Zeposia (ozanimod)
Policy Number: CXXXXX-X

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
07/09/2020	07/09/2020	07/09/2021
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J3490	RxPA	Q3 2020 20200722CXXXXX-X

PRODUCTS AFFECTED:
Zeposia (ozanimod)

DRUG CLASS:
Sphingosine 1-Phosphate (S1P) Receptor Modulators

ROUTE OF ADMINISTRATION:
oral

PLACE OF SERVICE:
Specialty Pharmacy
The recommendation is that medications in this policy will be for pharmacy benefit coverage and patient self-administered

AVAILABLE DOSAGE FORMS:
Zeposia CAPS 0.92MG (30ct bottle), Zeposia 7-Day Starter Pack CPPK 4 x 0.23MG &3 x 0.46MG (7 tabs), Zeposia Starter Kit CPPK 0.23MG & 0.46MG& 0.92MG (37 TABS)

FDA-APPROVED USES: 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

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease

REQUIRED MEDICAL INFORMATION:

A. MULTIPLE SCLEROSIS:
   1. Documentation of a definitive diagnosis of: (i) a relapsing form of multiple sclerosis as defined by the McDonald criteria(see Appendix), including relapsing- remitting multiple sclerosis [RRMS], secondary-progressive multiple sclerosis [SPMS] with relapses, (ii) first clinical episode with MRI features consistent with multiple sclerosis (clinically isolated syndrome) or (iii) active secondary progressive disease
      AND

2. The member is not currently being treated with a disease modifying agent (DMA) other than the requested agent
   AND
3. Documentation member has completed the following: complete blood count including lymphocyte count (within last 6 months or after discontinuation of prior MS therapy),electrocardiogram (ECG), transaminase and billirubin levels (within last 6 months), Ophthalmic evaluation, Current medication evaluation for immunosuppressive therapies, Varicella zoster vaccination or titers
   AND
4. Prescriber attests that member does not have any FDA labeled contraindications to Zeposia (ozanimod)
   AND
5. Documentation of trial/failure of or intolerance to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s)

DURATION OF APPROVAL:
Initial authorization: 12 months, Continuation of Therapy: 12 months

QUANTITY: Days 1-4 0.23 mg once daily, Days 5-7 0.46 mg once daily, Day 8 and thereafter 0.92 mg once daily- maximum of 4-week supply per dispense

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified neurologist or a multiple sclerosis specialist. Please submit consultation notes if prescribed after consultation

AGE RESTRICTIONS:
18 years of age and older

CONTINUATION OF THERAPY:
A. MULTIPLE SCLEROSIS:
   1. (a) Documentation of a stable number or decrease in acute attacks (relapses) within the last 6 months
      OR
      (b) Documentation of lack of progression or sustained disability
      OR
      (c) Recent (within last 6 months) MRI shows lack of development of new asymptomatic lesions
      AND
   2. Documentation member has been adherent to therapy at least 85% of the time as verified by Prescriber and member's medication fill history
      AND
   3. Member had not experienced any intolerable adverse effects or drug toxicity

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Zeposia (ozanimod) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Zeposia (ozanimod) include member experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure, within the last 6 months; Presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick

sinus syndrome, or sino-atrial block, unless the member has a functioning pacemaker; severe untreated sleep apnea or concomitant use of a monoamine oxidase inhibitor

OTHER SPECIAL CONSIDERATIONS:
None

BACKGROUND:
Multiple Sclerosis (MS)
MS is a chronic, inflammatory, autoimmune disease of the central nervous system that disrupts communications between the brain and other parts of the body. Most people experience their first symptoms of MS between the ages of 20 and 40 years of age. MS is among the most common causes of neurological disability in young adults and occurs more frequently in women than in men. MS is the most common immune-mediated inflammatory demyelinating disease of the central nervous system. MS is characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. Axonal injury is also a prominent pathologic feature, especially in the later stages. Certain clinical features are typical of MS, but the disease has a highly variable pace and many atypical forms. For most people, MS starts with a relapsing-remitting course, in which episodes of worsening function (relapses) are followed by recovery periods (remissions). These remissions may not be complete and may leave patients with some degree of residual disability. Many, but not all, patients with MS experience some degree of persistent disability that gradually worsens over time. In some patients, disability may progress independent of relapses, a process termed secondary progressive multiple sclerosis (SPMS). In the first few years of this process, many patients continue to experience relapses, a phase of the disease described as active SPMS. Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS. MS Unites4 On average, up to 80% of patients with RRMS – the most common form of MS at diagnosis – will develop SPMS. SPMS is a form of MS characterized by progressive and irreversible neurological disability. Most patients transition from RRMS to SPMS over time, which can vary if a patient is on disease modifying drug treatment or not.
RRMS – the most common disease course – is characterized by clearly defined attacks of new or increasing neurologic symptoms. These attacks – also called relapses or exacerbations – are followed by periods of partial or complete recovery (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission. At different points in time, RRMS can be further characterized as either active (with relapses and/or evidence of new MRI activity) or not active, as well as worsening (a confirmed increase in disability over a specified period of time following a relapse) or not worsening. An increase in disability is confirmed when the person exhibits the same level of disability at the next scheduled neurological evaluation, typically 6 to 12 months later.
The Zeposia approval was based on data from two Phase 3 trials, SUNBEAM and RADIANCE, head-to-head studies comparing Biogen's Avonex (interferon beta 1a) in more than 2,600 adults with RMS.

RADIANCE-
1320 participants were enrolled and randomly assigned to a group, of whom 1313 received study drug (433 assigned to ozanimod 1·0 mg, 439 assigned to ozanimod 0·5 mg, and 441 assigned to

interferon beta-1a) and 1138 (86·7%) completed 24 months of treatment. Adjusted ARRs were 0·17 (95% CI 0·14-0·21) with ozanimod 1·0 mg, 0·22 (0·18-0·26) with ozanimod 0·5 mg, and 0·28 (0·23-0·32) with interferon beta-1a, with rate ratios versus interferon beta-1a of 0·62 (95% CI 0·51-0·77; p<0·0001) for ozanimod 1·0 mg and 0·79 (0·65 to 0·96; p=0·0167) for ozanimod 0·5 mg. The incidence of treatment-emergent adverse events was higher in the interferon beta-1a group (365 [83·0%] of 440 participants) than in the ozanimod 1·0 mg group (324 [74·7%] of 434) or the ozanimod 0·5 mg group (326 [74·3%] of 439). More participants in the interferon beta-1a group had treatment-emergent adverse events leading to treatment discontinuation than in the ozanimod groups. Incidences of infections and serious treatment-emergent adverse events were similar across treatment groups. No cases of ozanimod-related symptomatic reduction in heart rate and no second-degree or third-degree cases of atrioventricular block were reported.

SUNBEAM-
1346 participants were enrolled and randomly assigned to ozanimod 1·0 mg (n=447), ozanimod 0·5 mg (n=451), or interferon beta-1a (n=448). 91 (6·8%) participants discontinued the study drug (29 in the ozanimod 1·0 mg group; 26 in the ozanimod 0·5 mg group; and 36 in the interferon beta-1a group). Adjusted ARRs were 0·35 (0·28-0·44) for interferon beta-1a, 0·18 (95% CI 0·14-0·24) for ozanimod 1·0 mg (rate ratio [RR] of 0·52 [0·41-0·66] vs interferon beta-1a; p<0·0001), and 0·24 (0·19-0·31) for ozanimod 0·5 mg (RR 0·69 [0·55-0·86] vs interferon beta-1a; p=0·0013). Few ozanimod-treated participants discontinued treatment because of adverse events (13 [2·9%] who received ozanimod 1·0 mg; seven [1·5%] who received ozanimod 0·5 mg; and 16 [3·6%] who received interferon beta-1a). No first-dose, clinically significant bradycardia or second-degree or third-degree atrioventricular block was reported. The incidence of serious adverse events was low and similar across treatment groups (13 [2·9%] participants who received ozanimod 1·0 mg; 16 [3·5%] who received ozanimod 0·5 mg; and 11 [2·5%] who received interferon beta-1a). No serious opportunistic infections occurred in ozanimod-treated participants.

APPENDIX:
Summary of 2017 McDonald Criteria for the Diagnosis of MS

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
...in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None. DIS and DIT have been met.
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by one of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by one of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by one of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord **AND** DIT shown by one of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
...in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least two of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

DIT = Dissemination in time **CNS** = central nervous system **CSF** = cerebrospinal fluid
DIS = Dissemination in space **T2 lesion** = hyperintense lesion on T2-weighted MRI

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REFERENCES:

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2. Zeposia [prescribing information]. Summit, NJ: Celgene Corporation; March 2020
3. Cohen JA, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicenter, randomized, 24-month, phase 3 trial. Lancet Neurol. 2019; 18:1021-1033. doi: 10.1016/S1474-4422(19)30238-8
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