Drug and Biologic Coverage Policy

Effective Date **11/1/2024**
Coverage Policy Number **IP0214**

Ozanimod

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Related Coverage Resources

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. 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.

Overview

This policy supports medical necessity review for ozanimod (**Zeposia®**).

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

Medical Necessity Criteria

Ozanimod (Zeposia) is considered medically necessary when ONE of the following is met:

1. **Multiple Sclerosis.** Individual meets **ALL** of the following criteria:
   A. Documented diagnosis of **ONE** of the following relapsing forms of Multiple Sclerosis:
      i. Active Secondary Progressive Multiple Sclerosis (SPMS) (for example, SPMS with a documented relapse)
      ii. Clinically Isolated Syndrome (CIS)
      iii. Relapsing-Remitting Multiple Sclerosis (RRMS)
   B. Preferred Product Step Therapy criteria is met, refer to below table(s):

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, iii and iv):
   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 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.
   iv. Preferred Product Step Therapy criteria is met, refer to below table(s):

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.

Employer Group Plans	
Condition	**Preferred Product with Step Therapy Criteria**
Multiple Sclerosis	Multiple Sclerosis Treatment Naïve Individuals AND **ONE** of the following: 1. Documentation of failure or intolerance to **ONE** of the following: A. dimethyl fumarate (generic for Tecfidera) [may require prior authorization] B. fingolimod (generic for Gilenya) [may require prior authorization] 2. Documented contraindication to **BOTH** of the following: A. dimethyl fumarate (generic for Tecfidera) [may require prior authorization] B. fingolimod (generic for Gilenya) [may require prior authorization]
Ulcerative Colitis	**1. Ulcerative Colitis – Initial Therapy.** **A)** Approve for 6 months if the patient meets BOTH of the following (i and ii): **i.** Patient meets the standard *Ulcerative Colitis* criteria (above); AND **ii.** Patient has tried TWO of an adalimumab product, Skyrizi subcutaneous, Stelara subcutaneous, and Zymfentra. Note: Examples of adalimumab products include Humira, Abrilada, adalimumab-aacf, adalimumab-adaz, adalimumab-adbm, adalimumab-fkjp, adalimumab-aaty, adalimumab-ryvk, Simlandi, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Yuflyma, and Yusimry. A trial of an infliximab intravenous product (e.g., Remicade, biosimilars), Simponi subcutaneous, Entyvio intravenous or subcutaneous, Omvoh intravenous or subcutaneous, Skyrizi intravenous, or Stelara intravenous also counts.

Employer Group Plans	
Condition	**Preferred Product with Step Therapy Criteria**
	B) If the patient has met criterion 2Ai (*Ulcerative Colitis* criteria [above]), but criterion 2Aii is not met, offer to review for a Preferred Product (Humira [NDCs starting with 00074], adalimumab-adaz, adalimumab-adbm, Cyltezo, Hyrimoz [NDCs starting with 61314], adalimumab-ryvk, Simlandi, Skyrizi subcutaneous (on-body injector), Stelara subcutaneous, Zymfentra) using the respective standard *Inflammatory Conditions Prior Authorization Policy* criteria. **2. Ulcerative Colitis – Patient is Currently Receiving Zeposia.** **A)** Approve for 1 year if the patient meets BOTH of the following (i and ii): **i.** Patient meets the standard *Ulcerative Colitis* criteria (above); AND **ii.** Patient meets ONE of the following conditions (a or b): **a)** Patient has tried TWO of an adalimumab product, Skyrizi subcutaneous, Stelara subcutaneous, and Zymfentra; OR Note: Examples of adalimumab products include Humira, Abrilada, adalimumab-aacf, adalimumab-adaz, adalimumab-adbm, adalimumab-fkjp, adalimumab-aaty, adalimumab-ryvk, Simlandi, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Yuflyma, and Yusimry. A trial of an infliximab intravenous product (e.g., Remicade, biosimilars), Simponi subcutaneous, Entyvio intravenous or subcutaneous, Omvoh intravenous or subcutaneous, Skyrizi intravenous, or Stelara intravenous or also counts. **b)** Patient has been established on Zeposia for at least 90 days and prescription claims history indicates at least a 90-day supply of Zeposia was dispensed within the past 130 days **[verification in prescription claims history required]** if claims history is not available, according to the prescriber **[verification by prescriber required]**. Note: In cases where 130 days of the patient's prescription claim history file is unavailable to be verified, an exception to this requirement is allowed if the prescriber has verified that the patient has been receiving Zeposia for at least 90 days AND the patient has been receiving Zeposia via paid claims (e.g., patient has not been receiving samples or coupons or other types of waivers in order to obtain access to Zeposia). **B)** If the patient has met criterion 3Ai (*Ulcerative Colitis* criteria [above]), but criterion 3Aii is not met, offer to review for a Preferred Product (Humira [NDCs starting with 00074], adalimumab-adaz, adalimumab-adbm, Cyltezo, Hyrimoz [NDCs starting with 61314], adalimumab-ryvk, Simlandi, Skyrizi subcutaneous (on-body injector), Stelara subcutaneous, Zymfentra) using the respective standard *Inflammatory Conditions Prior Authorization Policy* criteria.

Individual and Family Plan	
Condition	**Non-Preferred Product with Step Therapy Criteria**
Multiple Sclerosis	Documentation of **ONE** of the following: 1. Failure, contraindication, or intolerance to dimethyl fumarate (generic for Tecfidera) [may require prior authorization] 2. Currently receiving Zeposia
Ulcerative Colitis	**1. Ulcerative Colitis – Initial Therapy.**

Individual and Family Plan	
Condition	**Non-Preferred Product with Step Therapy Criteria**
	A) Approve for 6 months if the patient meets BOTH of the following (i and ii): **i.** Patient meets the standard *Ulcerative Colitis* criteria (above); AND **ii.** Patient has tried TWO of an adalimumab product, Skyrizi subcutaneous, and Stelara subcutaneous. Note: Examples of adalimumab products include Humira, Abrilada, adalimumab-aacf, adalimumab-adaz, adalimumab-adbm, adalimumab-fkjp, adalimumab-aaty, adalimumab-ryvk, Simlandi, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Yuflyma, and Yusimry. A trial of an infliximab intravenous product (e.g., Remicade, biosimilars, Zymfentra), Simponi subcutaneous, Entyvio intravenous or subcutaneous, Omvoh intravenous or subcutaneous, Skyrizi intravenous, or Stelara intravenous also counts. **B)** If the patient has met criterion 2Ai (*Ulcerative Colitis* criteria [above]), but criterion 2Aii is not met, offer to review for a Preferred Product (Humira [NDCs starting with 00074], adalimumab-adaz, adalimumab-adbm, Cyltezo, Hyrimoz [NDCs starting with 61314], adalimumab-ryvk, Simlandi, Skyrizi subcutaneous (on-body injector), Stelara subcutaneous) using the respective standard *Inflammatory Conditions Prior Authorization Policy* criteria. **2. Ulcerative Colitis – Patient is Currently Receiving Zeposia.** **A)** Approve for 1 year if the patient meets BOTH of the following (i and ii): **i.** Patient meets the standard *Ulcerative Colitis* criteria (above); AND **ii.** Patient meets ONE of the following conditions (a or b): **a)** Patient has tried TWO of an adalimumab product, Skyrizi subcutaneous, and Stelara subcutaneous; OR Note: Examples of adalimumab products include Humira, Abrilada, adalimumab-aacf, adalimumab-adaz, adalimumab-adbm, adalimumab-fkjp, adalimumab-aaty, adalimumab-ryvk, Simlandi, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Yuflyma, and Yusimry. A trial of an infliximab intravenous product (e.g., Remicade, biosimilars, Zymfentra), Simponi subcutaneous, Entyvio intravenous or subcutaneous, Omvoh intravenous or subcutaneous, Skyrizi intravenous, or Stelara intravenous or also counts. **b)** Patient has been established on Zeposia for at least 90 days and prescription claims history indicates at least a 90-day supply of Zeposia was dispensed within the past 130 days **[verification in prescription claims history required]** if claims history is not available, according to the prescriber **[verification by prescriber required]**. Note: In cases where 130 days of the patient's prescription claim history file is unavailable to be verified, an exception to this requirement is allowed if the prescriber has verified that the patient has been receiving Zeposia for at least 90 days AND the patient has been receiving Zeposia via paid claims (e.g., patient has not been receiving samples or coupons or other types of waivers in order to obtain access to Zeposia). **B)** If the patient has met criterion 3Ai (*Ulcerative Colitis* criteria [above]), but criterion 3Aii is not met, offer to review for a Preferred Product (Humira [NDCs starting with 00074], adalimumab-adaz, adalimumab-adbm, Cyltezo, Hyrimoz [NDCs starting with 61314], adalimumab-ryvk, Simlandi, Skyrizi subcutaneous (on-body injector), Stelara

Individual and Family Plan	
Condition	**Non-Preferred Product with Step Therapy Criteria**
	subcutaneous) using the respective standard *Inflammatory Conditions Prior Authorization Policy* criteria.

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.

Reauthorization Criteria

Continuation of ozanimod (Zeposia) is considered medically necessary for Multiple Sclerosis when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration:
- Multiple Sclerosis: up to 12 months
- Ulcerative Colitis: up to 6 months

Reauthorization approval duration:
- Multiple Sclerosis: up to 12 months
- Ulcerative Colitis: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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 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]

3. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-modifying Antirheumatic Drug (DMARD) for Ulcerative Colitis.**
   In the 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 (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. There are no data evaluating combination of Zeposia with a targeted synthetic DMARD (for example, Xeljanz/Xeljanz XR (tofacitinib tablets/extended-release tablets); therefore, safety and efficacy of this combination is unknown.

Background

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]

Appendix A

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	JIA	AS	nr-axSpA	PsA	PsO	CD	UC
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Adalimumab products (Humira, biosimilars)	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitors; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Crohn's Disease	Ulcerative Colitis
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	√	--
Skyrizi Intravenous	--	--	--	--	√#	--
Skyrizi Subcutaneous	--	--	√	√	√^	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√^	√^

Stelara Intravenous	--	--	--	--	√[#]	√[#]

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; ^ Maintenance dosing only; [#] Induction dosing only

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Ankylosing Spondylitis**	**nr-axSpA**	**Psoriatic Arthritis**	**Plaque Psoriasis**	**Ulcerative Colitis**
Janus Kinases Inhibitors							
Olumiant	√	--	--	--	--	--	--
Rinvoq	√	--	√	√	√	--	√
Xeljanz tablets	√	√[#]	√	--	√	--	√
Xeljanz oral solution	--	√[#]	--	--	--	--	--
Xeljanz XR	√	--	√	--	√	--	√
Phosphodiesterase Type 4 Inhibitor							
Otezla	--	--	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator							
Zeposia	--	--	--	--	--	--	√
Tyrosine Kinase 2 Inhibitor							
Sotyktu	--	--	--	--	--	√	--

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; [#] Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology		
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Psoriatic Arthritis**
Interleukin-6 Blockers			
Actemra Intravenous	√	√[^]	--
Actemra Subcutaneous	√	√[^]	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√[#]	√
Orencia Subcutaneous	√	√[#]	√
CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; [#] Indicated in polyarticular JIA.

Appendix B

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	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
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
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

References

1. Zeposia® capsules [prescribing information]. Summit, NJ: Celgene/Bristol Myers Squibb; September 2022.
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 October 22, 2022.
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.