Clinical Policy: Ozanimod (Zeposia)
Reference Number: CP.PHAR.462
Effective Date: 03.25.20
Last Review Date: 02.21
Line of Business: Commercial, HIM, Medicaid

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

Description
Ozanimod (Zeposia®) is a sphingosine 1-phosphate receptor modulator.

FDA Approved Indication(s)
Zeposia 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 Zeposia 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 clinically significant adverse effects to one of the following at up to maximally indicated doses: an interferon-beta agent (Avonex®, Betaseron®, 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. Aubagio®;
            iii. Gilenya™;
            iv. An interferon-beta agent (Avonex, Betaseron, Rebif, or Plegridy) or glatiramer (Copaxone, Glatopa);
      *Prior authorization is required for all disease modifying therapies for MS
   c. Secondary progressive MS;
   2. Prescribed by or in consultation with a neurologist;
   3. Age ≥ 18 years;
   4. Zeposia is not prescribed concurrently with other disease modifying therapies for MS (see Appendix D);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. Dose does not exceed 0.92 mg (1 capsule) 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.PA.154 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 meets one of the following (a or b):
      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;
   3. Zeposia 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 0.92 mg (1 capsule) per day.

Approval duration: first re-authorization: 6 months; second and subsequent re-authorizations: 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.PA.154 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 –
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>Aubagio® (teriflunomide)</td>
<td>7 mg or 14 mg PO QD</td>
<td>14 mg/day</td>
</tr>
<tr>
<td>Avonex®, Rebif® (interferon beta-1a)</td>
<td>Avonex: 30 mcg IM Q week Rebif: 22 mcg or 44 mcg SC TIW</td>
<td>Avonex: 30 mcg/week Rebif: 44 mcg TIW</td>
</tr>
<tr>
<td>Betaseron® (interferon beta-1b)</td>
<td>250 mcg SC QOD</td>
<td>250 mg QOD</td>
</tr>
<tr>
<td>Plegridy® (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>dimethyl fumarate (Tecfidera®)</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): history of any of the following in the last 6 months: myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure; presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker; severe untreated sleep apnea; concomitant use of a monoamine oxidase inhibitor
- 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), teriflunomide (Aubagio), alemtuzumab (Lemtrada), mitoxantrone (Novantrone®, natalizumab (Tysabri®),
ocrelizumab (Ocrevus™), siponimod (Mayzent), cladribine (Mavenclad®), ozanimod (Zeposia), and ofatumumab (Kesimpta®).

- 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.
- Of the disease-modifying therapies for MS that are FDA-labeled for CIS, only the interferon products, glatiramer, and Aubagio have demonstrated any efficacy in decreasing the risk of conversion to MS compared to placebo. This is supported by the AAN 2018 MS guidelines.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
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<tbody>
<tr>
<td>MS</td>
<td>Days 1-4: 0.23 mg PO QD Days 5-7: 0.46 mg PO QD Day 8 and thereafter: 0.92 mg PO QD</td>
<td>0.92 mg/day</td>
</tr>
</tbody>
</table>

If a dose of Zeposia is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen. If a dose of Zeposia is missed after the first 2 weeks of treatment, continue with the treatment as planned.

VI. Product Availability
Capsules: 0.23 mg, 0.46 mg, 0.92 mg

VII. References
Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>01.21.20</td>
<td>02.20</td>
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<tr>
<td>05.12.20</td>
<td>08.20</td>
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**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.

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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.

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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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