once-daily ZEPOSIA™ (ozanimod) | 0.92 mg capsules

FOR YOUR PATIENTS WITH RMS[1]

PROTECT IT BEFORE IT'S GONE

WITH ZEPOSIA, YOU HAVE THE POWER TO HELP PRESERVE THEIR MOST VALUABLE RESOURCE[1]

- **Powerful efficacy** in reducing ARR, GdE lesions, and new/enlarging T2 lesions vs Avonex®[1a]

- **Data on brain volume and cognitive processing speed (SDMT)** in secondary, exploratory endpoints and post hoc analysis[2,3b]

- **Safety comparable to Avonex in overall incidence of adverse reactions[2,3c]** and generally similar safety demonstrated in the long-term extension study[4d]

[a]**Study designs: SUNBEAM** (1 year; N=1346) and **RADIANCE** (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-µg intramuscular injection. **Primary endpoint:** ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs. 0.35, respectively) and by 38% at 2 years (0.17 vs. 0.28, respectively). **Secondary endpoints:** ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.[1-3]

[b]**Brain volume loss** was analyzed as secondary (whole brain volume loss) and exploratory endpoints (thalamic volume loss and cortical grey matter volume loss) in the SUNBEAM and RADIANCE trials. **Volume loss endpoints were not part of the statistical analysis hierarchy. SDMT** is a tool that measures cognitive processing speed and was analyzed in a post hoc analysis of SUNBEAM and DAYBREAK, an ongoing open-label extension study. The MSFC was a secondary endpoint made up of 3 components: 9-hole peg test (arm/hand function), timed 25-foot walk (ambulation), and SDMT (cognitive function). SUNBEAM SDMT post hoc: ZEPOSIA (n=427), Avonex (n=426) at Month 12. DAYBREAK SDMT post hoc (SUNBEAM participants only): ZEPOSIA (n=376) at Month 42. **SDMT was not part of the statistical analysis hierarchy for SUNBEAM and was analyzed descriptively in DAYBREAK.**

[c]**Adverse reactions:** Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 23%); hepatic transaminase elevation, 10% (vs 5%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. **Severe adverse reactions:** The rate of severe adverse reactions at 1 year for ZEPOSIA was 1.6% vs 2.2% for Avonex and the rate at 2 years for ZEPOSIA was 3.5% vs 4.3% for Avonex. **Serious adverse reactions:** The rate of serious adverse reactions at 1 year for ZEPOSIA was 2.9% vs 2.5% for Avonex and the rate at 2 years for ZEPOSIA was 6.5% vs 6.4% for Avonex.[1-3] Please see full Prescribing Information for additional SUNBEAM and RADIANCE data.

[d]**Study design: DAYBREAK** is an ongoing open-label extension (OLE) trial that enrolled participants from multiple randomized phase 1 to 3 studies, including SUNBEAM and RADIANCE. These data are presented as an interim analysis with a data cutoff of February 2, 2021. Patients evaluated in this analysis included those receiving ZEPOSIA 0.92 mg (n=881) who completed the randomized phase 1 to 3 trials. Primary objective evaluated the long-term safety of ZEPOSIA. Secondary objectives included ARR, new/enlarging T2 lesions, and GdE lesions. Endpoints were analyzed descriptively.[4-5]

Treatment-emergent adverse events (TEAEs): At the data cutoff (up to 5 years), the overall incidence of TEAEs for ZEPOSIA in the DAYBREAK OLE trial was 84.7%. The most common TEAEs with an incidence of at least 4% in patients treated with ZEPOSIA, sorted by decreasing incidence, were as follows: nasopharyngitis, 19.3%; headache, 15.6%; upper respiratory tract infection, 10.9%; ALC decreased, 8.9%; lymphopenia, 8.7%; back pain, 8.1%; gamma-glutamyl transferase increased, 5.9%; bronchitis, 5.8%; urinary tract infection, 5.8%; hypertension, 5.4%; respiratory tract infection, 5.4%; viral respiratory tract infection, 5.0%; and depression-related TEAEs, 4.9%. The rate of TEAEs leading to permanent treatment discontinuation was 2.7%. **Severe TEAEs:** The rate of severe TEAEs was 6.0%. **Serious TEAEs:** The rate of serious TEAEs was 11.7%.[4]

A relapse was defined as the occurrence of new or worsening neurological symptoms persisting for more than 24 hours attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.[2,3]

ALC=absolute lymphocyte count; ARR=annualized relapse rate; GdE=gadolinium enhancing; MS=multiple sclerosis; MSFC=Multiple Sclerosis Functional Composite; RMS=relapsing multiple sclerosis; SDMT=Symbol Digit Modalities Test.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.

INDICATION

ZEPOSIA® (ozanimod) 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.

IMPORTANT SAFETY INFORMATION

Contraindications:

- Patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a 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
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of 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. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA.

- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (Continued):

- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another S1P receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.
- In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.
- Use of live attenuated vaccines should be avoided during and for 3 months after treatment with ZEPOSIA. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

Progressive Multifocal Leukoencephalopathy (PML): PML is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

PML has been reported in patients treated with S1P receptor modulators, including ZEPOSIA, and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation.

If confirmed, treatment with ZEPOSIA should be discontinued.

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. 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 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 Mobitz type II second-degree or higher AV block, sick sinus syndrome, or sino-atrial heart block

Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease.

Fetal Risk: There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA.

Increased Blood Pressure: Increase in systolic pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

Respiratory Effects: ZEPOSIA may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy, if clinically indicated.

Macular Edema: S1P modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a S1P receptor modulator. If a ZEPOSIA-treated patient develops unexpected neurological or psychiatric symptoms or any symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation. Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended.

Severe Increase in Multiple Sclerosis (MS) Disability After Stopping ZEPOSIA: In MS, severe exacerbation 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 so patients should be monitored upon discontinuation.

Immune System Effects After Stopping ZEPOSIA: After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 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, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA.

Most Common Adverse Reactions (≥ 4%): upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

Use in Specific Populations: Hepatic Impairment: Use is not recommended.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.

References: 1. ZEPOSIA. Prescribing information. Bristol Myers Squibb; 2021. **2.** Comi G, Kappos L, Selmaj KW, et al; SUNBEAM Study Investigators. 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):1009-1020. **3.** Cohen JA, Comi G, Selmaj KW, et al; RADIANCE Trial Investigators. 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):1021-1033. **4.** Selmaj KW, Steinman L, Comi G, et al. Long-term safety and efficacy of ozanimod in relapsing multiple sclerosis: interim analysis of the DAYBREAK open-label extension study. Presented at: 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 13-15 October 2021; The Digital Experience. **5.** Selmaj KW, Steinman L, Comi G, et al. Long-term safety and efficacy of ozanimod in relapsing multiple sclerosis in DAYBREAK: an open-label extension study of ozanimod phase 1-3 trials. Presented at: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11-13, 2020; MSVirtual2020. Poster P0217.

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