Clinical Policy: Siponimod (Mayzent)

Reference Number: OR.CP.PHAR.427
Effective Date: 10.01.21
Last Review Date: 05.24
Line of Business: Medicaid – Oregon Health Plan

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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

FDA Approved Indication(s)

Mayzent 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Trillium Community Health Plan that Mayzent is **medically necessary** when the following criteria are met:

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, and member is contraindicated to both or has experienced significant adverse effects to one of the following at up to maximally indicated doses: an **interferon-beta agent** (Avonex®, Betaseron®/Extavia®†, Rebif®, or Plegridy®), **glatiramer** (Copaxone®, Glatopa®);
   b. Relapsing-remitting MS, and failure of all of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated (i, ii, iii, and iv):*
      i. **Dimethyl fumarate** (generic Tecfidera®);
      ii. **Teriflunomide** (generic Aubagio®);
      iii. **Fingolimod** (Gilenya®);
      iv. An **interferon-beta agent** (Avonex, Betaseron/Extavia†, Rebif, or Plegridy) or **glatiramer** (Copaxone, Glatopa);

      **Prior authorization may be required for all disease modifying therapies for MS*
      † Extavia is preferred
   c. Secondary progressive MS;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Documentation that member does not have a CYP2C9*3/*3 genotype (*see Appendix D*);

5. Mayzent is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
6. Documentation of baseline number of relapses per year or expanded disability status scale (EDSS) score;
7. Dose does not exceed 2 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member meets one of the following (a, b or c):
   a. If member has received < 1 year of total treatment: Member is responding positively to therapy;
   b. If member has received ≥ 1 year of total treatment: Member meets one of the following (i, ii, iii, or iv):
      i. Member has not had an increase in the number of relapses per year compared to baseline;
      ii. Member has not had ≥ 2 new MRI-detected lesions;
      iii. Member has not had an increase in EDSS score from baseline;
      iv. Medical justification supports that member is responding positively to therapy;
   c. Member is actively relapsing and all of the following are met (i, ii, iii):
      i. Prescribed by or in consultation with a neurologist;
      ii. Member is adherent to therapy as evidenced by claims for at least 144 days of therapy in the last 180 days;
      iii. Provider has completed evaluation of alternative treatment options or plans to do so at next scheduled office visit;

3. Mayzent is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
4. If request is for a dose increase, new dose does not exceed 2 mg per day.

Approval duration:
If member has received < 1 year of total treatment – up to a total of 12 months of treatment
If member has received ≥ 1 year of total treatment – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
EDSS: expanded disability status scale
FDA: Food and Drug Administration
MS: multiple sclerosis

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
teriflunomide (Aubagio®)	7 mg or 14 mg PO QD	14 mg/day
Avonex®, Rebif® (interferon beta-1a)	*Avonex*: 30 mcg IM Q week *Rebif*: 22 mcg or 44 mcg SC TIW	*Avonex*: 30 mcg/week *Rebif*: 44 mcg TIW
Betaseron®, Extavia® (interferon beta-1b)	250 mcg SC QOD	250 mg QOD
Plegridy® (peginterferon beta-1a)	125 mcg SC Q2 weeks	125 mcg/2 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
glatiramer acetate (Copaxone®, Glatopa®)	20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
fingolimod (Gilenya®)	0.5 mg PO QD	0.5 mg/day
dimethyl fumarate (Tecfidera®)	120 mg PO BID for 7 days, followed by 240 mg PO BID	480 mg/day

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, TIA, 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 are: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity®), monomethyl fumarate (Bafiertam™), fingolimod (Gilenya®, Tascenso ODT™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®, and biosimilar Tyruko®), ocrelizumab (Ocrevus®), siponimod (Mayzent®), cladribine (Mavenclad®), ozanimod (Zeposia®), ponesimod (Ponvory™), ublituximab-xiiy (Briumvi™), and ofatumumab (Kesimpta®).
- 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MS	**All patients:** Day 1 and 2: 0.25 mg PO QD Day 3: 0.5 mg PO QD Day 4: 0.75 mg PO QD	2 mg/day

Indication	Dosing Regimen	Maximum Dose
	CYP2C9 genotypes *1/*1, *1/*2, or *2/*2: Day 5: 1.25 mg PO QD Day 6 and onward: 2 mg PO QD **CYP2C9 genotypes *1/*3 or *2/*3:** Day 5 and onward: 1 mg PO QD	

VI. Product Availability

Tablets: 0.25 mg, 1 mg, 2 mg

VII. References

1. Mayzent Prescribing Information. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; August 2023. Available at: www.mayzent.com. Accessed January 12, 2024.
2. The Food and Drug Administration. FDA Supplemental Approval Letter for Mayzent; August 24, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/209884Orig1s006CorrectedLtr.pdf. Accessed January 31, 2023.
3. 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. Reaffirmed on September 18, 2021.

Reviews, Revisions, and Approvals	Date	Plan Approval Date
Policy created: adapted from previously approved policy CP.PHAR.427 Siponimod; changed requirement to report EDSS score in I.A.6 to either baseline number of relapses per year; expanded II.A.2 to allow approval for actively relapsing		07.15.21
2Q 2022 annual review: no significant changes; clarified interferon-beta product redirections per SDC; references reviewed and updated.	03.17.22	04.07.22
2Q 2023 annual review: no significant changes; revised continued approval duration to reference the duration of total treatment received rather than the number of re-authorizations; template changes applied to other diagnoses/indications and continued therapy section; references reviewed and updated.	03.13.23	04.06.23
Per August SDC, added generic references to Aubagio and Gilenya redirections.	09.22.23	11.21.23
2Q 2024 annual review: no significant changes; references reviewed and updated.	03.29.24	05.21.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.