



Drug Coverage Policy

Effective Date12/01/2024

Coverage Policy Number.....IP0655

Policy Title.....Zeposia

Multiple Sclerosis and Ulcerative Colitis – Zeposia Prior Authorization Policy

- Zeposia® (ozanimod capsules – Celgene)

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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. 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.

Cigna Healthcare Coverage Policy

Overview

Zeposia, a sphingosine 1-phosphate receptor modulator, is indicated for the following uses:¹

- Relapsing forms of **multiple sclerosis** (MS), in adults to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
- **Ulcerative colitis** (UC), in adults with moderately to severely active disease.

Guidelines/Clinical Efficacy

Published guidelines address recommended treatments for the following conditions:

- **Multiple sclerosis (MS):** Zeposia is not currently addressed in MS guidelines. In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.² Many options from various pharmacologic classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.
- **Ulcerative colitis (UC):** Zeposia is not currently addressed in UC guidelines. The American Gastroenterological Association (2020) and the American College of Gastroenterology (2019) have clinical practice guidelines on the management of moderate to severe UC and make recommendations for induction and maintenance of remission in adults.^{3,4} Both endorse the use of biologic agents and give specific patient circumstances in the selection for induction and maintenance therapies. The 10-week, induction pivotal trial for Zeposia included adult patients with moderately to severely active UC who had an inadequate response or were intolerant to any of the following agents: oral aminosalicylates, corticosteroids, immunomodulators (e.g., 6-mercaptopurine and azathioprine), or a biologic (e.g., tumor necrosis factor inhibitor, Entyvio [vedolizumab injection]).¹

Medical Necessity Criteria

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information.

Policy Statement

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

NOTE: This product also requires the use of preferred products before approval of the requested product. Refer to the respective *Multiple Sclerosis and Ulcerative Colitis – Zeposia Preferred Specialty Management Policy for Employer Plans: Standard/Performance, Value/Advantage, Legacy, Total Savings Prescription Drug Lists (PSM004)* or *Multiple Sclerosis and Ulcerative Colitis – Zeposia Preferred Specialty Management Policy for Individual and Family Plans (PSM008)* for additional preferred product criteria requirements and exceptions.

Zeposia is considered medically necessary when ONE of the following is met (1 or 2):

FDA-Approved Indications

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):
 - A) **Initial Therapy.** Approve for 1 year if the patient meets the following (i and ii):
 - i. Documentation the patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
 - ii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; AND

- B) Patient is Currently Receiving Zeposia for \geq 1 Year.** Approve for 1 year if the patient meets the following (i, ii, and iii):
- i.** Documentation the patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
 - ii.** Patient meets one of the following (a or b):
 - a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
 - b)** Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
 - iii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

2. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

- i.** Patient is \geq 18 years of age; AND
- ii.** Patient has had a trial of ONE systemic agent for ulcerative colitis; AND
Note: Examples of systemic agents for ulcerative colitis include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of one biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to the [Appendix A](#) for examples of biologics used for ulcerative colitis.
- iii.** The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Zeposia. Approve for 1 year if the patient meets BOTH of the following (i and ii):

- i.** Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received $<$ 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
- ii.** Patient meets at least one of the following (a or b):
 - a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.
 - b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

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.

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

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

- 1. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (see [Appendix B](#) for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.
- 2. Non-Relapsing Forms of Multiple Sclerosis.** The efficacy of Zeposia has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.¹ Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.
- 3. Concurrent Use with a Biologic or with a Targeted Synthetic Oral Small Molecule Drug.** This medication should not be administered in combination with another biologic or with a targeted synthetic oral small molecule drug used for an inflammatory condition (see [Appendix A](#) for examples). Combination therapy is generally not recommended due to a potentially higher rate of adverse events and lack of controlled clinical data supporting additive efficacy.
- 4. Concurrent Use with Other Potent Immunosuppressants.** In pivotal trials, patients who received Velsipity were not to receive concomitant treatment with non-corticosteroid immunosuppressive or immune-modulating therapies used for the treatment of ulcerative colitis. Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of controlled clinical data supporting additive efficacy.¹ Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, and methotrexate.

References

1. Zeposia® capsules [prescribing information]. Princeton, NJ: Celgene/Bristol Myers Squibb; August 2023.
2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
3. Feuerstein JD, Isaac s KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158:1450-1461.
4. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. American College of Gastroenterology clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114:384-413.

APPENDIX A

| | Mechanism of Action | Examples of Indications* |
|---|----------------------------------|---|
| Biologics | | |
| Adalimumab SC Products (Humira®, biosimilars) | Inhibition of TNF | AS, CD, JIA, PsO, PsA, RA, UC |
| Cimzia® (certolizumab pegol SC injection) | Inhibition of TNF | AS, CD, nr-axSpA, PsO, PsA, RA |
| Etanercept SC Products (Enbrel®, biosimilars) | Inhibition of TNF | AS, JIA, PsO, PsA, RA |
| Infliximab IV Products (Remicade®, biosimilars) | Inhibition of TNF | AS, CD, PsO, PsA, RA, UC |
| Zymfentra® (infliximab-dyyb SC injection) | Inhibition of TNF | CD, UC |
| Simponi®, Simponi Aria® (golimumab SC injection, golimumab IV infusion) | Inhibition of TNF | SC formulation: AS, PsA, RA, UC |
| | | IV formulation: AS, PJIA, PsA, RA |
| Tocilizumab Products (Actemra® IV, biosimilar; Actemra SC, biosimilar) | 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: JIA, PSA, RA |
| | | IV formulation: JIA, PsA, RA |
| Rituximab IV Products (Rituxan®, biosimilars) | CD20-directed cytolytic antibody | RA |
| Kineret® (anakinra SC injection) | Inhibition of IL-1 | JIA^, RA |
| OmvoH® (mirikizumab IV infusion, SC injection) | Inhibition of IL-23 | UC |
| 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; secukinumab IV infusion) | Inhibition of IL-17A | SC formulation: AS, ERA, nr-axSpA, PsO, PsA |
| | | IV formulation: AS, nr-axSpA, PsA |
| Taltz® (ixekizumab SC injection) | Inhibition of IL-17A | AS, nr-axSpA, PsO, PsA |
| Bimzelx® (bimekizumab-bkzx SC injection) | Inhibition of IL-17A/17F | PsO |
| Ilumya® (tildrakizumab-asmn SC injection) | Inhibition of IL-23 | PsO |
| Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion) | Inhibition of IL-23 | SC formulation: CD, PSA, PsO, UC |
| | | IV formulation: CD, UC |
| Tremfya® (guselkumab SC injection, guselkumab IV infusion) | Inhibition of IL-23 | SC formulation: PsA, PsO, UC |
| | | IV formulation: UC |
| Entyvio® (vedolizumab IV infusion, vedolizumab SC injection) | Integrin receptor antagonist | CD, UC |
| Oral Therapies/Targeted Synthetic Oral Small Molecule Drugs | | |

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|---|--|-------------------------------|
| Otezla [®] (apremilast tablets) | Inhibition of PDE4 | PsO, PsA |
| Cibinqo [™] (abrocitinib tablets) | Inhibition of JAK pathways | AD |
| Olumiant [®] (baricitinib tablets) | Inhibition of JAK pathways | RA, AA |
| Litfulo [®] (ritlecitinib capsules) | Inhibition of JAK pathways | AA |
| Leqselvi [®] (deuruxolitinib tablets) | Inhibition of JAK pathways | AA |
| Rinvoq [®] (upadacitinib extended-release tablets) | Inhibition of JAK pathways | AD, AS, nr-axSpA, RA, PsA, UC |
| Rinvoq [®] LQ (upadacitinib oral solution) | Inhibition of JAK pathways | PsA, PJIA |
| Sotyktu [®] (deucravacitinib tablets) | Inhibition of TYK2 | PsO |
| Xeljanz [®] (tofacitinib tablets/oral solution) | Inhibition of JAK pathways | RA, PJIA, PsA, UC |
| Xeljanz [®] XR (tofacitinib extended-release tablets) | Inhibition of JAK pathways | RA, PsA, UC |
| Zeposia [®] (ozanimod tablets) | Sphingosine 1 phosphate receptor modulator | UC |
| Velsipity [®] (etrasimod tablets) | Sphingosine 1 phosphate receptor modulator | UC |

* Not an all-inclusive list of indications. Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn’s disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; AA – Alopecia areata; TYK2 – Tyrosine kinase 2.

Appendix

| Medication | Mode of Administration |
|--|-------------------------------|
| Aubagio [®] (teriflunomide tablets, generic) | Oral |
| Avonex [®] (interferon beta-1a intramuscular injection) | Injection (self-administered) |
| Bafiertam [®] (monomethyl fumarate delayed-release capsules) | Oral |
| Betaseron [®] (interferon beta-1b subcutaneous injection) | Injection (self-administered) |
| Briumvi [®] (ublituximab-xiyy intravenous infusion) | Intravenous infusion |
| Copaxone [®] (glatiramer acetate subcutaneous injection, generic) | Injection (self-administered) |
| Extavia [®] (interferon beta-1b subcutaneous injection) | Injection (self-administered) |
| Gilenya [®] (fingolimod capsules, generic) | Oral |
| Glatopa [®] (glatiramer acetate subcutaneous injection) | Injection (self-administered) |
| Kesimpta [®] (ofatumumab subcutaneous injection) | Injection (self-administered) |
| Lemtrada [®] (alemtuzumab intravenous infusion) | Intravenous infusion |
| Mavenclad [®] (cladribine tablets) | Oral |
| Mayzent [®] (siponimod tablets) | Oral |

| | |
|---|--|
| Ocrevus® (ocrelizumab intravenous infusion) | Intravenous infusion |
| Ocrevus Zunovo™ (ocrelizumab and hyaluronidase-ocsq subcutaneous injection) | Subcutaneous Injection (not self-administered) |
| Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection) | Injection (self-administered) |
| Ponvory® (ponesimod tablets) | Oral |
| Rebif® (interferon beta-1a subcutaneous injection) | Injection (self-administered) |
| Tascenso ODT® (fingolimod orally disintegrating tablets) | Oral |
| Tecfidera® (dimethyl fumarate delayed-release capsules, generic) | Oral |
| Tyruko® (natalizumab-sztn intravenous infusion) | Intravenous infusion |
| Tysabri® (natalizumab intravenous infusion) | Intravenous infusion |
| Vumerity® (diroximel fumarate delayed-release capsules) | Oral |
| Zeposia® (ozanimod capsules) | Oral |

Revision Details

| Type of Revision | Summary of Changes | Date |
|------------------|--------------------|------------|
| New | New policy | 12/01/2024 |

The policy effective date is in force until updated or retired.

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