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ZEPOSIA® (ozanimod), a Sphingosine 1-Phosphate Receptor Modulator for Relapsing Forms of Multiple Sclerosis

Sphingosine 1-phosphate (S1P) is an active phospholipid that regulates multiple cellular responses involved in immunity, heart rate, smooth muscle tone, and endothelial barrier function.¹ S1P receptors (S1PRs), which are composed of 7 transmembrane segments and are coupled to G proteins, are present in 5 subtypes (S1PR₁₋₅) and play an important role in egression of lymphocytes from lymph nodes.¹ Subtypes S1PR₁₋₃ are present in multiple tissue types, whereas S1PR₄ is expressed primarily in lymphoid tissue, and S1PR₅ is expressed in the spleen and oligodendrocytes.¹ B and T lymphocytes primarily express S1PR₁ (and S1PR₂ and S1PR₄ to a lesser extent), and S1PR modulators used for multiple sclerosis (MS) block the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which S1PR modulators exert a therapeutic effect in MS is unknown but may involve reduction of lymphocyte migration into the central nervous system.¹⁻⁴ Four S1PR modulators are currently available as disease-modifying therapeutic (DMT) options for relapsing forms of MS (clinically isolated syndrome [CIS], relapsing-remitting disease, and active secondary progressive disease). The therapeutic mechanism of action in MS is not fully known.²⁻⁵

ZEPOSIA, initially approved in the United States in 2020 based on results from the phase 3 SUNBEAM (NCT02294058)⁶ and RADIANCE trials (NCT02047734),⁷ binds with high affinity to S1PR₁ and S1PR₅ and is dosed orally once daily at a recommended maintenance dosage of 0.92 mg after a 7-day titration at treatment initiation (Figure 1^{2,8-13}).²

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.

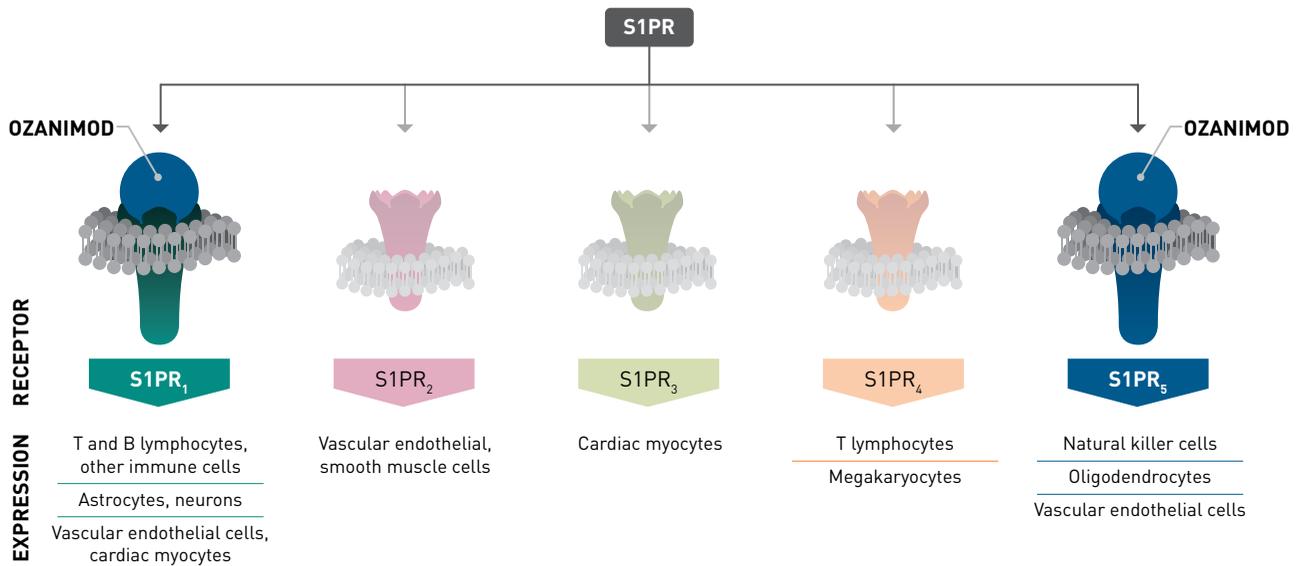
IMPORTANT SAFETY INFORMATION

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

For additional safety information,
please see the full **Prescribing Information and Medication Guide**.

Figure 1. Mechanism of Action of Ozanimod^{2,8-13}



S1PR, sphingosine 1-phosphate receptor.

SELECTIVITY AND INITIATION OF OZANIMOD

Ozanimod does not have affinity for S1PR₃.¹⁴ Following a 14-day titration regimen of once-daily doses of ozanimod 0.23 mg for 4 days, 0.46 mg for 3 days, 0.92 mg for 3 days, and 1.84 mg (2 times the maximum approved recommended dose) for 4 days in healthy subjects, ozanimod did not prolong the QTc interval to any clinically relevant extent.² Before initiating treatment with ozanimod, all patients require a recent complete blood count including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an

electrocardiogram (ECG) to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations. Patients without a confirmed history of varicella (chickenpox) or without documented varicella zoster virus (VZV) vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation. For patients with a history of uveitis or macular edema, an ophthalmic assessment is required. An uptitration scheme should be used to reach the maintenance dosage of ozanimod, as a transient decrease

IMPORTANT SAFETY INFORMATION (Continued)

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.

in heart rate and atrioventricular conduction delays may occur.² Coadministration of ozanimod with itraconazole (a P-gp and strong CYP3A inhibitor) does not result in clinically significant differences in pharmacokinetics of ozanimod and its major active metabolites (CC11273 and CC1084037).²

OZANIMOD CLINICAL TRIALS

SUNBEAM and RADIANCE

Trial Design

Ozanimod was evaluated in 2 randomized, double-blind, double-dummy, parallel-group, active comparator-controlled clinical trials of similar design in patients with relapsing forms of MS. Patients in study 1 (SUNBEAM) were treated until the last enrolled patient completed 1 year of treatment, and patients in study 2 (RADIANCE) were treated for 24 months.² Both studies included patients (aged 18–55 years) with a diagnosis of MS per the 2010 McDonald criteria and a relapsing clinical course (relapsing-remitting, progressive-relapsing, or secondary progressive). Patients also experienced 1 or more relapses within the prior year or 1 relapse within the prior 2 years with evidence of 1 or more gadolinium-enhancing lesions in the prior year; had an Expanded Disability Status Scale (EDSS) score from 0 to 5.0; and had no history of relapse or systemic corticosteroid or adrenocorticotropic hormone use from 30 days before screening up to randomization.^{2,6,7} Patients were excluded if they had primary progressive MS²; a resting heart rate less than 55 beats per minute (bpm) at screening; specific cardiac conditions (eg, recent myocardial infarction, stroke, prolonged QTcF interval)^{6,7}; or diabetes mellitus type 1 or uncontrolled diabetes mellitus type 2 with glycated hemoglobin greater than 9% (SUNBEAM) or greater than 7% (RADIANCE). Patients with diabetes who had significant comorbidities were also excluded.^{6,15}

In both the SUNBEAM and RADIANCE studies, patients were randomly assigned (1:1:1) to ozanimod 0.92 mg, ozanimod 0.46 mg (not approved for maintenance dose), or interferon β -1a 30 μ g.^{2,6,7} The dose of ozanimod was 0.92 mg and 0.46 mg given orally once daily.^{2,6,7}

There was a starting dose of 0.23 mg on days 1 to 4, followed by an escalation to 0.46 mg on days 5 to 7, and 0.92 mg on day 8 and thereafter.² The dose of interferon β -1a, the active comparator, was 30 μ g given intramuscularly once weekly.²

In the SUNBEAM trial, patients continued treatment until the last patient was treated for 12 months.¹⁶ Neurological evaluations were performed at baseline, every 3 months, and at the time of a suspected relapse.² Magnetic resonance imaging (MRI) was performed at baseline (SUNBEAM and RADIANCE), 6 months (SUNBEAM), 1 year (SUNBEAM and RADIANCE), and 2 years (RADIANCE).²

The primary end point for both studies was annualized relapse rate (ARR) over 12 or 24 months (SUNBEAM and RADIANCE, respectively).² Key secondary end points (at 12 and 24 months for SUNBEAM and RADIANCE, respectively) included the number of new or enlarging T2 brain MRI lesions over 12 and 24 months; the number of gadolinium-enhancing brain MRI lesions at 12 and 24 months; and the time to confirmed disability progression, defined as at least a 1-point increase from baseline EDSS score confirmed after 3 months and after 6 months.^{2,6,7} Confirmed disability progression was prospectively evaluated in a pooled analysis of SUNBEAM and RADIANCE.^{6,7}

Adverse events (AEs) were assessed at each visit.^{6,7} AEs of interest included cardiac abnormalities (eg, bradycardia, conduction abnormalities, or new ischemic changes on ECG), serious and opportunistic infections, hepatotoxicity (alanine transaminase or aspartate transaminase have at least 3 times the upper limit of normal), ophthalmic abnormalities (including macular edema), pulmonary function test abnormalities, and dermatological and other malignancies. Suicidality, which is increased in people with MS compared with the general population, was assessed at each visit.^{6,7}

Efficacy Results

Annualized Relapse Rates

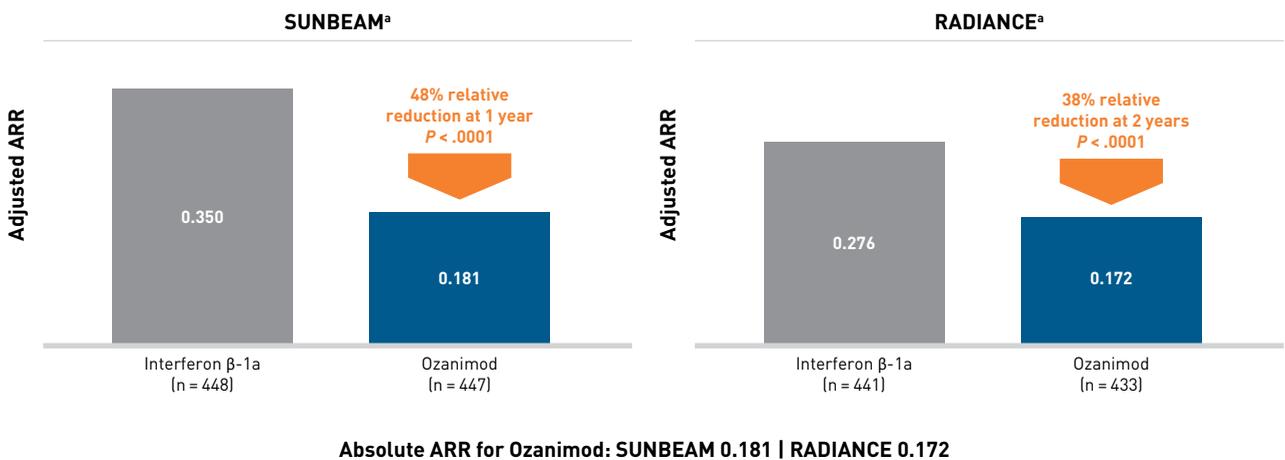
Both the SUNBEAM and RADIANCE trials met the primary end point of ARR.² In SUNBEAM, the ARRs were 0.181 with ozanimod versus 0.350 with interferon β -1a after at least 1 year of treatment, resulting in a 48% relative reduction.² In RADIANCE, the ARRs were 0.172

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.

Figure 2. Annualized Relapse Rate: Ozanimod Versus Interferon β -1a in SUNBEAM and RADIANCE Clinical Trials^{2,6,7}



ARR, annualized relapse rate; MS, multiple sclerosis.

^aA 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.

with ozanimod versus 0.276 with interferon β -1a after 2 years of treatment, resulting in a 38% relative reduction.² In both studies, a similar reduction on the ARR compared with interferon β -1a was observed in exploratory subgroups defined by sex, age, prior non-steroid therapy for MS, and baseline disease activity.² The efficacy differences of ozanimod versus interferon β -1a in SUNBEAM and RADIANCE can be seen in [Figure 2](#).^{2,6,7}

New or Enlarging T2 Lesions

Both the SUNBEAM and RADIANCE trials met the key secondary end point of number of new or enlarging MRI T2 hyperintense lesions.^{2,6,7} In SUNBEAM, the adjusted mean number of new or enlarging T2 lesions

per scan over 12 months was 1.47 with ozanimod versus 2.84 with interferon β -1a, resulting in a 48% relative reduction.² In RADIANCE, the adjusted mean number of new or enlarging T2 lesions per scan over 24 months was 1.84 with ozanimod versus 3.18 with interferon β -1a, resulting in a 42% relative reduction.²

Gadolinium-Enhancing Lesions

Both the SUNBEAM and RADIANCE trials met the key secondary end point of number of MRI T1 gadolinium-enhancing lesions.^{2,6,7} In SUNBEAM, the adjusted mean number of gadolinium-enhancing lesions at 12 months was 0.16 with ozanimod versus 0.43 with interferon β -1a, resulting in a 63% relative reduction.² In RADIANCE,

IMPORTANT SAFETY INFORMATION (Continued)

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.

the adjusted mean number of gadolinium-enhancing lesions at 24 months was 0.18 with ozanimod versus 0.37 with interferon β -1a, resulting in a 53% relative reduction.²

Confirmed Disability Progression

A key secondary end point in the SUNBEAM and RADIANCE trials was the time to confirmed disability progression, which was defined as at least a 1-point increase from baseline EDSS score confirmed after 3 months and after 6 months.^{2,6,7} This end point was evaluated in a pooled analysis of the SUNBEAM and RADIANCE trials.² In the pooled analysis, the proportions of patients with confirmed disability progression at 3 months were not statistically significantly different between treatment groups (7.6% of ozanimod-treated patients versus 7.8% of interferon β -1a-treated patients; $P = 0.77$).²

Safety

Overall Incidence of Adverse Events

In SUNBEAM, the overall incidence of AEs was 59.8% among patients treated with ozanimod and 75.5% among patients treated with interferon β -1a. In RADIANCE, the overall incidence of AEs was 74.7% among patients treated with ozanimod and 83.0% among patients treated with interferon β -1a.^{6,7} The AEs presented in **Table 1** are based on safety information from 882 patients treated with ozanimod 0.92 mg and 885 patients treated with interferon β -1a 30 μ g.² Because clinical trials are conducted under widely varying conditions, AE rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.²

Discontinuation Rates

In SUNBEAM and RADIANCE, 94% and 90% of ozanimod-treated patients completed the study versus 92% and 85% of those treated with interferon β -1a, respectively.² The discontinuation rates due to AEs were 3% or less with ozanimod in both SUNBEAM and RADIANCE.^{6,7} Additional data on discontinuations are presented in **Table 2** and **Table 3**.^{6,7,15,16}

Table 1. Adverse Events With an Incidence of at Least 2% in Ozanimod-Treated Patients and at Least 1% Greater Than With Interferon β -1a (Pooled SUNBEAM and RADIANCE)²

Adverse events	SUNBEAM and RADIANCE ^a	
	Ozanimod 0.92 mg n = 882	Interferon β -1a 30 μ g n = 885
Upper respiratory infection ^b	26%	23%
Hepatic transaminase elevation ^c	10%	5%
Orthostatic hypotension	4%	3%
Urinary tract infection	4%	3%
Back pain	4%	3%
Hypertension ^d	4%	2%
Upper abdominal pain	2%	1%

^aData are not an adequate basis for comparison of rates between ozanimod and the active control.

^bIncludes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis.

^cIncludes the following terms: alanine aminotransferase increased, γ -glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased.

^dIncludes hypertension, essential hypertension, and orthostatic hypertension.

Serious Infections, Severe Adverse Events, and Serious Adverse Events

In the SUNBEAM and RADIANCE trials, the overall rate of infections (35%) with ozanimod was similar to that of interferon β -1a.² The rate of serious infections was 1% with ozanimod versus 0.8% with interferon β -1a.² The rate of herpes zoster AEs was 0.6% with ozanimod versus 0.2% with interferon β -1a.² Ozanimod caused a reduction in peripheral blood lymphocyte count; it may increase risk of infection.² Ozanimod increased the risk of viral upper respiratory tract infections, urinary tract infections, and herpes zoster.²

IMPORTANT SAFETY INFORMATION (Continued)

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

Table 2. Discontinuations Due to Treatment-Emergent Adverse Events in SUNBEAM (≥ 1 Year)^{6,16}

	Ozanimod 0.92 mg (n = 448), n (%)	Interferon β -1a 30 μ g (n = 445), n (%)
Discontinuations due to treatment-emergent adverse events	13 (2.9)	16 (3.6)
Events leading to discontinuation in > 1 patient		
Back pain	2 (0.4)	1 (0.2)
Headache	2 (0.4)	0
Alanine aminotransferase increased	2 (0.4)	0

Table 3. Discontinuations Due to Treatment-Emergent Adverse Events in RADIANCE (2 Years)^{7,15}

	Ozanimod 0.92 mg (n = 434), n (%)	Interferon β -1a 30 μ g (n = 440), n (%)
Discontinuations due to treatment-emergent adverse events	13 (3.0)	18 (4.1)
Events leading to discontinuation in > 1 patient		
Alanine aminotransferase increased	2 (0.5)	3 (0.7)
Urticaria	2 (0.5)	0

Initiation of ozanimod should be delayed in patients with an active infection until the infection is resolved.² Patients should be informed that they may be more likely to get infections, some of which could be life-threatening, when taking ozanimod and for 3 months after stopping it, and that they should contact their physician if they develop symptoms of infection.² Because the elimination of ozanimod after

discontinuation may take up to 3 months, patients should continue to be monitored for infections throughout this period.²

Interruption of treatment with ozanimod should be considered if a patient develops a serious infection.² Patients should be advised that progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain, has been reported in patients treated with S1PR modulators, including ZEPOSIA, and other multiple sclerosis (MS) therapies and has been associated with some risk factors. If PML is suspected, treatment with ozanimod should be suspended until PML has been excluded by an appropriate diagnostic evaluation.² If PML is confirmed, treatment with ozanimod should be discontinued.²

In SUNBEAM, the overall rate of severe AEs was 2.2% with interferon β -1a and 1.6% with ozanimod.⁶ In RADIANCE, the overall rate of severe AEs was 4.3% with interferon β -1a and 3.5% with ozanimod.⁷ In SUNBEAM, the overall rate of serious AEs was 2.5% with interferon β -1a and 2.9% with ozanimod.⁶ In RADIANCE, the overall rate of serious AEs was 6.4% with interferon β -1a and 6.5% with ozanimod.⁷

Absolute Lymphocyte Counts

Ozanimod causes a mean reduction in peripheral blood lymphocyte count because of reversible sequestration of lymphocytes in lymphoid tissues. Ozanimod may therefore increase susceptibility to infections.² A recent (ie, within 6 months or after discontinuation of prior MS therapy) complete blood count including lymphocyte count should be obtained before initiation of ozanimod.² In active-controlled MS clinical trials, mean lymphocyte counts decreased to approximately 45% of baseline at 3 months, and low lymphocyte counts were maintained during treatment with ozanimod. Mean blood lymphocyte counts were approximately 0.8×10^9 cells/ μ L.² The proportion of patients who experienced lymphocyte counts less than 0.2×10^9 cells/ μ L was 3.3% with ozanimod, with values generally resolving to greater than 0.2×10^9 cells/ μ L while remaining on treatment. After discontinuing ozanimod, the median time to recovery of peripheral blood lymphocytes to the normal range was 30 days; approximately 90% of patients were in the normal range within 3 months.²

IMPORTANT SAFETY INFORMATION (Continued)

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.

Day 1 Heart Rate

Ozanimod may cause a transient decrease in heart rate on initiation of dosing. An uptitration schedule of ozanimod 0.23 mg followed by doses of 0.46 mg and 0.92 mg attenuates the magnitude of heart rate reductions.² Initiation of ZEPOSIA without titration may result in greater decreases in heart rate.² In the SUNBEAM and RADIANCE trials, the greatest mean reduction from baseline in heart rate on day 1 (after the initial dose of ozanimod 0.23 mg) was 1.2 bpm, which occurred at hour 5 and returned to near baseline at hour 6.² Across the SUNBEAM and RADIANCE trials, heart rates below 40 bpm were not observed.² After day 1, the incidence of bradycardia was 0.8% for patients on ozanimod versus 0.7% for patients on interferon β -1a.² With uptitration, no second- or third-degree atrioventricular blocks were reported with ozanimod.²

DAYBREAK Trial

DAYBREAK (NCT02576717) is an ongoing, open-label extension trial that enrolled participants from multiple, randomized, phase 1 to 3 studies including SUNBEAM and RADIANCE. The primary objective was to evaluate long-term safety of ozanimod. Secondary objectives included ARR, new/enlarging T2 lesions, and gadolinium-enhancing lesions. End points were analyzed descriptively. Results presented are from an interim analysis with a data cutoff of December 20, 2019. The patient population evaluated in this analysis included those receiving ozanimod 0.92 mg (n=846) who completed the randomized phase 1 to 3 trials. Exposure to ozanimod 0.92 mg in DAYBREAK was for up to 3 years; study period includes DAYBREAK day 1 through last treatment date or the data-cutoff date.¹⁷

Primary End Point: Treatment-Emergent Adverse Events

Table 4 provides a summary of the treatment-emergent adverse events (TEAEs) in DAYBREAK in patients treated with ozanimod, and **Table 5** lists the TEAEs that occurred in 4% or more of patients treated with ozanimod. Safety findings for up to 3 years were generally similar to previous studies of ozanimod.¹⁷

Table 4. Summary of Treatment-Emergent Adverse Events in DAYBREAK in Patients Treated With Ozanimod¹⁸

	Ozanimod (n = 846)
Any TEAE	80.6%
Severe TEAEs	4.6%
Serious TEAEs	9.5%
TEAEs leading to permanent treatment discontinuation	1.7%

TEAE, treatment-emergent adverse event.

Table 5. Treatment-Emergent Adverse Events That Occurred in at Least 4% of Patients Treated With Ozanimod¹⁷

	Ozanimod (n = 846)
Nasopharyngitis	17.1%
Headache	14.1%
Upper respiratory tract infection	9.5%
Lymphopenia	8.2%
Absolute lymphocyte count decreased	8.2%
Back pain	6.6%
Urinary tract infection	5.0%
γ -glutamyl transferase increased	4.7%
Hypertension	4.3%

Annualized Relapse Rate

ARR was the primary end point for SUNBEAM and RADIANCE and a secondary end point for DAYBREAK. As described previously, the ARRs were 0.181 in SUNBEAM and 0.172 in RADIANCE.² In DAYBREAK, the ARR was analyzed descriptively as a secondary end point and was 0.108.¹⁷

IMPORTANT SAFETY INFORMATION (Continued)

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.

Table 6. S1PR Modulators Vary in Trial Design^{2-5,a}

	Fingolimod		Siponimod	Ozanimod		Ponesimod	
	Study 1	Study 2	Study 1	Study 1	Study 2	Study 1	
Trial design	2-year placebo-controlled trial	1-year active-controlled trial	Time-to-event, placebo-controlled trial	1-year active-controlled trial	2-year active-controlled trial	2-year active-controlled trial	
Key inclusion criteria	<ul style="list-style-type: none"> • RRMS • ≥ 2 clinical relapses in 2 years prior or ≥ 1 clinical relapse during 1 year prior • EDSS score, 0–5.5 		<ul style="list-style-type: none"> • SPMS • Disability progression in 2 years prior • No relapse in 3 months prior • EDSS score, 3.0–6.5 		<ul style="list-style-type: none"> • RMS • ≥ 1 relapse within prior year or ≥ 1 relapse within prior 2 years with GdE lesion in prior year • EDSS score, 0–5.0 		<ul style="list-style-type: none"> • RMS • ≥ 1 relapse within prior year, or 2 relapses within prior 2 years, or ≥ 1 GdE lesion in prior 6 months or at baseline • EDSS score, 0–5.5
Intervention	Fingolimod 0.5 mg and 1.35 mg		Siponimod 2 mg	Ozanimod 0.92 mg		Ponesimod 20 mg	
Comparator	Placebo	Interferon β-1a	Placebo	Interferon β-1a		Teriflunomide	

EDSS, Expanded Disability Status Scale; GdE, gadolinium-enhancing; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; S1PR, sphingosine 1-phosphate receptor; SPMS, secondary progressive multiple sclerosis.

^aThere are no head-to-head comparison trials against oral competitors. No comparative claims can be made.

New/Enlarging T2 and Gadolinium-Enhancing Lesions

The number of new or enlarging T2 lesions was a secondary end point for SUNBEAM and RADIANCE,^{2,6,7} and it was a secondary end point that was analyzed descriptively in DAYBREAK. At month 12, the mean number of new or enlarging T2 lesions with ozanimod 0.92 mg was 2.7 in SUNBEAM and RADIANCE. During DAYBREAK, the mean number of new or enlarging T2 lesions was 2.1 at month 12, 1.9 at month 24, and 1.8 at month 36.¹⁷

The number of gadolinium-enhancing lesions was a secondary end point for SUNBEAM and RADIANCE, and it was a secondary end point that was analyzed descriptively in DAYBREAK.^{2,6,7} At month 12, the mean number of gadolinium-enhancing lesions with ozanimod 0.92 mg was 0.2 in SUNBEAM and RADIANCE. During DAYBREAK, the mean number of gadolinium-enhancing lesions was 0.3 at month 12, 0.4 at month 24, and 0.3 at month 36.¹⁷

S1PR modulators approved by the United States Food and Drug Administration and their respective clinical trials within the MS spectrum can be seen in [Table 6](#).^{2-5,a}

SUMMARY

S1PRs, which are composed of 7 transmembrane segments and are coupled to G proteins, are present in 5 subtypes (S1PR₁₋₅) and play an important role in egression of lymphocytes from lymph nodes.¹ Four S1PR modulators are currently available as DMT options for relapsing forms of MS (CIS, relapsing-remitting disease, and active secondary progressive disease) and block the capacity of lymphocytes to egress from lymph nodes, which reduces the number of lymphocytes in peripheral blood.²⁻⁵ The therapeutic mechanism of action in MS is not fully known but may involve reduction of lymphocyte migration

IMPORTANT SAFETY INFORMATION (Continued)

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.

into the central nervous system.²⁻⁵ Based on results from the phase 3 SUNBEAM (NCT02294058)⁶ and RADIANCE trials (NCT02047734),⁷ ozanimod binds with high affinity to S1PR₁ and S1PR₅ and is dosed orally once daily at a recommended maintenance dosage of 0.92 mg after a 7-day titration at treatment initiation.² •

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IMPORTANT SAFETY INFORMATION (Continued)

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.

Expert Perspectives on the Treatment Landscape of Relapsing-Remitting Multiple Sclerosis: a Q&A With Jeffrey English, MD



JEFFREY ENGLISH, MD

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***The American Journal of Managed Care®*: How has the treatment landscape of relapsing-remitting multiple sclerosis (MS) evolved over time?**

Jeffrey English, MD: When I go back to residency and medical school, I can say to patients and providers that I was there when there was nothing. Just at the beginning of my practice, we only had 1 or 2 medications. Back then it was about asking, “How do you keep people on therapies, considering the adverse effect profile?” It has really evolved into having therapies that we think are more effective. Then we began asking, “What am I really doing to this person’s immune system? What kind of things do I have to worry about down the road?”

There are a lot of data over the last 5 or 6 years that involve patients we consider high risk from the get-go versus your regular patients with MS. I think the whole treatment landscape in the beginning for routine MS seems very wide open. You can really pick medications and therapies that you think are good for the patient with more aggressive disease from the outset.

I was at a meeting once, and we were talking about a treatment diagram. I explained, “Well, if you take any individual, and you say if they are high risk or low risk, they may respond better to one medication versus another. There are so many patient factors in MS that come into it, like childbearing age versus not, young versus old, who the providers are, and what kind of support network patients have. I could take 10 people who look identical who could go on drug X, Y, and Z, as there are so many other variables. In the end, for each patient type, the decision could be one of many choices of therapies based on those variables.” It’s a good problem to have now, since we have over 20 therapies. From a provider standpoint, you probably have doctors and nurse practitioners who gravitate toward a handful of medicines that they use a lot, that they’re comfortable with from experience. That could differ from place to place. Because it’s so complex, it’s hard for most places that are not big MS centers to keep up with all the therapies.

***AJMC®*: What do you think payers should know regarding the main concerns regarding MS treatment with access that you hear from your patients?**

Jeffrey English, MD: From the patient standpoint, it’s copay. Again, the generics have hurt that, too, where some of my patients switch to 1 of the generics, and it’s free. They have no copay, or

IMPORTANT SAFETY INFORMATION (*Continued*)

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.

there's a \$5 copay. With other insurance companies, it is a \$2000 monthly copay for the same medicine, which is obviously not affordable. Patients with medications are concerned about their copay, and they're also concerned about adverse effects. I think we can coach them through the adverse effects. We can't really coach them through the copay.

AJMC®: How do you think those perspectives of your patients influence their treatment decisions?

Jeffrey English, MD: Most patients, when they're newly diagnosed, don't ask me initially about the cost. They're really digesting it, and they want something that's effective, but they're really worried about adverse effects and risks. People know more about the immune system now because of COVID-19 than they ever knew before. I think they're worried about the adverse effects and whether or not the drug is going to work for them. Then they have to go through the process to find out about the copay. And they may also be concerned about me putting them on something where they have to come to the office for the treatment or they have a lot of blood monitoring. How is it going to interfere with the patient's life depending upon work status? Things like that. I think it's the risk and lifestyle change that affects them first before the copay-type stuff affects them.

AJMC®: In your experience, how does the route of administration affect adherence?

Jeffrey English, MD: I think we do a good job with the infusible therapies of finding infusion centers located near our patients who are far away. Even our patients here often have to go to 2 or 3 other places just because of site of care issues with insurance. It's a lot of work for our staff. A lot of the companies will help out a little bit, but that's a lot of work to do. But at a center

like ours, we can do it. I imagine it's more challenging for other, smaller groups. And again my knee-jerk reaction is probably what everybody would think; you would rather be on a pill than a shot. I think this is probably the case the majority of the time, but not all the time.

I was talking to a group of patients the other night, and that was one of the main things we talked about. There are certain deal breakers people have with certain adverse effects, and there are deal breakers that patients have with the administration. For us, there are deal breakers in medications we just don't think are appropriate. Most of our patients prefer oral therapies and intravenous (IV) therapies. I have a few people who have had gastric bypass and have a feeding tube, where all kinds of prior oral pills didn't work for them. Or, they have poor venous access, and they really want to gravitate towards the injectables.

AJMC®: What factors do you consider when choosing the appropriate treatment plan for a patient?

Jeffrey English, MD: The first thing I think about is, "Where do I put this patient? To what extent am I worried about them?" Then that puts me into certain categories of therapies I would think about, and we talk about risks and route of administration. I saw someone today whom I've been taking care of for 15 years who has been on 1 or 2 therapies and is an antitherapeutic kind of person. I know things about their heart and their gut and all these things that I've learned about them over the years, which is going to really push me adverse effect-wise one way versus the other.

I think efficacy is probably the first thing. There are definitely studies that always look at what the doctor cares about and what the patient cares about, and they're not exactly the same thing. The doctors are very high on relapse rate and disability. Patients also care about relapse rates and worsening, but adverse effects and route of administration are also very high on their lists.

IMPORTANT SAFETY INFORMATION (Continued)

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.

“That’s the reason I use ZEPOSIA for appropriate patients: data show it is effective, and there are support services for pre-initiation requirements. ZEPOSIA keeps lymphocyte counts near the lower limit of normal and has low incidence of discontinuation due to adverse events.”

The once-a-day drugs matter very much, so there are some orals, like ZEPOSIA® (ozanimod), we will gravitate toward. In addition to once-a-day dosing, tolerability is also very important. ZEPOSIA had low rates of discontinuation that were due to adverse events.

The S1PR modulators are one class of medication I would use, as they are effective. There are no head-to-head trials, so we can’t tell you that S1PR modulators are better than some of the other treatments, other than ones that have been studied. Doctors also consider treatment selection from a risk standpoint. For a huge range of our patients, there are some that you want to go right to IV therapies, and that’s a different class of person. That’s the reason I use ZEPOSIA for appropriate patients: data show it is effective, and there are support services for the pre-initiation requirements. ZEPOSIA keeps lymphocyte counts near the lower limit of normal and has a low incidence of discontinuation due to adverse events.

AJMC®: As new drug treatments come to the market, what types of evidence are you looking for?

Jeffrey English, MD: I like the statement that somebody said at some point, “We pretty much have cornered the market on this inflammation relapse thing.” We have all these different mechanisms, and, again, they’re going to be effective in a large number of people. Is there going to be something that comes out that shows a drastic improvement over what we already have? That’s going to be a big game-changer and kind of hard to prove, because you’re going against known therapies and not placebo. It would be great if someone can do something that shows improvement in quality of life or even remyelination ... I’m a little over halfway through my career and I’m hoping sometime soon we’ll have reparative therapies and things like that to use.

I tell patients that all of these drugs are effective in the right person; I just don’t know who you are yet until I’ve tried it with you. I’m big on safety. When you have a class like the S1PR modulators that have been around awhile, it’s very helpful. This differs from a new class of drugs that comes out or a new group within a class, as you can’t extrapolate and say it has similar safety. You have a pretty good idea that it’s probably not going to have anything overly rare pop up. When a whole new class of drugs comes out, I’m more interested in how safe it is. As far as efficacy goes, for example, if you had a product with a 1% relapse rate reduction and a new one comes out with a 99% relapse rate reduction, then obviously that’s going to be very impressive. Most of the time, they’re within a certain range. Patients really care about how long things have been out for unless they’re in real dire straits and we have to put them on something regardless.

AJMC®: How long does a new treatment need to be available before you feel comfortable prescribing it? What are you looking for in the drug trials that come out for new treatments?

IMPORTANT SAFETY INFORMATION (Continued)

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.

Jeffrey English, MD: I feel comfortable using therapies right away from an MS standpoint. Now if you ask me about epilepsy or Parkinson disease or something like that, I'm probably like, "Whatever my expert partner says." They've had a lot of experience with not all of the drugs, but most of them. We have been in most of the MS clinical trials. I'm the medical director now, but I used to be the research director, and I was using these therapies for years before a lot of them were approved. If a new drug is coming out, I really want to sit down with the medical science liaison, and I want to go over mechanism of action, because I want to know what I'm doing to the person's body. I've always, even before this role, come up with treatment protocols and things that the nurses and medical assistants had to do before and during therapies, so that is really important to me. Physicians at MS centers tend to be earlier adopters, because we'll have larger numbers of

patients who have failed so many other things that really don't have anything available. I'll feel very comfortable putting such patients on those agents once I understand the risks and mechanisms of action.

I really like MRI and relapse rate reduction data. Disability data often fluctuates as to how it is being measured. In an MS center like mine, we go into the weeds with these things with brain atrophy and various MRI metrics and things like that. When a new treatment is first launched, you hear: relapsed rate reduction, MRI, disability progression. Those are the standard need-to-know disease activities. In the end, we love to hear what is happening to the lymphocyte counts, what we think is happening biologically, the MRI data, and explore any atrophy data, and information like this is interesting to clinicians. Certainly, with ZEPOSIA, we had that data when it launched. •

IMPORTANT SAFETY INFORMATION (*Continued*)

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.

