Clinical Policy: Ozanimod (Zeposia)

Reference Number: CP.PHAR.462
Effective Date: 03.25.20
Last Review Date: 11.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Ozanimod (Zeposia®) is a sphingosine 1-phosphate receptor modulator.

FDA Approved Indication(s)

Zeposia 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.
- Moderately to severely active ulcerative colitis (UC) in adults.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Zeposia is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome, and member is contraindicated to both, or has experienced clinically significant adverse effects to one, of the following at up to maximally indicated doses: an **interferon-beta agent** (Avonex®, Betaseron®/Extavia®†, Rebif®, or Plegridy®), **glatiramer** (Copaxone®, Glatopa®);^
      ^For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395
   b. Relapsing-remitting MS, and failure of all of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated (i, ii, iii, and iv):^
      ^For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395
      i. **Dimethyl fumarate** (generic Tecfidera®);
      ii. **Teriflunomide** (generic Aubagio®);
      iii. **Fingolimod** (Gilenya®);
      iv. An **interferon-beta agent** (Avonex, Betaseron/Extavia†, Rebif, or Plegridy) or **glatiramer** (Copaxone, Glatopa);

**Prior authorization is required for all disease modifying therapies for MS*
†Betaseron is the preferred interferon beta-1b product for the Commercial and HIM lines of business

c. Secondary progressive MS;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Zeposia is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Dose does not exceed the following (a and b):
   a. 0.92 mg per day;
   b. 1 capsule per day.

Approval duration: 6 months

B. Ulcerative Colitis – *FOR MEDICAID ONLY** (must meet all)**:**
**Refer to CP.CPA.194 Biologic DMARDs for commercial and HIM.PA.SP60 Biologic DMARDs for HIM*
1. Diagnosis of UC;
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 18 years;
4. Documentation of a Mayo Score ≥ 6, modified Mayo Score ≥ 5, or Mayo Endoscopic Score ≥ 2 (*see Appendix E*);
5. Failure of an 8-week trial of systemic corticosteroids, unless contraindicated, clinically significant adverse effects are experienced, or previously failed a biologic agent for UC;^
   ^For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395
6. Failure of one of the following, used for ≥ 3 consecutive months, unless clinically significant adverse effects are experienced or all are contraindicated (a or b):^
   ^For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395
   a. One adalimumab product (e.g., *Hadlima, Simlandi, Yusimry, adalimumab-aaty, adalimumab-adaz, adalimumab-adbm, and adalimumab-fkjp are preferred*), unless the member has had a history of failure of two TNF blockers;
   b. One ustekinumab product (e.g., *Otulfi®, Pyzchiva® (branded), Selarsdi™, Steqeyma®, Yesintek™ are preferred*);
   **Prior authorization may be required for adalimumab products and ustekinumab products*
7. Dose does not exceed the following (a and b):
   a. 0.92 mg per day;
   b. 1 capsule per day.

Approval duration: 6 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Multiple Sclerosis (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. Zeposia is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
4. If request is for a dose increase, new dose does not exceed the following (a and b):
   a. 0.92 mg per day;
   b. 1 capsule per day.

Approval duration: 12 months

B. Ulcerative Colitis – *FOR MEDICAID ONLY** (must meet all):

**Refer to CP.CPA.194 Biologic DMARDs for commercial and HIM.PA.SP60 Biologic DMARDs for HIM*

1. Currently Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the following (a and b):
   a. 0.92 mg per day;
   b. 1 capsule per day.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Primary progressive MS.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
UC: ulcerative colitis
MS: multiple sclerosis

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
teriflunomide (Aubagio®)	**MS** 7 mg or 14 mg PO QD	14 mg/day
Avonex®, Rebif® (interferon beta-1a)	**MS** *Avonex*: 30 mcg IM Q week *Rebif*: 22 mcg or 44 mcg SC TIW	*Avonex*: 30 mcg/week *Rebif*: 44 mcg TIW
Betaseron®, Extavia® (interferon beta-1b)	**MS** 250 mcg SC QOD	250 mg QOD
Plegridy® (peginterferon beta-1a)	**MS** 125 mcg SC Q2 weeks	125 mcg/2 weeks
glatiramer acetate (Copaxone®, Glatopa®)	**MS** 20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
fingolimod (Gilenya®)	**MS** 0.5 mg PO QD	0.5 mg/day
dimethyl fumarate (Tecfidera®)	**MS**	480 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	120 mg PO BID for 7 days, followed by 240 mg PO BID	
corticosteroids	**UC** budesonide (Uceris®) 9 mg PO QD	budesonide 9 mg/day
Hadlima (adalimumab-bwwd), Simlandi (adalimumab-ryvk), Yusimry (adalimumab-aqvh), adalimumab-aaty (Yuflyma®), adalimumab-adaz (Hyrimoz®), adalimumab-fkjp (Hulio®), adalimumab-adbm (Cyltezo®)	**UC** Initial dose: 160 mg SC on Day 1, then 80 mg SC on Day 15 Maintenance dose: 40 mg SC every other week starting on Day 29	40 mg every other week
Otulfi® (ustekinumab-aauz), Pyzchiva® (ustekinumab-ttwe), Selarsdi™ (ustekinumab-aekn), Steqeyma® (ustekinumab-stba), Yesintek™ (ustekinumab-kfce)	**UC** Weight based dosing IV at initial dose: Weight ≤ 55 kg: 260 mg Weight > 55 kg to 85 kg: 390 mg Weight > 85 kg: 520 mg Maintenance dose: 90 mg SC every 8 weeks	90 mg every 8 weeks

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): history of any of the following in the last 6 months: 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; concomitant use of a monoamine oxidase inhibitor
- Boxed warning(s): none reported

Appendix D: General Information

- Disease-modifying therapies for MS are: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity®), monomethyl fumarate (Bafiertam™), fingolimod (Gilenya®, Tascenso

ODT™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®, and biosimilar Tyruko®), ocrelizumab (Ocrevus®), ocrelizumab/hyaluronidase-ocsq (Ocrevus Zunovo™), siponimod (Mayzent®), cladribine (Mavenclad®), ozanimod (Zeposia®), ponesimod (Ponvory™), ublituximab-xiiy (Briumvi™), and ofatumumab (Kesimpta®).

- The American Academy of Neurology 2018 MS guidelines recommend the use of Gilenya, Tysabri, and Lemtrada for patients with highly active MS. Definitions of highly active MS vary and can include measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions.
- Of the disease-modifying therapies for MS that are FDA-labeled for clinically isolated syndrome, only the interferon products, glatiramer, and Aubagio have demonstrated any efficacy in decreasing the risk of conversion to MS compared to placebo. This is supported by the American Academy of Neurology 2018 MS guidelines.
- TNF blockers:
  - Etanercept (Enbrel®), adalimumab (Humira®) and its biosimilars, infliximab (Remicade®) and its biosimilars (Avsola™, Renflexis™, Inflectra®), certolizumab pegol (Cimzia®), and golimumab (Simponi®, Simponi Aria®).

Appendix E: Mayo Score, modified Mayo Score, or Mayo Endoscopic Score

- Mayo Score: evaluates UC stage, based on four parameters: stool frequency, rectal bleeding, endoscopic evaluation, and Physician's global assessment. Each parameter of the score ranges from zero (normal or inactive disease) to 3 (severe activity) with an overall score of 12.

Score	Decoding
0 – 2	Remission
3 – 5	Mild activity
6 – 10	Moderate activity
> 10	Severe activity

- Modified Mayo Score: developed from the full Mayo score and evaluates ulcerative colitis stage, based on three parameters: stool frequency, rectal bleeding, and endoscopic evaluation. The modified Mayo Score gives a maximum overall score of 9. The FDA currently accepts the modified Mayo Score for the assessment of disease activity in pivotal UC clinical trials.
- Mayo Endoscopic Score: tool used to assess severity based on endoscopic findings during a colonoscopy and ranges from 0 to 3. A score of 2 or higher means there is moderate-to-severe inflammation.

Score	Decoding
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, moderate friability, erosions)
3	Severe disease (spontaneous bleeding, ulcerations)

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MS, UC	Days 1-4: 0.23 mg PO QD Days 5-7: 0.46 mg PO QD Day 8 and thereafter: 0.92 mg PO QD; in patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B), QOD dosing is recommended If a dose of Zeposia is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen. If a dose of Zeposia is missed after the first 2 weeks of treatment, continue with the treatment as planned.	0.92 mg/day

VI. Product Availability

Capsules: 0.23 mg, 0.46 mg, 0.92 mg

VII. References

1. Zeposia Prescribing Information. Summit, NJ: Celgene Corporation; August 2024. Available at: https://www.zeposia.com. Accessed January 24, 2025.
2. Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol. 2019; 18 (11): 1021-1033. doi:10.1016/S1474-4422(19)30238-8.
3. Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol. 2019; 18 (11): 1009-1020. doi:10.1016/S1474-4422(19)30239-X.
4. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018; 90(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/898. Reaffirmed on October 19, 2024.
5. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology 2020;158:1450–1461. https://doi.org/10.1053/j.gastro.2020.01.006.
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7. Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry. Silver Spring, MD. Food and Drug Administration.; July 2016. Available at: https://www.fda.gov/files/drugs/published/Ulcerative-Colitis--Clinical-Trial-Endpoints-Guidance-for-Industry.pdf. Accessed February 3, 2025.
8. Naegeli AN, Hunter T, Dong Y, et al. Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients.

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9. Singh S, Loftus EV Jr, Limketkai BN, et al. AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis. Gastroenterology. 2024 Dec;167(7):1307-1343. doi: 10.1053/j.gastro.2024.10.001. PMID: 39572132.
10. Buchner AM, Farraye FA, Iacucci M. AGA Clinical Practice Update on Endoscopic Scoring Systems in Inflammatory Bowel Disease: Commentary. Clin Gastroenterol Hepatol. 2024 Nov;22(11):2188-2196. doi: 10.1016/j.cgh.2024.06.048. Epub 2024 Sep 20. PMID: 39297813.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: no significant changes; references reviewed and updated.	02.08.21	05.21
RT4: added criteria for newly FDA-approved indication for ulcerative colitis based on previously P&T-approved clinical guidance; references reviewed and updated.	06.14.21	08.21
Per August SDC and prior clinical guidance, for UC modified redirection to require Humira and Simponi.	08.25.21	11.21
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.08.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.28.22	
Per February SDC, added Amjevita as an alternative option to Humira for UC.	02.13.23	
2Q 2023 annual review: for UC, added TNFi criteria to allow bypass if member has had history of failure of two TNF blockers; for MS, to be inclusive of members continuing therapy from a different benefit, revised continued approval duration to reference the duration of total treatment received rather than the number of re-authorizations; references reviewed and updated.	02.21.23	05.23
Per July SDC: for UC, removed criteria requiring use of Simponi, Humira, and Amjevita; for UC, added criteria requiring use of one adalimumab product and stating Yusimry, Hadlima, unbranded adalimumab-fkjp, and unbranded adalimumab-adaz as preferred; updated Appendix B with relevant therapeutic alternatives.	07.25.23	
Per August SDC, added generic references to Aubagio and Gilenya redirections.	08.22.23	11.23
Per December SDC, added adalimumab-adbm to listed examples of preferred adalimumab products.	12.06.23	02.24
2Q 2024 annual review: no significant changes; references reviewed and updated.	01.30.24	05.24
Per June SDC: for UC, added Simlandi to listed examples of preferred adalimumab products.	07.23.24	08.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Per SDC: for UC, added unbranded adalimumab-aaty to listed examples of preferred adalimumab products.		
2Q 2025 annual review: for MS, removed requirements for documentation of baseline relapses/expanded disability status score and specific measures of positive response per competitor analysis and removed notation that Extavia is the preferred interferon beta-1b product for the Medicaid line of business as it is no longer available on market per SDC; for MS continued therapy, modified approval duration from "if member has received < 1 year of total treatment – up to a total of 12 months of treatment and if member has received ≥ 1 year of total treatment – 12 months" to "12 months"; for UC, added option for documentation of modified Mayo Score ≥ 5; removed redirection to preferred adalimumab products as adalimumab is not recommended due to low efficacy per 2024 AGA guidelines; for Appendix E, added supplemental information on modified Mayo Score; references reviewed and updated.	02.12.25	05.25
Per April SDC: for UC, added criteria requiring use of one preferred Stelara biosimilar (Otulfi, Pyzchiva (branded), Selarsdi, Yesintek, and Steqeyma are preferred) or one preferred adalimumab product.	04.23.25	06.25
Added step therapy bypass for IL HIM per IL HB 5395.	06.25.25	
For UC, added option for Mayo Endoscopic Score ≥ 2 to define moderate-to-severe UC; for UC, added bypass of conventional therapies if a member has failed a biologic agent to clarify intention of not stepping back from biologic agent to conventional therapy.	09.04.25	11.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage

decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.