Drug Monograph

Drug Name: **Zeposia® (ozanimod) Capsule**
Drug Class: **Multiple Sclerosis Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Zeposia is available as oral capsules containing 0.23mg, 0.46mg or 0.92mg of ozanimod
Manufacturer:	Manufactured for: Celgene Corporation Summit, NJ 07901
Summary of Findings:	The efficacy of Zeposia was evaluated in two randomized, double-blind, double-dummy, parallel-group, active comparator-controlled clinical trials in which 1,769 patients were randomized to receive either Zeposia 0.92 mg orally once daily or interferon (IFN) beta-1a 30 mcg intramuscularly once weekly. The primary endpoint of both studies was the annualized relapse rate (ARR) over the treatment period (Study 1) and 24 months (Study 2). The ARR was statistically significantly lower in the treatment group than in the control group. In Study 1, the percentage of patients without relapse was 78% in the treatment group vs 66% in the control group (relative reduction 48%, p<0.0001). In Study 2, 76% of patients in the treatment group had no relapse vs 64% in the placebo group (relative reduction 38%, p<0.0001).
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☐ Open Access ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Multiple sclerosis (MS) is an autoimmune condition that damages the brain and spinal cord which make up the central nervous system (CNS). In MS, the immune system attacks the protective sheath (myelin) that covers nerve fibers and causes communication problems between the brain and the rest of the body. The disease can cause permanent damage or deterioration of the nerves. Signs and symptoms of MS vary widely and depend on the amount of nerve damage and which nerves are affected. People with severe MS may lose the ability to walk independently, or at all, while others may experience long remission periods without any new symptoms.

Dosage Form [3]

Zeposia is available as oral capsules containing 0.23mg, 0.46mg or 0.92mg of ozanimod

Manufacturer [3]

Manufactured for: Celgene Corporation Summit, NJ 07901

Indication(s) [3]

Zeposia is indicated for adults to treat the relapsing forms of multiple sclerosis (MS) which may include relapsing-remitting disease, clinically isolated syndrome and active secondary progressive.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Zeposia is a once-daily selective modulator of sphingosine-1-phosphate (S1P) receptor. It binds to S1P receptors 1 and 5. Zeposia blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in the peripheral blood. How this plays into the therapeutic effect in MS is unknown, however, it may involve the reduction of lymphocyte migration into the CNS.

Pharmacokinetics:

Absorption	T_{max} is approximately 6-8 hours
Metabolism	Metabolized into active metabolites by multiple enzymes
Excretion	26% recovered in urine, 37% in feces Clearance: 192 L/hr
Half-life	21 hours

Clinical Trials Experience

"Phase 3 Study of RPC1063 in Relapsing MS"

STUDY 1 DESIGN	Phase 3, randomized, double-blind, double-dummy, parallel-group, multinational clinical trial (n=1346)
INCLUSION CRITERIA	• Multiple sclerosis as diagnosed by the revised 2010 McDonald criteria • Expanded Disability Status Scale (EDSS) score between 0 and 5.0 at baseline
EXCLUSION CRITERIA	• Patients with primary progressive MS
TREATMENT REGIMEN	Patients were randomized to receive oral ozanimod 0.92 mg once daily vs 30 mcg IM interferon (IFN) beta-1a once weekly. The neurological functions were evaluated at baseline, every 3 months and at the time of a suspected relapse. The primary outcome was the annualized relapse rate (ARR) for Zeposia and IFN beta-1a at 1 year.
RESULTS	94% of patients treated with Zeposia and 92% treated with IFN beta-1a completed the study. Prior to the study, 31% of patients had been treated with non-steroid therapy. The ARR, the primary outcome was statistically significantly lower in patients treated with Zeposia than in patients who received IFN beta-1a (0.181 vs 0.350) The relative reduction was 48%, $p<0.0001$. The percentage of patients without relapse was 78% for Zeposia and 66% for IFN beta-1a.
SAFETY	Discussed in the Adverse Effects section below.

"Efficacy and Safety Study of Ozanimod in Relapsing Multiple Sclerosis (Radiance Study)"

STUDY 2 DESIGN	Phase 2/3, multicenter, randomized, quadruple controlled, parallel group study (n=1320)
INCLUSION CRITERIA	• Multiple sclerosis as diagnosed by the revised 2010 McDonald criteria EDSS score between 0 and 5.0 at baseline
EXCLUSION CRITERIA	• Patients with primary progressive MS
TREATMENT REGIMEN	Patients were randomized to receive either oral ozanimod 0.92 mg given once daily, beginning with a dose titration or IFN beta-1a 30 mcg IM once weekly. The primary outcome was the ARR over the treatment period (Study 1) and 24 months (Study 2).
RESULTS	90% of patients who received Zeposia and 85% who received IFN beta-1a completed the study. The primary outcome, ARR, was statistically significantly lower in patients treated with Zeposia than in patients who received IFN beta-1a (0.172 vs. 0.276). The relative reduction was 38%, $p<0.0001$. The percentage of patients without relapse was 76% for Zeposia and 64% for IFN beta-1a.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- Myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure in the last 6 months
- 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
- Monoamine oxidase inhibitor (MAOI) use

Warnings and Precautions [3,4]

- Risk of infection: Zeposia may increase the risk of infection. It is important to obtain a complete blood count prior to the treatment with Zeposia. Life-threatening and rare fatal infection has been reported. In cases of active infection, treatment should be postponed until the infection resolution. Continued monitoring for infection up 3 months after end of therapy is also recommended. Live attenuated vaccines should be avoided during and up to 3 months after end of therapy. If unable to postpone live vaccine administration, vaccines must be given at least one month prior to treatment with Zeposia.
- Bradyarrhythmia and atrioventricular conduction delays: Zeposia may cause a decrease in heart rate and atrioventricular conduction delays. Therefore, it is important to titrate the dose especially in patients with significant QT prolongation, taking Class 1a or III arrhythmia medications, ischemic heart disease, heart failure, history of cardiac arrest, myocardial infarction, cerebrovascular disease, uncontrolled hypertension, history of Mobitz type II second-degree or higher AV block, sick-sinus syndrome or sinoatrial heart block.
- Liver injury: Zeposia may elevate aminotransferase levels. It is recommended to obtain liver function tests prior to treatment. If patients develop liver dysfunction symptoms while taking Zeposia, hepatic enzyme levels should be checked. If significant liver injury occurs, therapy must be discontinued.
- Fetal risk: Fetal harm may occur based on animal studies. Concomitant contraceptive use is recommended while on Zeposia and 3 months after discontinuation.
- Increased blood pressure: Zeposia may elevate systolic blood pressure. Blood pressure should be monitored during use and for 3 months after therapy. Foods containing high amounts of tyramine should also be avoided.
- Respiratory effects: Pulmonary function tests are recommended due to potential of declining pulmonary function.
- Macular edema: Zeposia may increase the risk of macular edema particularly in patients with a history of uveitis or diabetes mellitus. Ophthalmic tests should be performed throughout therapy.
- Posterior reversible encephalopathy syndrome (PRES): There were a several cases of PRES in patients treated with Zeposia. Symptoms are often reversible; however, may evolve into ischemic stroke or cerebral hemorrhage. Therapy must be discontinued if PRES symptoms occur.
- Unintended additive immunosuppressive or immune-modulating drugs: Caution should be taken when switching from drugs with prolonged immune effects.

Initiating treatment after alemtuzumab is not recommended.

- Severe increase in disability after stopping Zeposia: Severe exacerbation of disease after Zeposia discontinuation has been reported.
- Immune system effects after stopping Zeposia: Peripheral blood lymphocytes return to normal at a median of 30 days, with approximately 90% of patients in the normal range within 3 months. Caution should be used when administering immunosuppressants within 4 weeks after last dose of Zeposia.

Adverse Effects [3,4]

Most common, ≥ 2 %	Zeposia (n=882) %	IFN beta-1a (n=885) %
Upper respiratory infection	26	23
Hepatic transaminase elevation	10	5
Orthostatic hypotension	4	3
Urinary tract infection	4	3
Back pain	4	3
Hypertension	4	2
Upper abdominal pain	2	1

Drug Interactions [3,4]

- Contraindication in patients currently taking monoamine oxidase inhibitors (MAOI)
- Co-administration of Zeposia with strong CYP2C8 inducers should be avoided due to reducing the exposure of the major active metabolites of Zeposia
- Co-administration of Zeposia with anti-arrhythmic drugs, QT prolonging drugs, anti-neoplastic, immune-modulating, immunosuppressive therapies, strong CYP2C8 inducers/inhibitors, breast cancer resistance protein inhibitors, adrenergic and serotonergic drugs are not recommended.
- The large amount of tyramine food should be avoided while taking Zeposia
- Live vaccine should also be avoided during Zeposia treatment and for up to 3 months after discontinuation of the therapy.

Dosage and Administration [3,4]

- Prior to the treatment, obtaining a complete blood count (CBC), cardiac evaluation, liver function tests and ophthalmic assessment are recommended.
- The titration is required as following:
    - Day 1 through day 2, the dose is 0.23mg once daily
    - Day 5 through 7, the recommendation dose is 0.46 mg once daily
    - Then after that, the maintenance dosage is 0.92 mg orally once daily
- If patient misses a dose within the first 2 weeks of treatment, the titration regimen needs to be reinitiated.
- If patient misses a dose after the first 2 weeks of treatment, the therapy regimen can continue as planned.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/Month
ozanimod	Zeposia®	Celgene	Maintenance dose: 0.92 mg per day	$7,050

** Wholesale Acquisition Cost

Conclusion

Zeposia is a sphingosine 1-phosphate receptor modulator with a maintenance dose of 0.92 mg once daily. 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. The efficacy of Zeposia was evaluated in two clinical studies that evaluated the ARR between Zeposia and IFN beta-1a. A total of 1,769 patients with MS were enrolled in the trials which showed statistically significantly difference between Zeposia and IFN beta-1a. The most common adverse effects with Zeposia were upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, hypertension and upper abdominal pain.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List as non-preferred.

References

1) Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet Neurol*. 2019;18(11):1021–33
2) Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol*. 2019;18(11):1009–20
3) Lamb, Y.N. Ozanimod: First Approval. *Drugs.* 2020; 80: 841–848.
4) Zeposia® (fenfluramine) oral solution, [package insert]. Summit, NJ: Celgene Corporation; 2020.

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