PDL DRUG REVIEW

Proprietary Name: Zeposia®
Common Name: ozanimod
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Gilenya	Preferred with Conditions
Mayzent	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Ozanimod, the active ingredient of Zeposia®, is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. It blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which it exerts its therapeutic effects in multiple sclerosis is not known but may involve the reduction of lymphocyte migration into the CNS.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate data on the developmental risk associated with use in pregnant women. In animal studies, use during pregnancy produced adverse effects on development, in the absence of maternal toxicity. Before initiation of Zeposia®, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for contraception during treatment with Zeposia®. Because of the time it takes to eliminate the drug from the body after stopping treatment, the potential risk to the fetus may persist and women of childbearing age should also use effective contraception for 3 months after stopping Zeposia®. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 0.23mg, 0.46mg, and 0.92mg

Recommended Dosage: Before initiation of treatment, assess the following:

- Complete blood count: obtain a recent (i.e. within the last 6 months or after discontinuation of prior MS therapy) complete blood count (CBC), including lymphocyte count.
- Cardiac evaluation: obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist should be sought.
- Liver function tests: obtain recent (i.e. within the last 6 months) transaminase and bilirubin levels
- Ophthalmic assessment: in patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula.
- Current or prior medications
    - If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with Zeposia®.
    - Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction
- Vaccinations: test patients for antibodies to varicella-zoster virus (VZV) before starting Zeposia®. VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Zeposia®. If live attenuated vaccine immunizations are required, administer at least 1 month prior to the start of Zeposia®.

Initiate Zeposia® with a 7-day titration, to include 0.23mg PO QD on days 1-4 and then 0.46mg PO QD on days 5-7. After initial titration, the recommended maintenance dosage is 0.92mg PO QD starting on day 8 and thereafter. Swallow capsules whole and administer with or without food. If a dose is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen. If a dose is missed after the first 2 weeks of treatment, continue with the treatment as planned.

Use of Zeposia® in patients with hepatic impairment is not recommended.

Drug Interactions: Zeposia® has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration. Initiating treatment with Zeposia® after alemtuzumab is not recommended. Zeposia® can generally be started immediately after discontinuation of beta interferon or glatiramer.

Zeposia® has not been studied in patients taking QT prolonging drugs. Class Ia (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with Zeposia® is considered, advice from a cardiologist should be sought. Treatment with Zeposia® should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties.

During, and for up to 3 months after, discontinuation of treatment with Zeposia®, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should thus be avoided during Zeposia® treatment and for up to 3 months after discontinuation of treatment with Zeposia®.

Coadministration of Zeposia® with strong CYP2C8 inhibitors increases the exposure of the active metabolites of ozanimod, which may increase the risk of Zeposia® adverse reactions. Thus, coadministration of Zeposia® with strong CYP2C8 inhibitors (e.g. gemfibrozil) is not recommended.

Coadministration of Zeposia® with breast cancer resistance protein (BCRP) inhibitors increases the exposure of the active metabolites of ozanimod, which may increase the risk of Zeposia® adverse reactions. Thus, coadministration of Zeposia® with inhibitors of BCRP (e.g. cyclosporine, eltrombopag) is not recommended.

Coadministration of Zeposia® with strong CYP2C8 inducers (e.g. rifampin) reduces the exposure of the major active metabolites of ozanimod, which may decrease the efficacy of Zeposia®. Thus, coadministration of Zeposia® with strong CYP2C8 inducers should be avoided.

Coadministration of Zeposia® with MAO inhibitors (e.g. selegiline, phenelzine, linezolid) is contraindicated.

Coadministration of Zeposia® with drugs or OTC medications that can increase norepinephrine or serotonin (e.g. opioid drugs, SSRIs, SNRIs, tricyclics, tyramine) is not recommended. Monitor patients for hypertension with concomitant use. Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of Zeposia®.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zeposia® 0.92mg) minus reported % incidence for interferon beta-1a 30mcg IM QW. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse event included upper respiratory infection (3%), hepatic transaminase elevation (5%), orthostatic hypotension (1%), urinary tract infection (1%), back pain (1%), hypertension (2%), and abdominal pain upper (1%).

Zeposia® causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values. Zeposia® may thus increase the susceptibility to infections, some serious in nature. Life-threatening and rare fatal infections have occurred in patients receiving Zeposia®. Delay initiation of Zeposia® in patients with an active infection until the infection is resolved. Consider interruption of treatment with Zeposia® if a patient develops a serious infection.

Progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain caused by the JC virus, has been reported in patients treated with S1P receptor modulators and other MS therapies and has been associated with some

risk factors. If PML is suspected, treatment with Zeposia® should be suspended until PML has been excluded by an appropriate diagnostic evaluation.

Since initiation of Zeposia® may result in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of Zeposia®. If treatment with Zeposia® is considered, advice from a cardiologist should be sought for those individuals:

- With significant QT prolongation
- With arrhythmias requiring treatment with Class 1a or Class III anti-arrhythmic drugs
- With ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- With a history of or with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block

Elevations of aminotransferases may occur in patients treated with Zeposia®. Obtain transaminase and bilirubin levels, if not recently available, before the start of treatment. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and Zeposia® should be discontinued if significant liver injury is confirmed.

As patients in clinical trials treated with Zeposia® had increases in systolic blood pressure, blood pressure should be monitored during treatment with Zeposia® and managed appropriately. In addition, certain foods that may contain very high amounts of tyramine could cause severe hypertension. Patients should be advised to avoid foods containing a very large amount of tyramine while taking Zeposia®.

Dose dependent reductions in absolute FEV1 were observed in patients treated with Zeposia® as early as 3 months after the start of treatment. There is insufficient information to determine the reversibility of the decrease in FEV1 or forced vital capacity after drug discontinuation. Spirometric evaluation of respiratory function should be performed during therapy with Zeposia®, if clinically indicated.

S1P receptor modulators, including Zeposia®, have been associated with an increased risk of macular edema. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking Zeposia®. Patients with a history of uveitis and patients with a history of diabetes mellitus are at increased risk of macular edema during Zeposia® therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with DM or a history of uveitis should have regular follow-up exams.

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. If PRES is suspected, treatment with Zeposia® should be discontinued.

Severe exacerbations of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping Zeposia® treatment. Patients should be observed for a severe increase in disability with Zeposia® discontinuation and appropriate treatment should be started, as required.

After discontinuing Zeposia®, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with about 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and thus caution should be applied when starting other drugs 4 weeks after the last dose of Zeposia®.

Contraindications: In patients who:

- In the last 6 months have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Have the 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
- Have severe untreated sleep apnea
- Are taking a monoamine oxidase inhibitor

Manufacturer: Celgene Corporation

Analysis: The safety and efficacy of Zeposia® were assessed in 2 randomized, double-blind, double-dummy, parallel-group, active comparator-controlled trials of similar design that included patients with relapsing forms of MS. Patients in study 1 were treated until the last enrolled patient completed 1 year of treatment, while patients in study 2 were treated for 24 months. Both studies included patients who had experienced at least 1 relapse within the prior year, or 1 relapse within the prior 2 years with evidence of at least a gadolinium-enhancing (GdE) lesion in the prior year and had an Expanded Disability Status Scale (EDSS) Score from 0 to 5.0 at baseline. Patients with primary progressive MS were excluded.

In study 1, patients were randomized to Zeposia® (N=447) or interferon beta-1a (N=448). The mean age of included adults was 35.4 years, while 99.8% were White and 65% were female. The mean time since MS symptom-onset was 6.9 years, and the median EDSS score at baseline was 2.5. Furthermore, 31% had been treated with a non-steroid therapy for MS, the mean number of relapses in the prior year was 1.3, and 48% had one or more T1 Gd-enhancing lesions (mean 1.8) on their baseline MRI scan.

In study 2, patients were randomized to Zeposia® (N=433) or interferon beta-1a (N=441). The mean age of included adults was 35.6 years, while 98% were White and 68% were female. The mean time since MS symptom onset was 6.6 years, and the median EDSS score at baseline was 2.5. Furthermore, 29% of patients had been treated with a non-steroid therapy for MS, the mean number of relapses in the prior year was 1.3, and 43% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The primary endpoint of both studies was the annualized relapse rate (ARR) over the treatment period (study 1) and 24 months (study 2). Additional outcome measures included the number of new or enlarging MRI T2 hyperintense lesions over 12 and 24 months; the number of MRI T1 Gadolinium-enhancing (Gd+) lesions at 12 and 24 months; and the time to confirmed disability progression, defined as at least a 1-point increase from baseline EDSS confirmed after 3 months and after 6 months. Confirmed disability progression was assessed in a pooled analysis of studies 1 and 2.

Results suggested that the ARR was statistically significantly lower in patients treated with Zeposia® 0.92mg daily than in patients who received interferon beta-1a 30mcg IM. The number of new or enlarging T2 lesions and the number of GdE lesions were statistically significantly lower in patients treated with Zeposia® than in patients who received interferon beta-1a. In addition, there was no statistically significant difference in the 3-month and 6-month confirmed disability progression between Zeposia® and interferon beta-1a treated patients over 2 years. Results can be seen in the table below, which was adapted from the prescribing information.

	Study 1		Study 2	
Treatment	Zeposia® (N=447)	Interferon beta-1a (N=448)	Zeposia® (N=433)	Interferon beta-1a (N=441)
Clinical Endpoints				
ARR (primary endpoint)	0.181	0.350	0.172	0.276
Relative reduction	48% (p<0.0001)		38% (p<0.0001)	
Percentage of patients without relapse	78%	66%	76%	64%
Proportion with 3-month confirmed disability progression	7.6% Zeposia® Vs 7.8% interferon beta-1a			
Hazard ratio; p-value	0.95; p=0.77			
MRI Endpoints				
Mean # of new or enlarging T2 hyperintense lesions per MRI	1.47	2.84	1.84	3.18
Relative reduction	48% (p<0.0001)		42% (p<0.0001)	

	Study 1		Study 2	
Treatment	Zeposia® (N=447)	Interferon beta-1a (N=448)	Zeposia® (N=433)	Interferon beta-1a (N=441)
Mean # of T1 Gd-enhancing lesions	0.16	0.43	0.18	0.37
Relative reduction	63% (p<0.0001)		53% (p=0.0006)	

Place in Therapy: Zeposia® is indicated for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. In clinical trials, adults treated with Zeposia® had a statistically significantly lower ARR over 12 months in one study and over 24 months in a second study as compared with interferon beta-1a 30mcg IM in a population with relapsing MS. While MRI endpoints were also significantly improved with Zeposia® in both studies compared with interferon beta-1a, the pooled analysis of the proportion with 3 month confirmed disability progression was not significantly different between treatments.

In a 2020 matching adjusted indirect comparison by Swallow et al[2], indirectly comparing ozanimod with fingolimod for relapsing MS treatment, the results suggested that efficacy outcomes, including ARR and 3-month confirmed disability progression, were similar between treatments; however, ozanimod was associated with a significantly lower risk of adverse events and a significantly lower number of abnormal liver enzyme elevations at both adjusted analyses of 1-year and 2-year outcomes compared with fingolimod. At the adjusted analyses of 2-year outcomes, ozanimod was associated with a significantly lower risk of basal-cell carcinoma, bradycardia, and adverse events leading to discontinuation compared with fingolimod. In the adjusted analyses of first-dose cardiac monitoring outcomes, ozanimod was associated with significantly lower rates of conduction abnormalities and first-degree AV block, as well as a lower risk of requiring monitoring beyond 6 hours compared with fingolimod.

There is some evidence from two phase 3 studies to suggest that Zeposia® is more effective than interferon beta-1a 30mcg IM for improvement in ARR (the primary endpoint) and for several secondary endpoints. In addition, in an adjusted indirect comparison, there was some evidence to suggest that ozanimod may have a lower number of some adverse outcomes as compared with fingolimod, but with similar efficacy. However, there is no evidence to support that Zeposia® is more effective than interferon beta-1a for confirmed disability progression in the available studies. Since this is the only comparative data found, there is also no evidence found that Zeposia® is safer or more effective than other preferred treatments. It is therefore recommended that Zeposia® remain non-preferred with conditions and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Zeposia [package insert]. Summit, NJ: Celgene Corporation 2020.
[2] Swallow E, Patterson-Lomba O, Yin L, et al. Comparative safety and efficacy of ozanimod versus fingolimod for relapsing multiple sclerosis. J Comp Eff Res. 2020; 9(4): 275-285.