RXADVANCE
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# NEW DRUG APPROVAL

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| **Brand Name** | Zeposia® |
| **Generic Name** | ozanimod |
| **Drug Manufacturer** | Celgene Corporation |

## New Drug Approval

FDA Approval Date: March 25, 2020

Review Designation: Standard

Review Type: New Drug Application 209899

## Place in Therapy

### DISEASE DESCRIPTION & EPIDEMIOLOGY

Diseases that affect central nervous system myelin can be categorized as demyelinating (acquired, usually inflammatory) and dysmyelinating (abnormal formation of myelin, usually due to a genetic disease). The most common immune-mediated inflammatory demyelinating disease of the central nervous system is multiple sclerosis (MS). 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.

The disease causes vision problems, numbness and tingling, muscle weakness, and other problems.

Among central nervous system disorders, MS is the most frequent cause of permanent disability in young adults, aside from trauma. MS affects more women than men. A systematic review of 28 epidemiologic studies found that, from 1955 to 2000, the estimated female to male ratio of MS incidence increased from 1.4:1 to 2.3:1. Subsequent studies have also found that the female-to-male incidence ratio is increasing, mainly due to an increasing incidence of MS in females. The reason for this is unknown. A case-control study from Crete noted that an increase in the incidence of MS in women since 1980 was concurrent with a population shift from rural to urban areas, and speculated that environmental factors accompanying urbanization may trigger the development of MS

## Efficacy

The efficacy of Zeposia was demonstrated in 2 randomized, double-blind, double-dummy, parallel-group, active comparator-controlled clinical trials of similar design, in patients with relapsing forms of MS [Study 1 (NCT02294058) and Study 2 (NCT02047734)]. Patients in Study 1 were treated until the last enrolled patient completed 1 year of treatment. 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.

Patients were randomized to receive either ZEPOSIA 0.92 mg given orally once daily, beginning with a dose titration, or interferon (IFN) beta-1a, the active comparator, 30 mcg given intramuscularly once weekly. Neurological evaluations were performed at baseline, every 3 months, and at the time of a suspected relapse. Brain MRI scans were performed at baseline, 6 months (Study 1), 1 year (Studies 1 and 2), and 2 years (Study 2).

The primary endpoint of both Study 1 and Study 2 was the annualized relapse rate (ARR) over the treatment period (Study 1) and 24 months (Study 2). Additional outcome measures included: 1) the number of new or enlarging MRI T2 hyperintense lesions over 12 and 24 months, 2) the number of MRI T1 Gadolinium-enhancing

(Gd+) lesions at 12 and 24 months, and 3) 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 evaluated in a pooled analysis of Studies 1 and 2.

In Study 1, a total of 895 patients were randomized to receive ZEPOSIA (n=447) or IFN beta-1a (n=448); of these patients, 94% who received ZEPOSIA and 92% who received IFN beta-1a completed the study. The mean age was 35.4 years, 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; 31% had been treated with a non-steroid therapy for MS. At baseline, the mean number of relapses in the prior year was 1.3 and 48% of patients had one or more T1 Gd-enhancing lesions (mean 1.8) on their baseline MRI scan.

In Study 2, a total of 874 patients were randomized to receive ZEPOSIA (n=433) or IFN beta-1a (n=441); of these patients, 90% who received ZEPOSIA and 85% who received IFN beta-1a completed the study. The mean age was 35.6 years, 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; 29% of patients had been treated with a non-steroid therapy for MS. At baseline, 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 ARR was statistically significantly lower in patients treated with ZEPOSIA 0.92 mg than in patients who received IFN beta-1a 30 mcg IM. The number of new or enlarging T2 lesions and the number of GdE lesions were statistically significantly lower in patients treated with ZEPOSIA 0.92 mg than in patients who received IFN beta-1a.

There was no statistically significant difference in the three-month and six-month confirmed disability progression between ZEPOSIA and IFN beta-1a-treated patients over 2 years.

## Safety

### ADVERSE EVENTS

Most common adverse reactions (incidence ⩾4%): Upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

### WARNINGS & PRECAUTIONS

- Infections: ZEPOSIA may increase the risk of infections. Obtain a complete blood count (CBC) before initiation of treatment. Monitor for infection during treatment and for 3 months after discontinuation. Do not start ZEPOSIA in patients with active infections (5.1)
- Bradyarrhythmia and Atrioventricular Conduction Delays: ZEPOSIA may result in transient decrease in heart rate; titration is required for treatment initiation. Check an electrocardiogram (ECG) to assess for pre-existing cardiac conduction abnormalities before starting ZEPOSIA. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate
- Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating ZEPOSIA
- Fetal Risk: Women of childbearing potential should use effective contraception during treatment and for 3 months after stopping ZEPOSIA
- Increased Blood Pressure (BP): Monitor BP during treatment
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated
- Macular Edema: A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA. Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history

of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation

### CONTRAINDICATIONS

- In the last 6 months, experienced 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

## Clinical Pharmacology

### MECHANISMS OF ACTION

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Ozanimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which ozanimod exerts therapeutic effects in multiple sclerosis is unknown but may involve the reduction of lymphocyte migration into the central nervous system.

## Dose & Administration

### ADULTS

Initial: 0.23 mg once daily on days 1 through 4; then 0.46 mg once daily on days 5 through 7; maintenance dose: 0.92 mg once daily starting on day 8.

Note: If a dose is missed during the 2-week titration period, reinitiate the titration regimen with 0.23 mg once daily. If a dose is missed after the first 2 weeks of treatment continue with treatment as planned.

### PEDIATRICS

Safety and effectiveness in pediatric patients have not been established.

### GERIATRICS

Clinical studies of ZEPOSIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### RENAL IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling.

### HEPATIC IMPAIRMENT

The effect of hepatic impairment on the pharmacokinetics of the ozanimod major active metabolites is unknown. Use is not recommended in patients with hepatic impairment.

## Product Availability

### DOSAGE FORM(S) & STRENGTH(S)

Zeposia is available as capsules in the following dosage strengths (0.23 mg, 0.46 mg, 0.92mg).