Zeposia (ozanimod) Prior Authorization with Quantity Limit Program Summary

This program is implemented on FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
06-01-2024	08-01-2021

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Zeposia® (ozanimod) Capsule	• 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		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Multiple sclerosis	Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelination, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.(2) Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, pain, bladder and bowel issues, sexual dysfunction, movement and coordination problems, visual disturbances, and cognition and emotional changes.(18) There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).(9)
Clinically isolated syndrome	CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system. The episode, which by definition must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a diagnosis of MS because people who experience a CIS may or may not go on to develop MS.(9) When caused by an acute inflammatory demyelinating event, approximately 85% of all patients subsequently develop MS. The relationship between conventional brain MRI features and the short-term risk of CIS patients developing definite MS has been assessed by several studies and allows for the diagnosis of MS based on the 2017 McDonald criteria. However, in CIS patients with initial multifocal clinical symptom presentation the abnormal MRI did not stratify the risk for clinically definite disease conversion.(17)

<table>
<tr><td></td><td>CIS cohort studies spanning 7 through 20 years of follow-up investigated the long-term risk of MS development and found conversions rates of 65-80% for patients with an abnormal conventional MRI and 8-20% for those with an inconspicuous baseline MRI.(17)</td></tr>
<tr><td>Relapsing remitting multiple sclerosis</td><td>RRMS is characterized by clearly defined attacks (relapses) of new or increasing neurologic symptoms. These relapses are followed by periods of partial or complete recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability. The course of MS varies, however, about 85-90% of individuals with MS demonstrate a relapsing pattern at onset, which transitions over time in the majority of untreated patients to a pattern of progressive worsening with few or no relapses or MRI activity.(9)</td></tr>
<tr><td>Secondary progressive multiple sclerosis</td><td>SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Most people with RRMS will transition to SPMS. In SPMS there is no progressive worsening of symptoms over time with no definite periods of remission.(9)</td></tr>
<tr><td>2017 McDonald Criteria for the diagnosis of Multiple Sclerosis:</td><td>Diagnostic criteria for multiple sclerosis combining clinical, imaging, and laboratory evidence have evolved over time. The increasing incorporation of paraclinical assessments, especially imaging, to supplement clinical findings has allowed earlier, more sensitive, and more specific diagnosis.(7,8)

The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time.(7)

Misdiagnosis of multiple sclerosis remains an issue in clinical practice, and several factors that potentially increase this risk have been identified. Multiple sclerosis has heterogeneous clinical and imaging manifestations, which differ between patients over time. There is no single pathognomonic clinical feature or diagnostic test; diagnosis of multiple sclerosis relies on the integration of clinical, imaging, and laboratory findings. MRI abnormalities associated with other diseases and non-specific MRI findings, which are common in the general population, can be mistaken for multiple sclerosis. The increasingly strong focus on timely diagnosis to alleviate uncertainty for patients and allow initiation of disease-modifying therapies might also increase the risk of misdiagnosis.(7)

With increasing availability and use of MRI, incidental T2 hyperintensities on brain imaging are common, the subset of individuals with MRI findings that are strongly suggestive of multiple sclerosis lesions but with no neurological manifestations or other clear-cut explanation are said to have radiologically isolated syndrome. There is no consensus on whether patients with radiologically isolated syndrome will develop MS. Some practitioners argue that these patients have a high likelihood of developing MS while others argue that up to two-thirds of these patients will not receive a diagnosis of MS in 5 years. A consensus panel decided to require clinical manifestations to make the diagnosis of MS (2017 McDonald Criteria for the diagnosis of Multiple Sclerosis).(7)

The 2017 McDonald criteria to diagnose MS is shown in the chart below.(7,8)

<table>
<tr><th>Clinical Presentation</th><th>Additional Data needed to make MS diagnosis</th></tr>
<tr><td colspan="2">In a person with a typical attack/CIS at onset</td></tr>
<tr><td>Greater than or equal to 2 attacks and objective clinical evidence of greater than or equal to 2 lesions

OR

Greater than or equal to 2 attacks and objective clinical</td><td>None. Dissemination in space* and dissemination in time** have been met</td></tr>
</table>
</td></tr>
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evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	
Greater than or equal to 2 attacks and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional clinical attack implicating different CNS site OR Greater than or equal to 1 symptomatic or asymptomatic MS-typical T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord
1 attack and objective clinical evidence of greater than or equal to 2 lesions	**ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF specific (i.e., not in serum) oligoclonal bands
1 attack and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional attack implicating different CNS site OR Greater than or equal to 1 MS-Typical symptomatic or asymptomatic T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord **AND** **ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF-specific (i.e., not in serum) oligoclonal bands

* - Dissemination in space is defined as one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in 2 or more of four areas of the CNS (periventricular, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord) demonstrated by an additional clinical attack implicating a different CNS site or by MRI.(8)

** - Dissemination in time is defined as simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI. The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.(8)

Treatment of MS	Both the Multiple Sclerosis Coalition and the American Academy of Neurology recommend initiating treatment with a DMA FDA approved for the patient's phenotype as soon as possible following the diagnosis of multiple sclerosis. There are several DMAs with at least 10 mechanisms of action available to people with MS. The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and the treating clinician.(2,5) There is a subgroup of RRMS patients who have a more aggressive disease course marked by a rapid accumulation of physical and cognitive deficit, despite treatment with 1 or more DMTs. In the past, this disease phenotype was called aggressive MS; it is now called highly active MS. It is generally agreed that the severe nature of this phenotype requires different treatment decisions. There is no consensus on the definition of highly active MS or the treatment algorithm.(12) The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.(6) The Multiple Sclerosis Coalition recommends that clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, natalizumab or ocrelizumab for newly diagnosed individuals with highly active MS. Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another DMA regardless of the number of previously used agents.(2) The American Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS. There lacks a consensus for what constitutes as highly active MS, however.(5) The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.(19) Lack of response to DMAs is hard to define, as most patients with MS are not free of all disease activity. Relapses or new MRI detected lesions may develop after initiation of a DMA and before the treatment becomes effective for patients. When determining efficacy, sufficient time for the DMA therapy to take full effect and patient adherence are important considerations. Evidence of one or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination while being treated with a DMA for a 1 year period suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.(5) A National MS Society consensus statement recommends changing from one disease modifying therapy to another only for medically appropriate reasons (e.g. lack of efficacy, adverse effects, or if better treatments options become available).(2) Existing MS therapies are partly effective in halting ongoing inflammatory tissue damage and clinical progression. MS pathogenesis is complex and probably heterogeneous among patients, suggesting that combination therapy strategies that target a range of disease mechanisms might be more effective than medications used as monotherapy. Although preliminary studies have provided favorable results, however, several subsequent large, randomized, controlled trials have had negative of conflicting results. There also may be more adverse reactions associated with combination therapies due to the additive effect.(10) In 2020 a Canadian MS working group published recommendations on optimal therapy in relapsing forms of MS. This group notes that there are few studies that have directly compared injectable and oral DMTs. A recent network meta-analysis suggested that pegylated interferon-β-1a and dimethyl fumarate have superior efficacy to other base therapies, there is insufficient data to demonstrate that one base injectable or oral DMT is superior to another. As a result, the choice of initial treatment will need to be individualized according to disease activity, severity, and comorbidities.(11)

In addition to base therapies, the working group considers 5 DMTs to be of higher efficacy which although can be used as initial therapy, they are generally reserved for patients with a poor response or tolerability with a base therapy. Patients presenting with high disease activity or aggressive/rapidly evolving MS at onset could be considered to initiate therapy with one of these more effective therapies, but the most common treatment initiation is to start on a base therapy with the view of switching within 6-12 months. The 5 agents considered to be of higher efficacy are:(11)

- Oral agents
  - Fingolimod
  - Cladribine
- Monoclonal antibodies
  - Natalizumab
  - Ocrelizumab
  - Alemtuzumab

The MS working group discussed the criteria for switching therapies in RRMS and recommends a change in DMT is indicated for patients who meet any of the Major criteria below:(11)

	Minor	**Major**
Relapse rate	• One relapse in first 2 years of treatment	• Greater than or equal to 2 relapses in first year of treatment
Severity	• Mild • No functional impairment (school, work, daily activities, etc.) • No motor/cerebellar/brain stem/sphincter involvement	• Moderate to severe • Functional impairment • Motor/cerebellar/brain stem/sphincter involvement
Recovery	• Full recovery at 6 months • No functional impairment • EDSS change from baseline less than or equal to 1 point at 6 months unless baseline EDSS greater than 5.5	• Incomplete recovery • Functional impairment • If EDSS at baseline was 0 then a greater than 1.5 point change from baseline • If EDSS is greater than 0 but less than 5.5 at baseline then greater than 1 point change at 6 months • If EDSS is greater than 5.5 any

		change would be a major concern
MRI	• One new lesion	• Greater than or equal to 3 new lesions during treatment excluding spinal cord lesions • Greater than 1 spinal cord lesion

The workgroup does note that on-treatment relapses should only be performed once the drug has achieved a full clinical effect (typically 2-6 months after drug initiation). Relapses that occur before the maximal efficacy of the drug has been reached should be given less weight, but major criteria should take precedence regardless of timing.(11)

For patients with SPMS, the workgroup states that is generally advised to continue with the current DMT after onset of SPMS since many patients will have ongoing inflammatory disease and subclinical disease activity may worsen if treatment is withdrawn. A change in treatment may be warranted in patients with active SPMS who continue to have relapses or new MRI lesions, with the caveat that there is insufficient evidence to identify criteria for a suboptimal response in patients with SPMS.(11)

For patients with primary progressive MS, clinicians should offer ocrelizumab to patients with active disease provided the benefits outweigh the risks. Caution is recommended when considering treatment for PPMS subgroups that are less likely to benefit from treatment, such as older patients, those with long-standing stable disease, and/or significant neurological deficits, since the limited benefits may not justify the risk associated with treatment. Rituximab may be considered as an alternative therapy for PPMS in regions that permit off-label use in MS due to cost or other considerations.(11)

The Institute for Clinical and Economic Review (ICER) evaluated a new IV treatment, ublituximab against current FDA and accepted use DMT for adults with RRMS. Only in the case of ublituximab vs placebo/no DMT is ublituximab superior rated. The ratings are noted below.(3)

Adults with RRMS

Treatment	Comparator	Evidence Rating
Ublituximab	Natalizumab	I: Insufficient
	Ofatumumab	I: Insufficient
	Ocrelizumab	I: Insufficient
	Rituximab	I: Insufficient
	Fumarate class (dimethyl, diroximel, monomethyl	C++: Comparable or better
	Fingolimod	C++: Comparable or better

	<table><tr><td></td><td>Ozanimod</td><td>C++: Comparable or better</td></tr><tr><td></td><td>Ponesimod</td><td>C++: Comparable or better</td></tr><tr><td></td><td>Siponimod</td><td>I: Insufficient</td></tr><tr><td></td><td>Teriflunomide</td><td>B: Incremental</td></tr><tr><td></td><td>Placebo/no DMT</td><td>A: Superior</td></tr></table> A: Superior - High certainty of a substantial (moderate-large) net health benefit B: Incremental - High certainty of a small net health benefit C++: Comparable or better - Moderate certainty of a comparable, small, or substantial net health benefit, with which certainty of at least a comparable net health benefit I: Insufficient - Any situation where the level of certainty in the evidence is low ICER does note that payers should consider the following:(3) Payors should remove barriers to access to rituximab for RMS patients who are appropriate candidates for this therapy. This includes coverage of biosimilar rituximab with little or no prior authorization given the lack of concern regarding use in appropriate patients and how inexpensive it is compared with other monoclonal antibodies of equal effectiveness Payers should not unilaterally implement policies to switch RMS patients who are stable on their chosen DMT over to lower-cost biosimilar rituximab
Ulcerative Colitis (UC)	Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the large intestine associated with inflammation of the rectum, but that can extend to involve additional areas of the colon. The American College of Gastroenterology (ACG) recommends a treat-to-target approach and recommend therapeutic management should be guided by diagnosis (i.e., Montreal classification), assessment of disease activity (i.e., mild, moderate, and severe), and disease prognosis. The ACG treatment recommendations are further broken down into induction therapies and maintenance of remission. The 2019 ACG treatment guidelines recommend the following for therapeutic management of UC:(14) <u>Induction of remission</u>: • Mildly active disease: o Rectal 5-ASA at a dose of 1 g/day with or without oral 5-ASA at a dose of at least 2 g/day for left-sided UC o Rectal 5-ASA at a dose of 1 g/day for ulcerative proctitis o Oral 5-ASA at a dose of at least 2 g/day for extensive UC o Add oral budesonide multi-matrix (MMX) 9 mg/day for patients that are intolerant or non-responsive to oral and/or rectal and oral 5-ASA at appropriate doses • Moderately active disease: o Oral budesonide multi-matrix (MMX) 9 mg/day for induction of remission • Moderately to severely active disease: o Oral systemic corticosteroids, TNF inhibitors (i.e., adalimumab, golimumab, or infliximab), tofacitinib, or vedolizumab to induce remission o Combination of infliximab with thiopurine therapy when using infliximab for induction o Switch to tofacitinib or vedolizumab for induction in patients that have failed TNF inhibitors o Patients with initial response to TNF inhibitors that lose response should have antibody levels and serum drug levels tested to assess

	reason for loss of response. If serum levels are adequate, use of another TNF inhibitor is not likely to be of benefit.
	
	Maintenance of remission:
	
	• Previously mildly active disease:
	  ○ Rectal 5-ASA at a dose of 1 g/day in patients with ulcerative proctitis
	  ○ Oral 5-ASA at a dose of at least 2 g/day in patients with left-sided or extensive UC
	• Previously moderately to severely active disease:
	  ○ Thiopurines in patients that achieved remission due to corticosteroid induction
	  ○ Continue TNF inhibitors (i.e., adalimumab, golimumab, or infliximab) for remission due to TNF induction
	  ○ Continue vedolizumab for remission due to vedolizumab induction
	  ○ Continue tofacitinib for remission due to tofacitinib induction
	
	The American Gastroenterology Association (AGA) published recommendations for the management of mild to moderate UC:(15)
	
	• Use either standard-dose mesalamine (2-3 g/day) or diazo-bonded 5-ASA for patients with extensive UC for induction of remission and maintenance of remission
	• May add rectal mesalamine to oral 5-ASA in patients with extensive or left-sided UC for induction of remission and maintenance of remission
	• Use high dose mesalamine (greater than 3 g/day) with rectal mesalamine in patients with suboptimal response to standard-dose mesalamine, diazo-bonded 5-ASA, or with moderate disease activity for induction of remission and maintenance of remission
	• Add either oral prednisone or budesonide MMX in patients that are refractory to optimized oral and rectal 5-ASA regardless of disease extent
	
	The American Gastroenterology Association (AGA) published recommendations for the management of moderate to severe UC:(16)
	
	• Standard of care is to continue agents initiated for induction therapy as maintenance therapy, if they are effective (excluding corticosteroids and cyclosporine)
	• Adult outpatients with moderate to severe UC:
	  ○ Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab are strongly recommended over no treatment
	  ○ Biologic naïve patients:
	  ▪ infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission
	  ▪ Recommend tofacitinib only be used in the setting of a clinical or registry study
	  ○ Previous exposure to infliximab, particularly those with primary non-response, ustekinumab or tofacitinib are conditionally recommended over vedolizumab or adalimumab for induction of remission
	  ○ Conditionally recommend against use of thiopurine monotherapy for induction, but may be used for maintenance of remission over no treatment

Safety	Zeposia (ozanimod) is contraindicated in:(1) • In patients who 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 • Concomitant use with a monoamine oxidase inhibitor

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Number	Reference
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3	Institute for Clinical and Economic Review (ICER). Oral and monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value. February 21,2023.
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POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Zeposia starter kit	ozanimod cap pack	0.23MG &0.46MG 0.92MG(21)	M ; N ; O ; Y	N		
Zeposia starter kit	Ozanimod Cap Pack 4 x 0.23 MG & 3 x 0.46 MG & 30 x 0.92 MG	0.23MG & 0.46MG & 0.92MG	M ; N ; O ; Y	N		
Zeposia	ozanimod hcl cap	0.92 MG	M ; N ; O ; Y	N		
Zeposia 7-day starter pac	ozanimod cap pack	4 x 0.23MG & 3 x 0.46MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Zeposia	ozanimod hcl cap	0.92 MG	30	Capsules	30	DAYS			
Zeposia 7-day starter pac	Ozanimod Cap Pack 4 x 0.23 MG & 3 x 0.46 MG	4 x 0.23MG & 3 x 0.46MG	7	Capsules	180	DAYS			
Zeposia starter kit	ozanimod cap pack	0.23MG &0.46MG 0.92MG(21)	28	Capsules	180	DAYS			
Zeposia starter kit	Ozanimod Cap Pack 4 x 0.23 MG & 3 x 0.46 MG & 30 x 0.92 MG	0.23MG & 0.46MG & 0.92MG	37	Capsules	180	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Zeposia	ozanimod hcl cap	0.92 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Zeposia 7-day starter pac	ozanimod cap pack	4 x 0.23MG & 3 x 0.46MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Zeposia starter kit	ozanimod cap pack	0.23MG &0.46MG 0.92MG(21)	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
			Marketplace/BasicRx ; KeyRx
Zeposia starter kit	Ozanimod Cap Pack 4 x 0.23 MG & 3 x 0.46 MG & 30 x 0.92 MG	0.23MG & 0.46MG & 0.92MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Zeposia	ozanimod hcl cap	0.92 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Zeposia 7-day starter pac	Ozanimod Cap Pack 4 x 0.23 MG & 3 x 0.46 MG	4 x 0.23MG & 3 x 0.46MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Zeposia starter kit	ozanimod cap pack	0.23MG &0.46MG 0.92MG(21)	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Zeposia starter kit	Ozanimod Cap Pack 4 x 0.23 MG & 3 x 0.46 MG & 30 x 0.92 MG	0.23MG & 0.46MG & 0.92MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Zeposia PA with MS Step	**Initial Evaluation** **Target Agent(s)** will be approved when ONE of the following is met: 1. The requested agent is eligible for continuation of therapy AND ONE of following: **Agents Eligible for Continuation of Therapy** Zeposia (ozanimod) A. The patient has been treated with the requested agent within the past 90 days **OR** B. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR** 2. The patient has a diagnosis of multiple sclerosis (MS) AND BOTH of the following: A. ONE of the following: 1. The patient has highly active MS disease activity AND BOTH of the following: A. The patient has greater than or equal to 2 relapses in the previous year **AND** B. ONE of the following: 1. The patient has greater than or equal to 1 gadolinium enhancing lesion on MRI **OR**

Module	Clinical Criteria for Approval
	2. The patient has significant increase in T2 lesion load compared with a previous MRI **OR** 2. The patient has been treated with at least 3 MS agents from different drug classes (see MS disease modifying agents drug class table) **OR** 3. ONE of the following A. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** B. The patient's medication history incudes use of ONE Preferred generic MS agent* **OR** C. BOTH of the following: 1. The prescriber has stated that the patient has tried a preferred generic MS agent* **AND** 2. The preferred generic MS agent* was discontinued due to lack of effectiveness or an adverse event **OR** D. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE preferred generic MS agent* **OR** E. The patient has an FDA labeled contraindication to ALL preferred generic MS agents* **OR** F. The prescriber has provided documentation that ALL preferred generic MS agents* cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** B. The patient will NOT be using the requested agent in combination with another MS disease modifying agent (DMA) (Please refer to "Multiple Sclerosis Disease Modifying Agents" contraindicated use table) **OR** 3. The patient has a diagnosis of moderately to severely active ulcerative colitis (UC) AND ALL of the following: A. ONE of the following: 1. The patient is currently being treated with the requested agent as indicated by ALL of the following: A. A statement by the prescriber that the patient is currently taking the requested agent **AND** B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** C. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 2. The patient has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, sulfasalazine) used in the treatment of UC **OR** 3. The patient has severely active ulcerative colitis **OR** 4. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of UC **OR** 5. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of UC **OR** 6. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of UC **OR** 7. The prescriber has provided documentation that ALL of the conventional agents (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, steroid suppositories, sulfasalazine) used in the treatment of UC cannot be used due to a documented medical

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	condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** B. ONE of the following: 1. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 2. The patient has tried and had an inadequate response to TWO Step 1a and/or Step 1b immunomodulatory agents (see Immunomodulatory Agent Step table) **OR** 3. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to at least TWO Step 1a and/or Step 1b immunomodulatory agents **OR** 4. The patient has an FDA labeled contraindication to ALL Step 1a AND Step1b immunomodulatory agents **OR** 5. The prescriber has provided documentation that ALL Step 1a AND Step1b immunomodulatory agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** C. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) (Please refer to "Immunomodulatory Agents NOT to be used Concomitantly" table) **AND** D. If the patient has an FDA labeled indication, then ONE of the following: 1. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** 2. There is support for using the requested agent for the patient's age for the requested indication **AND** E. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** F. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months. NOTE: The starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when BOTH of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (Note: patients not previously approved for the requested agent will require initial evaluation review) **AND**

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	2. ONE of the following: A. The patient has a diagnosis of multiple sclerosis (MS) AND BOTH of the following: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of following: Agents Eligible for Continuation of Therapy Zeposia (ozanimod) 1. The patient has been treated with the requested agent within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR** B. The patient has highly active MS disease activity AND BOTH of the following: 1. The patient has greater than or equal to 2 relapses in the previous year **AND** 2. ONE of the following: A. The patient has greater than or equal to 1 gadolinium enhancing lesion on MRI **OR** B. The patient has significant increase in T2 lesion load compared with a previous MRI OR C. The patient has been treated with at least 3 MS agents from different drug classes (see MS disease modifying agents drug class table) **OR** D. ONE of the following: 1. The patient is currently being treated with the requested agent as indicated by ALL of the following: A. A statement by the prescriber that the patient is currently taking the requested agent **AND** B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** C. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 2. The patient's medication history incudes use of ONE Preferred generic MS agent* **OR** 3. BOTH of the following: A. The prescriber has stated that the patient has tried a preferred generic MS agent* **AND** B. The preferred generic MS agent* was discontinued due to lack of effectiveness or an adverse event **OR** 4. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE preferred generic MS agent* **OR** 5. The patient has an FDA labeled contraindication to ALL preferred generic MS agents* **OR** 6. The prescriber has provided documentation that ALL preferred generic MS agents* cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 2. The patient will not be using the requested agent in combination with another MS disease modifying agent (DMA) (Please refer to "Multiple Sclerosis Disease Modifying Agents" contraindicated use table) **OR** B. The patient has a diagnosis of ulcerative colitis AND ALL of the following:

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1. The patient has had clinical benefit with the requested agent **AND**
2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**
4. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (see "Immunomodulatory Agents NOT to be used Concomitantly" table)

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

*** Preferred and Non-preferred MS agents**

Preferred generic agents
dimethyl fumarate
fingolimod
Glatopa (glatiramer)
glatiramer
teriflunomide

Preferred brand agents
Avonex (interferon b-1a)
Betaseron (interferon b-1b)
Kesimpta (ofatumumab)
Mavenclad (cladribine)
Mayzent (siponimod)***
Plegridy (peginterferon b-1a)
Rebif (interferon b-1a)
Vumerity (diroximel fumarate)
Zeposia (ozanimod)

Non-Preferred Agents
Aubagio (teriflunomide)**
Bafiertam (monomethyl fumarate)
Copaxone (glatiramer)**
Extavia (interferon b-1b)
Gilenya (fingolimod)**
Ponvory (ponesimod)
Tascenso ODT (fingolimod)
Tecfidera (dimethyl fumarate)**

** generic available

*** Mayzent preferred or non-preferred status is determined by the client

Immunomodulatory Agent Step table****

Formulary ID	Step 1a	Step 1b (Directed to ONE TNF inhibitor) NOTE please see Step 1a for	Step 2 (Directed to ONE step 1 agent)	Step 3a (Directed to TWO Step 1 agents)	Step 3b (Directed to TWO agents from step 1a and/or Step 1b)	Step 3c (Directed t THREE step 1 agents)

Module	Clinical Criteria for Approval						
			preferred TNF inhibitors				
	FocusRx	SQ: Cyltezo, Humira, Stelara	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Simponi (Cyltezo, Hadlima, or Humira is required Step 1 agent)	N/A	Zeposia (Cyltezo, Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are required Step 1 agents)	SQ: Abrilada*, Amjevita*, Entyvio, Hadlima*, Hulio*, Hyrimoz*, Idacio*, Omvoh, Yuflyma*, Yusimry*, Zymfentra Oral Velsipity *Cyltezo or Humira is required Step 1 agent
	FlexRx, GenRx, KeyRx, BasicRx	SQ: Hadlima, Humira, Stelara	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Simponi (Hadlima or Humira is required Step 1 agent)	N/A	Zeposia (Hadlima, Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are required Step 1 agents)	SQ: Abrilada*, Amjevita*, Cyltezo*, Entyvio, Hulio*, Hyrimoz*, Idacio*, Omvoh, Yuflyma*, Yusimry*, Zymfentra Oral Velsipity *Hadlima and Humira are required Step 1 agents
	**** Noted preferred status is effective upon launch						

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Zeposia PA through preferred and Zeposia PA with MS step	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following:

Module	Clinical Criteria for Approval
	A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months. NOTE: The starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months.

CLASS AGENTS

Class	Class Drug Agents
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	BRIUMVI*ublituximab-xiiy soln for iv infusion
MS Disease Modifying Agents drug classes: CD20 monoclonal antibody	
MS Disease Modifying Agents drug classes: CD20 monoclonal antibody	KESIMPTA*Ofatumumab Soln Auto-Injector
MS Disease Modifying Agents drug classes: CD20 monoclonal antibody	OCREVUS*Ocrelizumab Soln For IV Infusion
MS Disease Modifying Agents drug classes: CD52 monoclonal antibody	
MS Disease Modifying Agents drug classes: CD52 monoclonal antibody	LEMTRADA*Alemtuzumab IV Inj
MS Disease Modifying Agents drug classes: Fumarates	
MS Disease Modifying Agents drug classes: Fumarates	BAFIERTAM*Monomethyl Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug classes: Fumarates	TECFIDERA*Dimethyl Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug classes: Fumarates	VUMERITY*Diroximel Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug classes: Glatiramer	
MS Disease Modifying Agents drug classes: Glatiramer	COPAXONE*Glatiramer Acetate Soln Prefilled Syringe
MS Disease Modifying Agents drug classes: Glatiramer	GLATOPA*Glatiramer Acetate Soln Prefilled Syringe
MS Disease Modifying Agents drug classes: IgG4k monoclonal antibody	
MS Disease Modifying Agents drug classes: IgG4k monoclonal antibody	TYSABRI*Natalizumab for IV Inj Conc
MS Disease Modifying Agents drug classes: Interferons	
MS Disease Modifying Agents drug classes: Interferons	AVONEX*Interferon beta-1a injection
MS Disease Modifying Agents drug classes: Interferons	BETASERON*Interferon beta-1b injection
MS Disease Modifying Agents drug classes: Interferons	EXTAVIA*Interferon beta-1b injection
MS Disease Modifying Agents drug classes: Interferons	PLEGRIDY*Peginterferon beta-1a injection
MS Disease Modifying Agents drug classes: Interferons	REBIF*Interferon beta-1a injection
MS Disease Modifying Agents drug classes: Purine antimetabolite	
MS Disease Modifying Agents drug classes: Purine antimetabolite	MAVENCLAD*Cladribine Tab Therapy Pack
MS Disease Modifying Agents drug classes: Pyrimidine synthesis inhibitor	
MS Disease Modifying Agents drug classes: Pyrimidine synthesis inhibitor	AUBAGIO*Teriflunomide Tab
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	GILENYA*Fingolimod HCl Cap

Class	Class Drug Agents
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	MAYZENT*Siponimod Fumarate Tab
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	PONVORY*Ponesimod Tab
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	TASCENSO*fingolimod lauryl sulfate tablet disintegrating
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	ZEPOSIA*Ozanimod capsule

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
MS Disease Modifying Agents Aubagio (teriflunomide) Avonex (interferon b-1a) Bafiertam (monomethyl fumarate) Betaseron (interferon b-1b) Briumvi (ublituximab-xiiy) Copaxone (glatiramer) dimethyl fumarate Extavia (interferon b-1b) fingolimod Gilenya (fingolimod) Glatopa (glatiramer) glatiramer Kesimpta (ofatumumab) Mavenclad (cladribine) Mayzent (siponimod) Plegridy (peginterferon b-1a) Ponvory (ponesimod) Rebif (interferon b-1a) Tascenso ODT (fingolimod) Tecfidera (dimethyl fumarate)

Contraindicated as Concomitant Therapy
Vumerity (diroximel fumarate) Zeposia (ozanimod) **Immunomodulatory Agents NOT to be used concomitantly** Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Enbrel (etanercept) Entyvio (vedolizumab) Fasenra (benralizumab) Hadlima (adalimumab-bwwd) Hulio (adalimumab-fkjp) Humira (adalimumab) Hyrimoz (adalimumab-adaz) Idacio (adalimumab-aacf)

Contraindicated as Concomitant Therapy
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Litfulo (ritlecitinib)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Siliq (brodalumab)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Stelara (ustekinumab)
Taltz (ixekizumab)

Contraindicated as Concomitant Therapy
Tezspire (tezepelumab-ekko)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)