Mayzent (siponimod)
Policy Number: C16713-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
5/1/2019	5/6/2020	5/6/2021
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J8499 (NOC)	RxPA	Q3 2020 20200722C16713-A

PRODUCTS AFFECTED:
Mayzent (siponimod)

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

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy

AVAILABLE DOSAGE FORMS:
Mayzent 0.25mg (siponimod fumarate)- bottle of 28 tabs, Mayzent 2mg (siponimod fumarate)- bottle of 30 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)

REQUIRED MEDICAL INFORMATION:
A. RELAPSING FORM OF MULTIPLE SCLEROSIS:

1. Documentation of a definitive diagnosis of a relapsing form of multiple sclerosis (MS) as defined by the McDonald criteria (see Appendix), including: Relapsing-remitting multiple sclerosis [RRMS], secondary-progressive multiple sclerosis [SPMS] with relapses, and progressive-relapsing multiple sclerosis [PRMS] or First clinical episode with MRI features consistent with multiple sclerosis
   AND
2. Member is not currently being treated with a disease modifying agent (DMA) other than the requested agent (Appendix)
   AND

3. Documentation of the following: CYP2C9 genotype determination (member does not have a CYP2C9*3/*3 genotype), complete blood count (CBC), Ophthalmic evaluation (at baseline and if vision changes, more frequent with diabetes or a history of uveitis), Current medication evaluation for immunosuppressive therapies, Varicella zoster vaccination or titers and recent LFT completed
   AND
4. Cardiac evaluation documenting that member does NOT meet or have the following conditions:
   a) History of cardiac arrest or myocardial infarction, ischemic heart disease, unstable angina, stroke, TIA, cerebrovascular disease, uncontrolled hypertension, decompensated heart failure requiring hospitalization or Class III/IV heart failure within the last 6 months
      AND
   b) History or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless member has a functioning pacemaker
      AND
   c) Baseline QTc interval is greater than 500 msec
      AND
   d) Currently receiving treatment with Class Ia or Class III anti-arrhythmic drugs

   AND
5. Prescriber attestation that female members of reproductive potential has been counseled to use effective contraception during therapy and for 10 days after the last siponimod dose
   AND
6. 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:
0.25mg tablets Starter Pack – blister card of twelve 0.25 mg tablets in a calendarized blister wallet - NDC 0078-0979-12. This starter pack is only intended for patients who will receive the 2 mg maintenance dosage. Patients with CYP2C9*1/*3 or *2/*3 genotype: maintenance max dose is 1mg once daily, all others maintenance max dose is 2mg once daily

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. RELAPSING FORM OF 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
AND
4. Mayzent is not prescribed concurrently with other disease modifying therapies for MS

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Mayzent (siponimod) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy.

Contraindications include: A CYP2C9*3/*3 genotype, Myocardial infarction within the last 6 months, Unstable angina within the last 6 months, Stroke or TIA within the last 6 months, Decompensated heart failure requiring hospitalization within the last 6 months, Class III or IV heart failure within the last 6 months, Mobitz type II second-degree or third-degree atrioventricular block, unless patient has a functional pacemaker and Sick-sinus syndrome, unless patient has a functional pacemaker.

OTHER SPECIAL CONSIDERATIONS:

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.

Efficacy

The efficacy of Mayzent was demonstrated in the Phase III Expand study (Lancet, March 2018), a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with secondary progressive multiple sclerosis (SPMS) who had evidence of disability progression in the prior 2 years, no evidence of relapse in 3 months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5 at study entry. My-MS.org9 Patients were randomized to receive either once daily Mayzent 2 mg or placebo, beginning with a dose titration. Evaluations were performed at screening, every 3 months during the study, and at the time of a suspected relapse. MRI evaluations were performed at screening and every 12 months. The primary endpoint of the study was the time to 3-month confirmed disability progression (CDP), defined as at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5 or higher) sustained for 3 months. A pre-specified hierarchical analysis consisted of the primary endpoint and 2 secondary endpoints, the time to 3- month confirmed worsening of at least 20% from baseline on the timed 25-foot walk test and the change from baseline in T2 lesion volume. Additional endpoints included annualized relapse rate (relapses/year) and MRI measures of inflammatory disease activity. Study duration was variable for individual patients (median study duration was 21 months, range 1 day-37 months). EXPAND randomized 1651 patients to either Mayzent 2 mg (N = 1105) or placebo (N = 546); 82% of Mayzent treated patients and 78% of placebo-treated patients completed the study. Median age was 49.0 years, 95% of patients were white, and 60% female. The median disease duration was 16.0 years, and median EDSS score at baseline was 6.0 (56% of patients had ≥ 6.0 EDSS at baseline); 36% of patients had one or more relapses in the 2 years prior to study entry; 22% of those patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI scan; 78% of patients had been previously treated with an MS therapy. Mayzent was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (hazard ratio 0.79, $p < 0.0134$; see Figure 1). Mayzent did not significantly delay the time to 20% deterioration in the timed 25-foot walk, compared to placebo. Patients treated with Mayzent had a 55% relative reduction in annualized relapse rate, compared to patients on placebo (nominal pvalue < 0.0001). The absolute reduction in the annualized relapse rate was 0.089. Although Mayzent had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2 years prior to the study), the effect of Mayzent in patients with non-active SPMS was not statistically significant.

Adverse Effects

A total of 1737 MS patients have received Mayzent at doses of at least 2 mg daily. These patients were included in Phase III studies and in a Phase 2 placebo-controlled study in patients with MS. In Phase III Study 1, 67% of Mayzent treated patients completed the double-blind part of the study,

compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of Mayzent treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in Mayzent treated patients were headache, hypertension, and transaminase increase.

APPENDIX:

Disease-modifying therapies for MS include: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), fingolimod (Gilenya™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), ocreliuzmab (Ocrevus™), siponimod (Mayzent®), and cladribine (Mavenclad®).

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

REFERENCES:

1. Mayzent (siponimod) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2019.
2. Kappos L, Bar-Or A, Cree BAC, et al: Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018; 391(10127):1263-1273.
3. Gardin A, Gray C, Neelakantham S, et al: Siponimod pharmacokinetics, safety, and

tolerability in combination with rifampin, a CYP2C9/3A4 inducer, in healthy subjects. Eur J Clin Pharmacol 2018; 74(12):1593-1604.

5. 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 [published correction appears in Neurology. 2019;92(2):112]. Neurology. 2018;90(17):777-788.[PubMed 29686116]10.1212/WNL.0000000000005347