Clinical Policy Title:	siponimod
Policy Number:	RxA.215
Drug(s) Applied:	Mayzent®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Siponimod (Mayzent®) is a sphingosine 1-phosphate receptor modulator. It is 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
siponimod (Mayzent®)	MS	**All patients:** Day 1 and 2: 0.25 mg orally daily Day 3: 0.5 mg orally daily Day 4: 0.75 mg orally daily **CYP2C9 genotypes *1/*1, *1/*2, or *2/*2:** Day 5: 1.25 mg orally daily Day 6 and onward: 2 mg orally daily **CYP2C9 genotypes *1/*3 or *2/*3:** Day 5 and onward: 1 mg orally daily	2 mg/day

Dosage Forms

- Tablets: 0.25 mg, 2 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome,
   b. Relapsing-remitting MS,
   c. Secondary progressive Multiple Sclerosis;
2. Prescribed by or in consultation with a neurologist;
3. Trial and failure of at least 2 preferred disease modifying therapies, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for all disease modifying therapies for MS*
4. Age 18 years or older;
5. Documentation that member does not have a CYP2C9*3/*3 genotype (*see Appendix D*);
6. Mayzent® is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
7. Dose does not exceed 2 mg per day.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Multiple Sclerosis (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Mayzent® is not prescribed concurrently with other disease modifying therapies for Multiple Sclerosis (*see Appendix D*);
4. If request is for a dose increase, new dose does not exceed 2 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
MS: Multiple Sclerosis
S1P: sphingosine 1-phosphate
BCC: basal cell carcinoma
PUVA: psoralen and ultraviolet A

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
interferon beta-1a (Avonex®)	30 mcg intramuscular every week	30 mcg/week
peginterferon beta-1a (Plegridy®)	125 mcg subcutaneous every 2 weeks	125 mcg/2 weeks

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
glatiramer acetate (Glatopa®)	20 mg subcutaneous daily or 40 mg subcutaneous three times a week	20 mg/day or 40 mg three times a week

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Patients with a CYP2C9*3/*3 genotype
  - In the last 6 months, experienced myocardial infarction, unstable angina, stroke, Transient Ischemic Attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
  - Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker

- Boxed Warning(s):
  - None reported

APPENDIX D: General Information

Disease-modifying therapies for MS include:

- Infusion therapies
  - natalizumab (Tysabri®)
  - mitoxantrone
  - ocrelizumab (Ocrevus™)
  - alemtuzumab (Lemtrada®)
- Injectable therapies
  - glatiramer (Copaxone®, Glatopa®)
  - interferon beta-1a (Avonex®, Rebif®)
  - interferon beta-1b (Betaseron®, Extavia®)
  - peginterferon beta-1a (Plegridy®)
- Oral therapies
  - dimethyl fumarate (Tecfidera®)
  - monomethyl fumarate (Bafiertam™)
  - diroximel fumarate (Vumerity®)
  - teriflunomide (Aubagio®)
  - fingolimod (Gilenya™)
  - siponimod (Mayzent®)
  - ozanimod (Zeposia®)
  - cladribine (Mavenclad®)
  - dalfampridine (Ampyra®)
- The CYP2C9 genotype has a significant impact on siponimod metabolism. Mayzent® is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4%-0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. Mayzent® dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod.
- The American Academy of Neurology 2018 MS guidelines recommend the use of Gilenya™, Tysabri®, and Lemtrada® for patients with highly active MS. Definitions of highly active MS vary and can include

measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions.

- Long-term use of S1P modulators, including Mayzent®, have been associated with an increased risk of basal cell carcinoma (BCC). Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with Mayzent® and in patients treated with another S1P modulator.
- Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy is not recommended in patients taking Mayzent®.

References

1. Mayzent® Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2021. Available at: www.mayzent.com. Accessed March 03, 2021.
2. 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. Neurology. 2018; 90(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/904. Accessed March 03, 2021.
3. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Updated January 14, 2020. Accessed March 03, 2021.
4. Siponimod, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed March 03, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy reviewed. 1. Formatting updated. 2. References updated. 3. Clinical policy title updated. 4. Drug(s) Applied updated. 5. Line of Business updated. 6. Language added to Initial Approval – "Trial and failure of at least 2 preferred disease modifying therapies, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced." 7. Continued Therapy criteria updated to "Currently receiving medication that has	06/23/2020	09/14/2020

been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy." 8. Appendix D updated		
Policy was reviewed: 1. Clinical policy verbiage has been updated as 'The provision of prescriber samples…' 2. Continued therapy criteria II.A.1. was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance.." 3. Approval duration for Continued Therapy Approval criteria has been changed from 1 year to 12 months. 4. APPENDIX A: Abbreviation /Acronym Key was updated. 5. Appendix D: General Information was updated. 6. References were updated.	03/04/2021	06/10/2021