Clinical Policy: Siponimod (Mayzent)
Reference Number: CP.PHAR.427
Effective Date: 05.14.19
Last Review Date: 08.19
Line of Business: Commercial, HIM, Medicaid

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 health plans affiliated with Centene Corporation® 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;
         b. Relapsing-remitting MS;
         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. Dose does not exceed 2 mg per day.
      Approval duration: 6 months
   
   B. Other diagnoses/indications
      1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.
II. Continued Therapy

A. Multiple Sclerosis (must meet all):
   1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   2. Member is responding positively to therapy;
   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: 12 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or
   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex® (interferon beta-1a)</td>
<td>30 mcg IM Q week</td>
<td>30 mcg/week</td>
</tr>
<tr>
<td>Pregnyl® (peginterferon beta-1a)</td>
<td>125 mcg SC Q2 weeks</td>
<td>125 mcg/2 weeks</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone®, Glatopa®)</td>
<td>20 mg SC QD or 40 mg SC TIW</td>
<td>20 mg/day or 40 mg TIW</td>
</tr>
<tr>
<td>Gilenya™ (fingolimod)</td>
<td>0.5 mg PO QD</td>
<td>0.5 mg/day</td>
</tr>
<tr>
<td>Tecfidera® (dimethyl fumarate)</td>
<td>120 mg PO BID for 7 days, followed by 240 mg PO BID</td>
<td>480 mg/day</td>
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</tbody>
</table>

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®), fingolimod (Gilenya™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), ocrelizumab (Ocrevus™), siponimod (Mayzent®), and cladribine (Mavenclad®).
- 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS</strong></td>
<td>Day 1 and 2: 0.25 mg PO QD</td>
<td>2 mg/day</td>
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<tr>
<td></td>
<td>Day 3: 0.5 mg PO QD</td>
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<td></td>
<td>Day 4: 0.75 mg PO QD</td>
<td></td>
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<tr>
<td>**CYP2C9 genotypes *1/*1, *1/*2, or <em>2/<em>2:</em></em></td>
<td>Day 5: 1.25 mg PO QD</td>
<td></td>
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<tr>
<td></td>
<td>Day 6 and onward: 2 mg PO QD</td>
<td></td>
</tr>
<tr>
<td>**CYP2C9 genotypes *1/*3 or <em>2/<em>3:</em></em></td>
<td>Day 5 and onward: 1 mg PO QD</td>
<td></td>
</tr>
</tbody>
</table>

VI. Product Availability
Tablets: 0.25 mg, 2 mg
VII. References

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>05.14.19</td>
<td>08.19</td>
</tr>
<tr>
<td>Added Commercial and HIM line of business to policy, retire CP.CPA.341 and HIM.PA.SP37; removed redirections for clinically isolated syndrome and relapsing-remitting MS per SDC and prior clinical guidance.</td>
<td>01.15.20</td>
<td></td>
</tr>
</tbody>
</table>

**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.

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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.

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