MEDICAL MUTUAL®

Drug Policy

Policy:	Zeposia (ozanimod capsules)	Annual Review Date: 01/16/2025 Last Revised Date: 01/16/2025

OVERVIEW

Zeposia, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.[1] Zeposia is contraindicated in patients who have experienced In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure, presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker, severe untreated sleep apnea, and is contraindicated in concomitant use of a monoamine oxidase inhibitor.

POLICY STATEMENT

This policy involves the use of Zeposia. Prior authorization is recommended for pharmacy benefit coverage of Zeposia. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

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, initial approval requires Zeposia be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

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

1. <u>Relapsing Forms of Multiple Sclerosis (MS):</u>
Criteria. *Approve for 1 year if the patient meets one of the following (A or B):*

A) <u>Initial Therapy</u>. Approve for 1 year if the patient meets the following (i <u>and</u> ii):
- **i.** Patient has a relapsing form of multiple sclerosis; AND
  <u>Note</u>: 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; OR

B) Patient is Currently Receiving Zeposia for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. 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:

Criteria. *Patient must meet the following criteria (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 ≥ 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; OR

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.

Approval Duration. See above criteria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zeposia 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

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.
   Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.[1]

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).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence supporting additive efficacy.

4. **Concurrent Use with Other Potent Immunosuppressants.** In pivotal trials, patients who received Zeposia 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.

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

Documentation Requirements:
The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company.

Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

APPENDIX A

	Mechanism of Action	Examples of Inflammatory 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
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Zymfentra™ (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
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
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
		IV formulation: CD, UC
Omvoh™ (mirikizumab-mrkz IV infusion and SC injection)	Inhibition of IL-23	UC
Tremfya™ (guselkumab SC injection, guselkumab IV infusion)	Inhibition of IL-23	SC formulation: PsA, PsO, UC
		IV formulation: UC
Entyvio™ (vedolizumab IV infusion and SC injection)	Integrin receptor antagonist	CD, UC
Oral Therapies/Targeted Synthetic Oral Small Molecule Drugs		
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 B

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-xiiy 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

REFERENCES

1. Zeposia® capsules [prescribing information]. Princeton, NJ: Celgene/Bristol Myers Squibb; August 2024.
2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019.
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.