 Gd-enhancing lesions on their baseline MRI scan. Zeposia demonstrated a 48% reduction in annualized relapse rate compared to interferon beta-1a ($p<0.0001$) with an ARR of 0.181 in the Zeposia group and 0.35 in the interferon beta-1a group.

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In RADIANCE, 874 patients were randomized to receive Zeposia (n=433) or interferon beta-1a (n=441). At baseline, the mean number of relapses in the prior year was 1.3 and 43% of patients had one or more T1 Gd-enhancing lesions on their baseline MRI scan. In this study, Zeposia demonstrated a 38% reduction in the ARR compared to interferon beta-1a ($p<0.0001$) with an ARR of 0.172 in the Zeposia group and 0.276 in the interferon beta-1a group.

Ulcerative Colitis

The efficacy and safety of Zeposia were evaluated in two multicenter, randomized, double-blind, placebo-controlled clinical studies [UC Study 1 (induction) and UC Study 2 (maintenance)] in adult patients with moderately to severely active ulcerative colitis.

In UC Study 1, a total of 645 patients were randomized 2:1 to either Zeposia 0.92 mg given orally once daily or placebo for 10 weeks, beginning with a dosage titration (see package insert for more details). The trial included adult patients with moderately to severely active UC (ulcerative colitis) who had an inadequate response or were intolerant to any of the following: oral aminosalicylates, corticosteroids, immunomodulators (e.g., 6-mercaptopurine and azathioprine), or a biologic (e.g., TNF blocker and/or vedolizumab). Patients were required to be on stable doses of oral aminosalicylates and/or corticosteroids (prednisone daily dose up to 20 mg equivalent or budesonide extended-release tablets) prior to enrollment. Seventy-one percent of patients were receiving mesalamine, 13% sulfasalazine, and 33% oral corticosteroids. A total of 30% of patients had previously failed or were intolerant to TNF blockers. Of these patients, 63% received at least two biologics including TNF blockers. The disease activity was assessed by the Mayo score (0 to 12) which consists of four subscores (0 to 3 for each subscore): stool frequency, rectal bleeding, findings on centrally-read endoscopy, and physician global assessment. An endoscopy subscore of 2 was defined by marked erythema, lack of vascular pattern, friability, and erosions; an endoscopy subscore of 3 was defined by spontaneous bleeding and ulceration. Enrolled patients had Mayo scores between 6 to 12; at baseline, patients had a median Mayo score of 9, with 86% of patients having moderate disease (Mayo score 6-10), and 14% having severe disease (Mayo score 11-12). Concomitant immunomodulators or biologic therapies were not permitted. The primary endpoint was clinical remission at Week 10, defined using a 3-component Mayo score without the physician global assessment: rectal bleeding subscore = 0, stool frequency subscore = 0 or 1 (and a decrease of ≥ 1 point from the baseline stool frequency subscore), and endoscopy subscore = 0 or 1 (an endoscopy subscore of 0 defined as normal or inactive disease, and an endoscopy subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability). The secondary

endpoints were clinical response, endoscopic improvement, and endoscopic-histologic mucosal improvement. Clinical response (reduction from baseline in the 3-component Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1), endoscopic improvement (Mayo endoscopy subscore of 0 or 1), and endoscopic-histologic mucosal improvement [combined endoscopic improvement and histologic improvement of colonic tissue (no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue, i.e., Geboes < 2.0)]. A significantly greater proportion of patients treated with Zeposia achieved clinical remission, clinical response, endoscopic improvement, and endoscopic-histologic mucosal improvement compared to placebo at Week 10. Clinical remission was achieved in 18% of Zeposia treated patients vs. 6% of those in the placebo group

UC Study 2 In UC Study 2, a total of 457 patients who received Zeposia in either UC Study 1 or in an open-label arm and achieved clinical response at Week 10 were re-randomized 1:1 and were treated with either Zeposia 0.92 mg (n=230) or placebo (n=227) for 42 weeks (UC Study 2), for a total of 52 weeks of treatment. Patients were permitted to be on stable doses of oral aminosalicylates. Corticosteroid tapering was required upon entering this study for patients who were receiving corticosteroids during the induction period. Concomitant oral immunomodulators or biologic therapies were not permitted. At study entry, 35% of patients were in clinical remission; 29% of patients were on corticosteroids; and 31% of patients had an inadequate response, loss of response, or intolerance to TNF blockers. The primary endpoint was the proportion of patients in clinical remission at Week 52. The secondary endpoints at Week 52 were the proportion of patients with clinical response, endoscopic improvement, endoscopic-histologic mucosal improvement, corticosteroid-free clinical remission, and maintenance of clinical remission at Week 52 among patients who achieved clinical remission at Week 10 in UC Study 1. Clinical remission was achieved in 37% of Zeposia treated patients vs. 19% of those in the placebo group

References

1. Zeposia [package insert]. Celgene Corporation. Summit, NJ. Updated May 2021.
2. Zeposia Drug Evaluation. Express Scripts. Updated April 2020

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02/04/2021 Medical Policy Committee review
02/10/2021 Medical Policy Implementation Committee approval. New policy.
07/01/2021 Medical Policy Committee review
07/14/2021 Medical Policy Implementation Committee approval. Added a new FDA indication and criteria for moderate to severe ulcerative colitis. Updated all sections of the policy to reflect changes.
Next Scheduled Review Date: 07/2022

*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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.