09-J3000-35

Original Effective Date: 07/01/19

Reviewed: 06/11/25

Revised: 10/01/25

Subject: Siponimod (Mayzent®) Tablets

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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 hierarchal 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 mm^3). 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.

NOTE: Avonex, Betaseron, Mavenclad, Kesimpta, Mayzent, Plegridy, Rebif, and Zeposia are the preferred brand products for treatment of relapsing forms of multiple sclerosis. The preferred generic products include dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan), and teriflunomide (generic). Dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), and teriflunomide (generic) do not require prior authorization.

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. Diroximel fumarate (Vumerity)
    e. Fingolimod (Gilenya, Tascenso ODT)
    f. Glatiramer acetate (Copaxone, Glatopa)
    g. Interferon beta-1a (Avonex, Rebif)
    h. Interferon beta-1b (Betaseron, Extavia)
    i. Mitoxantrone (Novantrone)
    j. Monomethyl fumarate (Bafiertam)
    k. Natalizumab (Tysabri)
    l. Ocrelizumab (Ocrevus)
    m. Ofatumumab (Kesimpta)
    n. Ozanimod (Zeposia)
    o. Peg-interferon beta-1a (Plegridy)
    p. Ponesimod (Ponvory)
    q. Rituximab (Rituxan or biosimilars)
    r. Teriflunomide (Aubagio)
    s. Ublituximab (Briumvi)
3. Member will receive varicella zoster vaccine at least 4 weeks prior to the start of simponimod 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 previously met 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. Diroximel fumarate (Vumerity)
    e. Fingolimod (Gilenya, Tascenso ODT)
    f. Glatiramer acetate (Copaxone, Glatopa)
    g. Interferon beta-1a (Avonex, Rebif)
    h. Interferon beta-1b (Betaseron, Extavia)
    i. Mitoxantrone (Novantrone)
    j. Monomethyl fumarate (Bafiertam)
    k. Natalizumab (Tysabri)
    l. Ocrelizumab (Ocrevus)
    m. Ofatumumab (Kesimpta)
    n. Ozanimod (Zeposia)
    o. Peg-interferon beta-1a (Plegridy)
    p. Ponesimod (Ponvory)
    q. Rituximab (Rituxan or biosimilars)
    r. Teriflunomide (Aubagio)
    s. Ublituximab (Briumvi)
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, skin examination, 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**: 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**: 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:** 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.
- **Respiratory Effects:** Pulmonary function should be assessed and may decline with treatment
- **Liver Injury:** Liver function should be assessed prior to treatment and monitored closely in patients with severe hepatic impairment.
- **Cutaneous Malignancies:** Skin examination at the start of treatment and periodically is recommended.
- **Increased Blood pressure:** Blood pressure should be monitored and could increase during treatment.
- **Fetal risk:** Women should use contraception during and for 10 days after stopping treatment due to potential fetal risk.
- **Progressive multifocal leukoencephalopathy (PML):** withhold at the first sign or symptom suggestive of PML. Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with fingolimod who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. Monitor for development of IRIS.
- 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:

HCPCS Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS

ICD-10 Diagnoses Codes That Support Medical Necessity

G35.A	Relapsing-remitting multiple sclerosis
G35.C1	Active secondary progressive multiple sclerosis
G37.9	Demyelinating disease of central nervous system, unspecified

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: Florida Blue 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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

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), Diroximel fumarate (Vumerity), and Monomethyl fumarate (Bafiertam), 09-J1000-96
Fingolimod (Gilenya), 09-J1000-30
Multiple Sclerosis Self Injectable Therapy, 09-J1000-39
Natalizumab (Tysabri) IV, 09-J0000-73
Ocrelizumab (Ocrevus), 09-J2000-78
Ofatumumab (Kesimpta), 09-J3000-84

Ozanimod (Zeposia), 09-J3000-70
Teriflunomide (Aubagio), 09-J1000-82

OTHER:

None applicable

REFERENCES:

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2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025-May-24.].
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.
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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 Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

07/01/19	New Medical Coverage Guideline.
11/15/19	Revision to guideline; consisting of updating the description, definition and references.
07/01/20	Revision to guideline; consisting of updating the position statement.
10/01/20	Revision to guideline; consisting of updating the position statement.
04/01/20	Revision to guideline; consisting of updating the position statement.
10/15/22	Review and revision to guideline; consisting of updating the list of agents not used in combination and update to warnings and references.
01/01/23	Review and revision to guideline; consisting of updating the position statement to include generic fingolimod as a preferred generic and removal of Gilenya as a preferred brand.
05/15/23	Revision to guideline; consisting of updating the position statement to include generic teriflunomide as a preferred generic and removal of Aubagio as a preferred brand. Updated list of agents not to be used in combination.

11/15/23	Review and revision to guideline; consisting of updating the position statement to include Glatopa and updated warnings.
07/15/24	Review and revision to guideline; consisting of updating the position statement to remove step requirement.
07/15/25	Review and revision to guideline; consisting of updating the references.
10/01/25	Update to ICD10 coding.