

09-J3000-35

Original Effective Date: 07/01/19

Reviewed: 05/08/19

Revised: 11/15/19

Subject: Siponimod (Mayzent[®]) Tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (CNS). It is characterized by inflammation, demyelination, and scarring of the central nervous system and manifests as pathological (immune-mediated CNS demyelination and axonal injury) and clinical (exacerbations, disability progression) dissemination in time and space. MS has been categorized into four types: clinically isolated syndrome (CIS), [relapsing-remitting \(RRMS\)](#), [secondary progressive \(SPMS\)](#), and [primary progressive \(PPMS\)](#). The most common type is RRMS, which is characterized by acute attacks followed by periods of remission. An initial attack may present as a clinically isolated syndrome (CIS); individuals presenting with this syndrome are high risk for subsequent conversion to clinically definite MS (CDMS) when coupled with MRI lesions consistent with MS.

The Food and Drug Administration (FDA) approved siponimod (Mayzent[®]) in March 2019 for the treatment of relapsing forms of MS, to include clinical isolated syndrome, relapsing-remitting disease and active secondary progressive disease. Siponimod is a sphingosine 1-phosphate receptor modulator that reduces the number of lymphocytes in peripheral blood. The exact mechanism in MS is unknown but it may reduce lymphocyte migration into the central nervous system. In 2018, the American Academy of Neurology published a practice guideline on the use of disease-modifying therapy for adults with multiple sclerosis but the report did not include an assessment of the effectiveness and safety of siponimod in the treatment of MS.

The efficacy of siponimod was evaluated in a randomized, double-blind, placebo-controlled time-to-event study in patients with secondary progressive multiple sclerosis 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. Patients received either siponimod 2 mg

after dose titration (n=1105), or placebo (n=546). The primary endpoint was time to 3-month confirmed disability progression, defined as at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with a baseline EDSS of 5.5 or higher) sustained for 3 months. 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. A prespecified 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. The median study duration was 21 months and was variable for patients. There were 36% of patients with one or more relapses in the 2 years prior to study entry, 22% of patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI, and 78% of patients who had previously been treated with an MS therapy. Compared to placebo, siponimod significantly reduced the risk of confirmed disability progression at 3 months in patients with active SPMS, who had a relapse in the 2 years prior to the study (26% vs 32%, HR 0.79, P<0.013). There was a 55% relative reduction in the annualized relapse rate compared to placebo (0.071 vs 0.160, p<0.01) and a significantly lower change from baseline to 12 months in mean total volume of lesions on T2-weighted images (204.9 vs 818 mm³). The effect of siponimod was not statistically different from placebo in patients with non-active SPMS. The proportion of patients with confirmed worsening in the timed 25-foot walk did not differ between groups. The most common adverse reactions that occurred at a higher rate than placebo included hypertension, transaminase increase, peripheral edema, bradycardia, nausea, dizziness, diarrhea, headache, falls, and pain in extremity. Additional adverse reactions occurring at a higher rate than placebo included herpes zoster, lymphopenia, seizure, tremor, macular edema, AV block, asthenia and pulmonary function test decreased.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of siponimod (Mayzent®) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. The member has a diagnosis of **ONE** of the following:
 - a. Relapsing-remitting MS (RRMS)
 - b. Active secondary-progressive MS (SPMS)
 - c. First clinical episode and has MRI features consistent with MS
2. Siponimod will not be used in combination with **ANY** of the following:
 - a. Alemtuzumab (Lemtrada)
 - b. Cladribine (Mavenclad)
 - c. Dimethyl fumarate (Tecfidera)
 - d. Fingolimod (Gilenya)

- e. Glatiramer acetate (Copaxone, Glatopa)
 - f. Interferon beta-1a (Avonex, Rebif)
 - g. Interferon beta-1b (Betaseron, Extavia)
 - h. Mitoxantrone (Novantrone)
 - i. Natalizumab (Tysabri)
 - j. Ocrelizumab (Ocrevus)
 - k. Peg-interferon beta-1a (Plegridy)
 - l. Teriflunomide (Aubagio)
3. Member will receive varicella zoster vaccine at least 4 weeks prior to the start of siponimod if the member is antibody-negative for varicella zoster virus
 4. Member does not have any of the following:
 - a. CYP2C9*3/*3 genotype
 - b. History (within the last 6 months) of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or NYHA Class III/IV heart failure
 - c. History or presence of Mobitz Type II second- or third-degree AV block or sick sinus syndrome (unless member has a functioning pacemaker)
 5. The dose does not exceed the following:
 - a. CYP2C9*1/*1 or *1/*2, or *2/*2 genotype: 2 mg daily using the fewest number of tablets per day
 - b. CYP2C9*1/*3 or *2/*3 genotype: 1 mg daily using the fewest number of tablets per day

Approval duration: 1 year

Continuation of siponimod therapy **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has demonstrated a beneficial response to therapy for treatment of RRMS, active SPMS, or clinically isolated syndrome
2. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member currently meets all indication-specific initiation criteria
3. Siponimod will not be used in combination with **ANY** of the following:
 - a. Alemtuzumab (Lemtrada)
 - b. Cladribine (Mavenclad)
 - c. Dimethyl fumarate (Tecfidera)
 - d. Fingolimod (Gilenya)
 - e. Glatiramer acetate (Copaxone, Glatopa)
 - f. Interferon beta-1a (Avonex, Rebif)
 - g. Interferon beta-1b (Betaseron, Extavia)
 - h. Mitoxantrone (Novantrone)
 - i. Natalizumab (Tysabri)

- j. Ocrelizumab (Ocrevus)
 - k. Peg-interferon beta-1a (Plegridy)
 - l. Teriflunomide (Aubagio)
4. The dose does not exceed the following:
- a. CYP2C9*1/*1 or *1/*2, or *2/*2 genotype: 2 mg daily using the fewest number of tablets per day
 - b. CYP2C9*1/*3 or *2/*3 genotype: 1 mg daily using the fewest number of tablets per day

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Siponimod is FDA-approved 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. Test patients for CYP2C9 variants to determine genotype prior to treatment. Assess all of the following prior to treatment: complete blood count, an ophthalmic evaluation, cardiac evaluation, liver function test, varicella zoster antibody testing and current or prior use of immunosuppressive medications. First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure.
- CYP2C9*1/*1 or *1/*2, or *2/*2 genotype: Titration is required for the first 5 days of treatment initiation. See prescribing information for the titration regimen. The recommended maintenance dosage is 2 mg.

Dose Adjustments

- CYP2C9*1/*3 or *2/*3 genotype: Titration is required for the first 4 days of treatment initiation. See prescribing information for the titration regimen. The recommended maintenance dose in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg.

Drug Availability

- 0.25 mg and 2 mg tablets

PRECAUTIONS:

Boxed Warning

- none

Contraindications

- CYP2C9*3/*3 genotype

- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker

Precautions/Warnings

- Infection risk is increased. Obtain a complete blood count and monitor for infection. Do not start treatment in patients with an active infection. A dose-dependent reduction in peripheral lymphocyte count to 20-30% of baseline values occurs because of reversible sequestration of lymphocytes in lymphoid tissues.
- Macular edema may occur. An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision. Diabetes mellitus and uveitis increase the risk.
- Bradyarrhythmia and Atrioventricular conduction delays may occur. Titration is required for treatment initiation. Consider cardiologist consultation before use with other drugs that decrease heart rate. Consider resting heart rate prior to concomitant beta-blocker use.
- Pulmonary function should be assessed and may decline with treatment
- Liver function should be assessed prior to treatment and monitored closely in patients with severe hepatic impairment.
- Blood pressure should be monitored and could increase during treatment.
- Women should use contraception during and for 10 days after stopping treatment due to potential fetal risk.
- Posterior reversible encephalopathy syndrome has been reported in patients receiving a sphingosine 1-phosphate receptor modulator.
- There is an unintended additive immunosuppressive effects from prior treatment with immunosuppressive modulating therapies; do not initiate treatment following alemtuzumab.
- Severe increase in disability after discontinuation is possible.
- Immune system effects after discontinuation may persist for up to 4 weeks after treatment is stopped.
- Live vaccines should be avoided during treatment and for up to 4 weeks after treatment is stopped.
- Use is not recommended with moderate CYP2C9 and moderate or strong CYP3A4 inhibitors; use may result in increased exposure to siponimod.
- Use is not recommended with moderate CYP2C9 and strong CYP3A4 inducers; use may result in decreased exposure to siponimod.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPSC Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS
-------	---

ICD-10 Diagnoses Codes That Support Medical Necessity

G35	Multiple sclerosis
-----	--------------------

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Clinically isolated syndrome (CIS): the first clinical presentation of disease that shows characteristics of inflammatory demyelination that could be MS but has yet to fulfill criteria of dissemination in time.

Primary-progressive multiple sclerosis (PPMS): Steadily progressive course from onset; occurs in 10-15% of patients with MS.

Progressive multifocal leukoencephalopathy (PML): an opportunistic viral infection of the brain that usually leads to death or severe disability.

Relapsing-remitting multiple sclerosis (RRMS): Characterized by acute attacks followed by periods of remission; primary form of MS that occurs in approximately 85% of patients.

Secondary-progressive multiple sclerosis (SPMS): An initial period of RRMS, followed by a steadily progressive course, with acute relapses (active disease) or without acute relapses (not active disease); 75-85% of patients diagnosed with RRMS will transition to SPMS.

RELATED GUIDELINES:

[Alemtuzumab \(Lemtrada\), 09-J2000-27](#)

[Cladribine \(Mavenclad\), 09-J3000-34](#)

[Dimethyl Fumarate \(Tecfidera\), 09-J1000-96](#)

[Fingolimod \(Gilenya™\), 09-J1000-30](#)

[Magnetic Resonance Imaging \(MRI\) Brain and Head, 04-70540-11](#)

[Multiple Sclerosis Self Injectable Therapy, 09-J1000-39](#)

[Natalizumab \(Tysabri®\) IV, 09-J0000-73](#)

[Ocrelizumab \(Ocrevus®\), 09-J2000-78](#)

[Teriflunomide \(Aubagio\), 09-J1000-82](#)

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2019 [cited 2019-4-24]. Available from: <http://www.clinicalpharmacology.com/>.
2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2019-4-24]. Available from: <http://www.thomsonhc.com/>.
3. Kappos L, Bar-Or A, Cree BA et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. *Lancet* 2018; 391: 1263-73.
4. Lublin FD, Reingold, SC, Cohen JA et al. Defining the clinical course of multiple sclerosis. *Neurology*. 2014; 83: 278-286.
5. Mayzent [prescribing information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. March 2019.
6. Multiple Sclerosis Coalition. Available at <http://www.nationalmssociety.org> Accessed 04/26/2019.
7. National Multiple Sclerosis Society. Accessed 10/02/19.
8. Rae-Grant A, Day GS, Marrie RA et al. Practice guideline: Disease-modifying therapies for adults with multiple sclerosis: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. April 2018. Available at: <https://www.aan.com/Guidelines/home/GuidelineDetail/898>

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 05/08/19.

GUIDELINE UPDATE INFORMATION:

07/01/19	New Medical Coverage Guideline.
11/15/19	Revision to guideline; consisting of updating the description, definition and references.