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

Discover an oral therapy for your patients with relapsing forms of multiple sclerosis (MS)[1]...

ZEPOSIA—FOCUSED ON WHAT COUNTS

Indication

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.

IMPORTANT SAFETY INFORMATION

Contraindications:

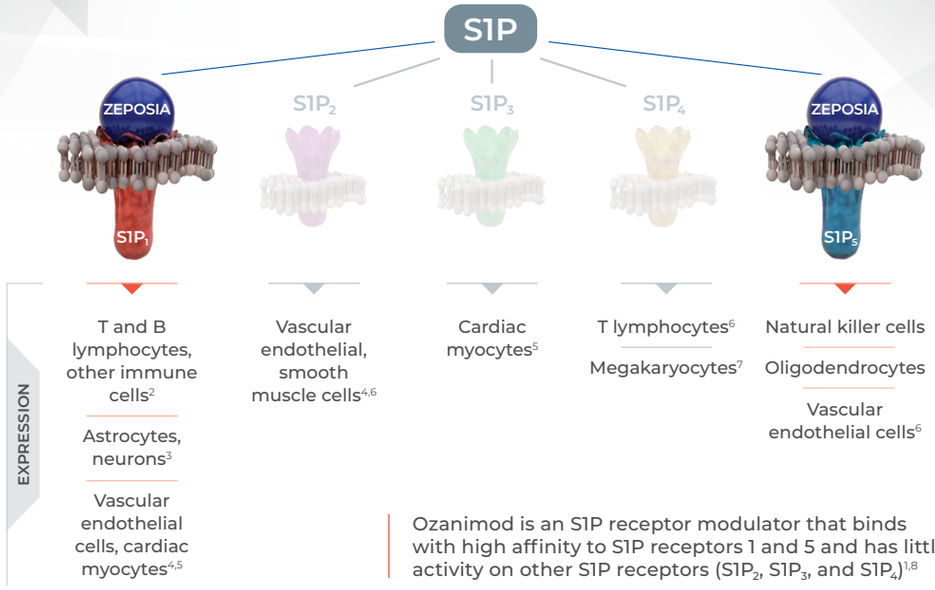
- Patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

Bristol Myers Squibb™

ZEPOSIA—Rediscover What S1P Therapy Can Mean for Your Patients

An S1P Optimized to Target With Selectivity



Ozanimod is an S1P receptor modulator that binds with high affinity to S1P receptors 1 and 5 and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$)[1,8]

ZEPOSIA blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood[1]

The mechanism by which ZEPOSIA exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the central nervous system.[1]

S1P=sphingosine-1-phosphate.

IMPORTANT SAFETY INFORMATION (CONTINUED)

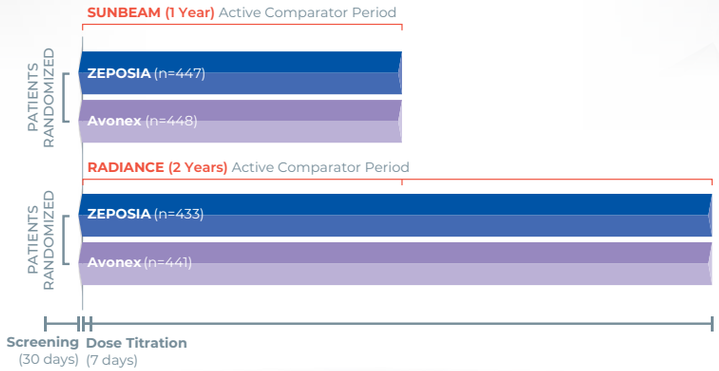
Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before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

Robust Data From 2 Clinical Trials With More Than 2600 Patients

The Largest Number of Patients With RMS Studied in Pivotal Head-to-Head Trials With an Active Comparator (N=2659)[9,10a]

Study Design



Baseline Characteristics

Baseline characteristics remained consistent across both studies[1,9,10b]

	Mean Age	Median EDSS Score	Mean Time Since Initial MS Diagnosis	Mean Number of Relapses in Previous 12 Months
SUNBEAM	35 Years	2.5	3.7 Years	1.3
RADIANCE	36 Years	2.5	3.8 Years	1.3

	Mean GdE Lesion Count	Mean T2 Lesion Count	Mean % of Patients Previously Treated With DMTs[c]
SUNBEAM	1.8	54	31%
RADIANCE	1.7	48	29%

KEY INCLUSION CRITERIA[9,10]

- Ages 18 to 55
- EDSS score of 0.0 to 5.0
- Patients who had experienced at least 1 relapse within the prior year before screening, or 1 relapse within the prior 2 years before screening with evidence of at least a GdE lesion in the prior year
- Clinically stable, with no relapse or corticosteroid treatment 1 month prior to screening until randomization

KEY EXCLUSION CRITERIA[9,10]

- Patients with primary progressive MS
- Disease duration >15 years with an EDSS score of ≤2.0
- Specific cardiac conditions (eg, recent MI, stroke, prolonged QTcF interval)
- Resting heart rate <55 bpm at screening
- Diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c >9% (SUNBEAM) or >7% (RADIANCE), or patients with diabetes who had significant comorbidities

[a]2659 patients includes all 3 arms of the study: the 0.92-mg dose of ZEPOSIA, the 0.46-mg dose of ZEPOSIA (not approved for maintenance dose), and the 30-µg dose of Avonex.[9,10]
[b]Baseline characteristics include the 0.92-mg dose of ZEPOSIA and the 30-µg dose of Avonex. The 0.46-mg dose of ZEPOSIA (not approved for maintenance dose) is not included.
[c]DMT includes a range of non-steroid therapies such as interferon beta-1a, pegylated interferon beta-1a, interferon beta-1b, glatiramer acetate, daclizumab, dimethyl fumarate, teriflunomide, and mitoxantrone (SUNBEAM only).
bpm=beats per minute; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; GdE=gadolinium enhancing; MI=myocardial infarction; QTcF=corrected QT interval using Fridericia's formula; RMS=relapsing multiple sclerosis.

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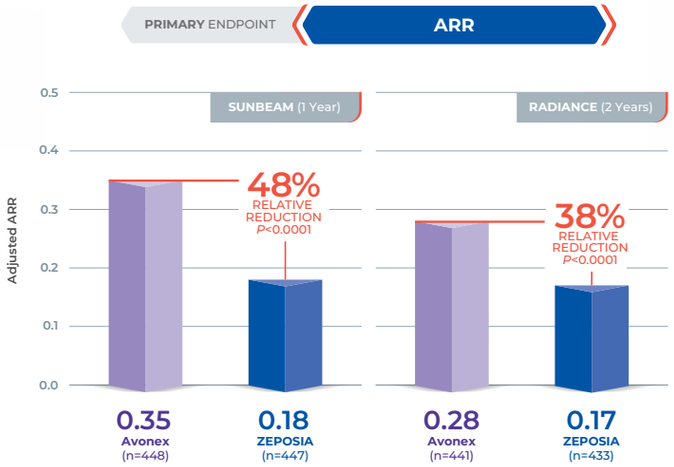
ZEPOSIA Delivers Powerful Efficacy vs Avonex

Proven Superior vs Avonex in Reducing ARR[1a]

Active Comparator | 2 Pivotal Head-to-Head Trials



Absolute ARR for ZEPOSIA

SUNBEAM 0.18 | RADIANCE 0.17

[a]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.[9,10]

ARR=annualized relapse rate.

Most Patients Experienced ZERO Relapses

The Majority of Patients Had No Relapses in Clinical Trials[1a]

Percent of Patients Who Were Without Relapse

SUNBEAM (1 Year)

78% of patients treated with ZEPOSIA (n=447) were without relapse vs 66% of patients treated with Avonex (n=448)

RADIANCE (2 Years)

76% of patients treated with ZEPOSIA (n=433) were without relapse vs 64% of patients treated with Avonex (n=441)

The mean number of relapses experienced during the 12 months prior to initiating therapy was

1.3 for both SUNBEAM and RADIANCE[1]

[a]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.[9,10]

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.
- Progressive Multifocal Leukoencephalopathy (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. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML 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, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued
- 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

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 sinoatrial heart block

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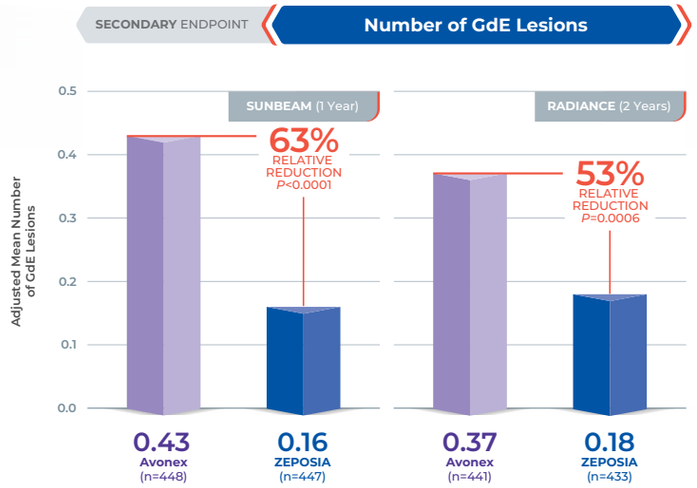
ZEPOSIA—Proven Superior With Up to 63% Fewer GdE Lesions vs Avonex

Significant Reductions vs Avonex Across All Secondary Measures of MRI Activity[1]

Active Comparator | 2 Pivotal Head-to-Head Trials



The mean number of GdE lesions observed in patients at baseline for both ZEPOSIA and Avonex was 1.8 in SUNBEAM and 1.7 in RADIANCE[9,10]

In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12.[9]

In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[10]

IMPORTANT SAFETY INFORMATION (CONTINUED)

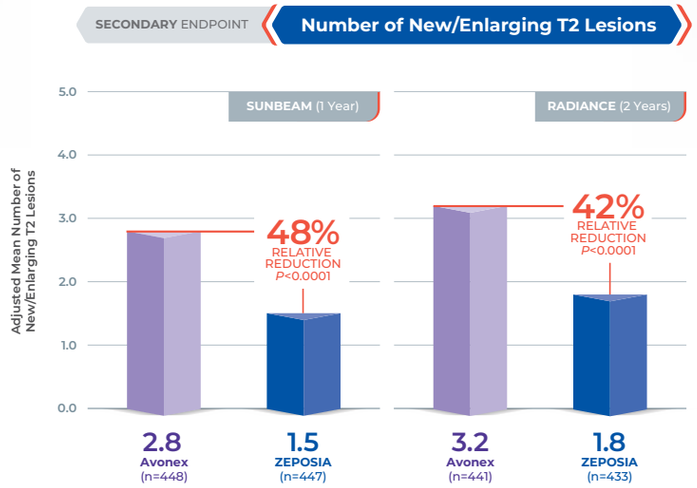
Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and 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

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

Proven Superior With Up to 48% Fewer New or Enlarging T2 Lesions vs Avonex

Significant Reductions vs Avonex Across All Secondary Measures of MRI Activity[1]

Active Comparator | 2 Pivotal Head-to-Head Trials



The mean number of T2 lesions observed in patients at baseline for both ZEPOSIA and Avonex was 54 in SUNBEAM and 48 in RADIANCE[9,10]

In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12.[9]

In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[10]

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

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9 of 10 Patients Showed No Confirmed 3-Month Disability Progression

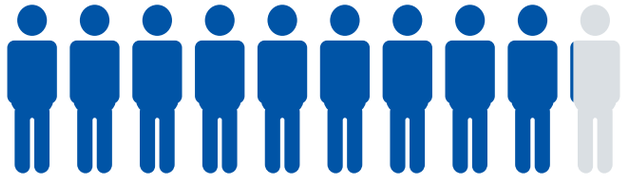
CDP Results From Clinical Trials[1]

SECONDARY ENDPOINT **Confirmed Disability Progression at 2 Years**

POOLED ANALYSIS[a]

92.4% vs **92.2%** for Avonex

Showed **No Confirmed** 3-Month **Disability Progression**



Patients classified as having no disability progression did not show sustained worsening for 3 consecutive months[1a]

7.6% of patients treated with ZEPOSIA (n=67/880) experienced 3-month CDP, as measured by EDSS, similar to Avonex (7.8%; n=69/889) (*P*=NS)[1,10]

Statistical significance was not reached for the pooled confirmed disability progression.[10]

[a]CDP was defined as at least a 1-point increase from baseline EDSS confirmed after 3 months and after 6 months. CDP was prospectively evaluated in a pooled analysis from the SUNBEAM (1 year) and RADIANCE (2 years) studies.[1]

CDP=confirmed disability progression; NS=nonsignificant.

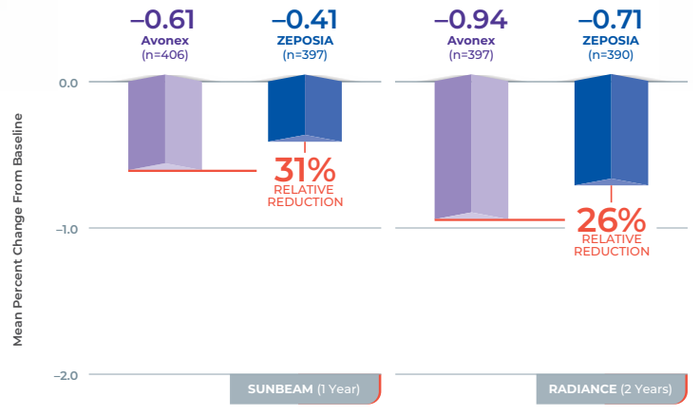
IMPORTANT SAFETY INFORMATION (CONTINUED)

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

ZEPOSIA Was Associated With

A Relative Reduction of Whole Brain Volume Loss of 31% at 1 Year and 26% at 2 Years[9,10]

SECONDARY ENDPOINT **Whole Brain Volume Loss**



Endpoint was not part of the statistical analysis hierarchy.[9,10]

In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12.[9]

In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[10]

Brain atrophy starts early and is an evolving measure of disease activity[11]

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

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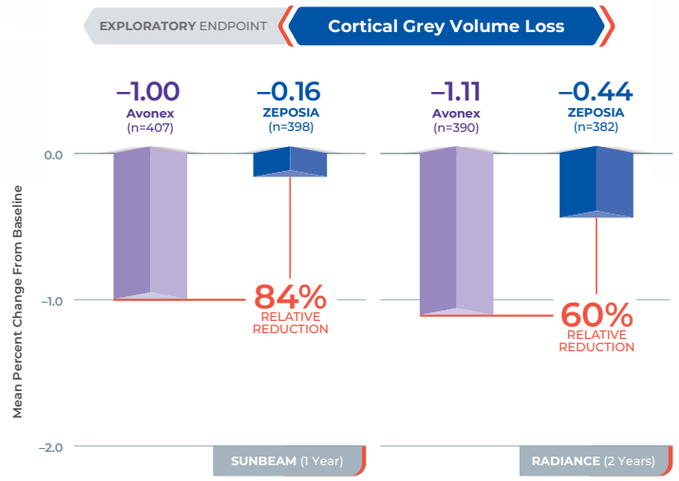
ZEPOSIA Was Associated With

A Relative Reduction of Cortical Grey Volume Loss of **84%** at 1 Year and **60%** at 2 Years[9,10]



Endpoint was not part of the statistical analysis hierarchy.[9,10]

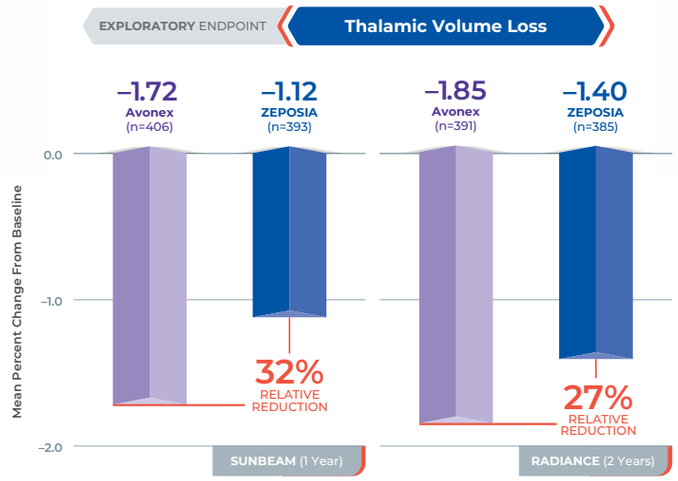
In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12.[9]

In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[10]

Grey Matter pathology affects both the cortex and the thalamus, a Deep Grey Matter structure[12,13]

ZEPOSIA Was Associated With

A Relative Reduction of Thalamic Volume Loss of **32%** at 1 Year and **27%** at 2 Years[9,10]



Endpoint was not part of the statistical analysis hierarchy.[9,10]

In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12.[9]

In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[10]

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

Severe Increase in Disability After Stopping ZEPOSIA: 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

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ZEPOSIA—A Safety Profile Comparable to Avonex in Overall Incidence of Adverse Reactions

Overall Incidence of Adverse Reactions Was Similar Across 2 Pivotal Head-to-Head Trials (N=2659)[9,10]

Overall Incidence of Adverse Reactions

SUNBEAM: Avonex **75.5%** | ZEPOSIA **59.8%** | **RADIANCE:** Avonex **83.0%** | ZEPOSIA **74.7%**

Adverse Reactions With an Incidence of at Least 2% in Patients Treated With ZEPOSIA and at Least 1% Greater Than Avonex[1a]

	SUNBEAM AND RADIANCE: POOLED DATA	
Adverse Reactions	**Avonex** n=885	**ZEPOSIA** n=882
Upper respiratory infection[b]	23%	26%
Hepatic transaminase elevation[c]	5%	10%
Orthostatic hypotension	3%	4%
Urinary tract infection	3%	4%
Back pain	3%	4%
Hypertension[d]	2%	4%
Abdominal pain upper	1%	2%

Adverse reactions are sorted by decreasing incidence in patients treated with ZEPOSIA.

For adverse reactions pertaining to liver function tests, increases were transient and generally resolved without discontinuation.[1]

Elevations of 3-fold the ULN or greater occurred in 5.5% of patients taking ZEPOSIA and in 3.1% of patients taking Avonex. The majority (79%) continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2 to 4 weeks.[1]

[a]Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.
[b]Includes 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.
[c]Includes the following terms: alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased.
[d]Includes hypertension, essential hypertension, and orthostatic hypertension.

ULN=upper limit of normal.

Consistently Low Discontinuation Rates vs Avonex

Discontinuation Rates Were ≤3% in 2 Large-Scale, Double-Blind Clinical Studies[9,10]

Overall Discontinuation Rates[1]

SUNBEAM: Avonex **8%** | ZEPOSIA **6%** | **RADIANCE:** Avonex **15%** | ZEPOSIA **10%**

Discontinuation Rates Due to Adverse Reactions

SUNBEAM (1 Year)

2.9% vs **3.6%** for Avonex

Adverse Reactions That Led to Discontinuation[9a]

Adverse Reactions	Avonex n=445	ZEPOSIA n=448
Alanine aminotransferase increased	0%	0.4%
Back pain	0.2%	0.4%
Headache	0%	0.4%

RADIANCE (2 Years)

3.0% vs **4.1%** for Avonex

Adverse Reactions That Led to Discontinuation[10a]

Adverse Reactions	Avonex n=440	ZEPOSIA n=434
Alanine aminotransferase increased	0.7%	0.5%
Urticaria	0%	0.5%

[a]Includes all adverse reactions ≥0.4% that led to discontinuation of ZEPOSIA.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

Indication

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.

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Consistent Rates of Serious Infections and Malignancies vs Avonex Through 2 Years

Results Were Consistent Across 2 Separate, Pivotal Head-to-Head Trials With More Than 2600 Patients[9,10]

Serious Infection Rates[9,10]

SUNBEAM (1 Year)

1.1% vs **0.7%** for Avonex

RADIANCE (2 Years)

0.9% vs **0.9%** for Avonex

Malignancy Rates[9,10]

SUNBEAM (1 Year)

0.2% vs **0%** for Avonex

RADIANCE (2 Years)

0.9% vs **0.5%** for Avonex

Herpetic Infections: In active-controlled MS trials, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ZEPOSIA 0.92 mg and in 0.2% of patients taking Avonex[1]

Overall Infections

In SUNBEAM and RADIANCE, the overall rate of infections with ZEPOSIA (35%) was similar to Avonex (34%)[1]

- ZEPOSIA causes a reduction in peripheral blood lymphocyte count and may increase the risk of infection

Progressive Multifocal Leukoencephalopathy (PML)

- PML has been reported in patients treated with S1P receptor modulators and other MS therapies and has been associated with some risk factors (eg, immunocompromised patients, polytherapy with immunosuppressants)[1]

IMPORTANT SAFETY INFORMATION

Contraindications:

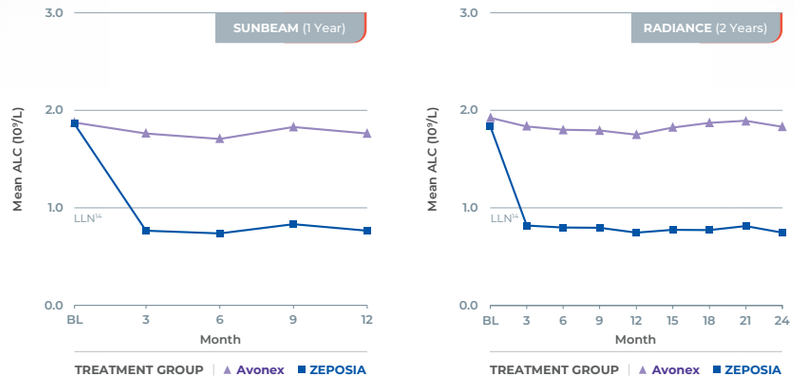
- Patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

ZEPOSIA Consistently Maintained ALC Near the LLN

ALCs Were Consistent Across Large-Scale 1-Year and 2-Year Pivotal Trials[9,10]

Mean ALC

Values Were at or Above the LLN



Lymphocyte numbers can be restored to normal values by discontinuing therapy[1,9,10,15]

- **ZEPOSIA causes a mean reduction** in peripheral blood lymphocyte count to 45% of baseline values because of reversible retention of lymphocytes in lymphoid tissues. ZEPOSIA may therefore increase the susceptibility to infections
- **Mean ALC** was 0.75 × 10^9 cells/L for both SUNBEAM and RADIANCE (at 1 year and 2 years, respectively)
- **During clinical trials**, a combined total of 29 patients treated with ZEPOSIA 0.92 mg from SUNBEAM and RADIANCE had an ALC of <200 cells/µL. If ALC counts <200 cells/µL were found and confirmed on repeat testing, treatment was temporarily stopped until lymphocyte counts reached >500 cells/µL
- **Upon discontinuation** of ZEPOSIA, median time to recovery of ALC to within a normal range was 30 days, with approximately 90% of patients recovering within 3 months

ALC=absolute lymphocyte count; BL=baseline; LLN=lower limit of normal.

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

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Based on the full Prescribing Information,

ZEPOSIA Is the First and Only S1P With No First-Dose Observation Required

A Different S1P That Lets Patients Start as Soon as Today[1,16,17]

Full Prescribing Information for ZEPOSIA Has

- **NO** First-Dose Observation Required
- **NO** Genetic Testing Required
- **NO** Ophthalmic Testing Required for Most Patients[18a]

Required Assessments Prior to Initiating ZEPOSIA[1]

- Obtain a **CBC** (within 6 months or after discontinuation of prior MS therapy), including lymphocyte count
- Obtain an **ECG** to determine whether preexisting conduction abnormalities are present
- Obtain **transaminase and bilirubin levels** (within 6 months)
- Evaluate **current and prior medications**
- Patients without a confirmed history of VZV or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated **immunizations** are required, administer at least 1 month prior to initiation

An up-titration schedule should be used to reach the maintenance dose, as a transient decrease in heart rate and AV conduction delays may occur[1]

- **Single maintenance dose** of 0.92 mg for all patients
- **If a dose is missed within the first 2 weeks** of treatment, re-initiate with the titration regimen
- If a dose is missed **after the first 2 weeks** of treatment, continue with the treatment as planned

The mean (CV%) plasma half-life ($t_{1/2}$) of ZEPOSIA was approximately 21 hours (15%).[1]

The mean (CV%) effective half-life ($t_{1/2}$) of the active metabolite CC112273 was approximately 11 days.[1]

One Capsule, Once a Day, From the Start[1]

DAYS 1-4	DAYS 5-7	DAY 8
ZEPOSIA 7-DAY TITRATION SCHEDULE		
0.23 mg	0.46 mg	0.92 mg

[a]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. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA.[1]

AV=atrioventricular; CBC=complete blood count; ECG=electrocardiogram; VZV=varicella-zoster virus.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (Continued):

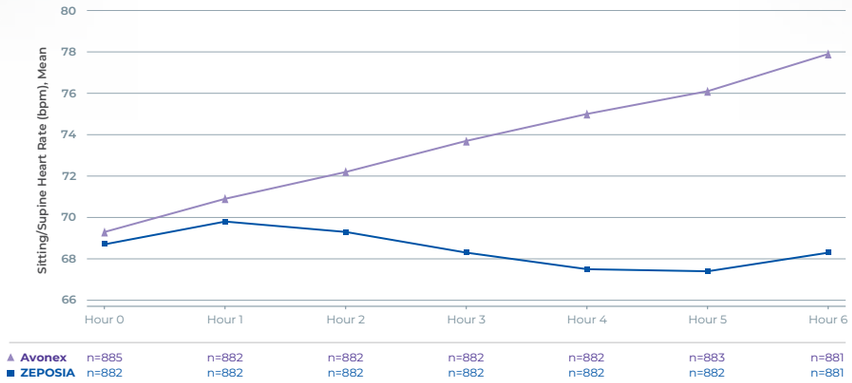
- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), 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

Heart Rate Data for Day 1 Initiation Dose (0.23 mg)

Changes in Heart Rate Observed Over First 6 Hours From 2 Clinical Trials[19]

Mean Supine Heart Rate Values

Day 1—Hours 1 Through 6 Following Initial Dose



Note: The heart rate data shown here represent pooled data from both pivotal trials for ZEPOSIA (SUNBEAM and RADIANCE), which included a combined total of 882 patients who received the 0.92-mg maintenance dose of ZEPOSIA and 885 patients who received Avonex 30 µg. All patients in the ZEPOSIA group received 0.23 mg on Day 1 and the dose was titrated upward over 8 days.

Heart rate data[1,19]

In data pooled from 2 trials, SUNBEAM (1 year) and RADIANCE (2 years), the following observations were made:

- **After the initial dose of ZEPOSIA** 0.23 mg, the greatest mean decrease in HR from baseline (1.2 bpm) occurred at Hour 5 on Day 1, returning to near baseline at Hour 6
- **Within 6 hours** of initiating therapy:
  - Mean supine HR for patients treated with ZEPOSIA did not drop below 66 bpm. Transient supine HR reductions <45 bpm were observed in 4 patients in the ZEPOSIA group
  - Patients in the Avonex group experienced an increase in mean HR of 8 bpm
- **On Day 1**, bradycardia was reported in 0.6% of patients taking ZEPOSIA and in 0% of patients taking Avonex
- **After Day 1**, the incidence of bradycardia was 0.8% in patients taking ZEPOSIA and 0.7% in patients taking Avonex
  - **With continued up-titration**, the maximal HR effect of ZEPOSIA occurred on Day 8. HRs below 40 bpm were not observed

HR=heart rate.

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.
- Progressive Multifocal Leukoencephalopathy (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. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML 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, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

once-daily ZEPOSIA® (ozanimod) 0.92 mg capsules

Support for Your Patients Every Step of the Way

ZEPOSIA 360 Support™ Can Help Appropriate Patients Start and Stay on Therapy

ZEPOSIA 360 Support™ Program—Services for Patients

Pre-Initiation Support

- **Pre-Initiation Testing Assistance**—includes comprehensive baseline testing[a]

Access Support

- **Access Assistance**—help with Benefits Investigation, Prior Authorization (PA), and Appeals

Financial Support

- **Third-Party Referrals**—suggestions for independent third-party foundations that may be able to assist with treatment costs

Dedicated **Nurse Navigators** provide a consistent point of contact for your patients taking ZEPOSIA

ZEPOSIA Bridge Program

a free supply of ZEPOSIA for up to 24 months to qualified, commercially insured patients who are at risk of an interruption in therapy[b]

- Up to **24 months of ZEPOSIA for $0**, as long as program eligibility rules are being met

Pay as little as $0

Co-Pay Assistance Program

helps patients with co-pay costs, including prescription and medical assessment/initiation costs[c]

- **Prescription Benefits**—eligible patients pay as little as $0 in out-of-pocket costs for their ZEPOSIA prescription
- **Medical Benefits**—commercially insured patients can be fully reimbursed for any out-of-pocket costs associated with medical assessments (required pre-initiation testing, such as blood tests and baseline heart tests)

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (Continued):

- 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

Additional Services for Your Patients

ZEPOSIA 360 Support™ Can Help You Keep Appropriate Patients on Therapy

ZEPOSIA 360 Support™ Program—Additional Services

Ongoing Support

- Payer Policy Research
- Ongoing Reverification of Benefits
- Shipment Coordination/Tracking

Support Coordinators

- Insurance Information and Support
- Regionally Assigned Points of Contact

AssistRx

AssistRx is a third-party service that simplifies patient access, provides resources, and accelerates time to therapy. Services are offered through a provider portal.

covermymeds®

CoverMyMeds offers electronic Prior Authorization (ePA) support. A prescriber-facing ePA is available for locating, submitting, and tracking PAs and pre-certifications.

[a]For patients with commercial coverage in all states except MA, MN, and RI.

[b]The Bridge Program is available at no cost for eligible commercially insured, on-label diagnosed patients if there is a delay in determining whether commercial prescription coverage is available, and is not contingent on any purchase requirement. The Bridge Program is not available to patients who have prescription insurance coverage through Medicare, Medicaid, or any other federal or state program, or MA or MI residents, and is available for no more than 6 months (180 days) to patients in MN and RI. Appeal of any prior authorization denial must be made within 90 days or as per payer guidelines, to remain in the Program. Eligibility will be re-verified in January for patients continuing into the following year, and may be at other times during Program participation. Up to 12 additional refills may be provided if needed. Offer is not health insurance, and may be modified or discontinued at any time without notice. Other limitations may apply.

[c]Depending on insurance coverage and where the full cost is not covered by patient's insurance, eligible patients may receive a prescription benefit offer for out-of-pocket drug costs and pay as little as $0 per prescription, as well as a medical assessment benefit offer for out-of-pocket costs for the initial blood tests and ECG screening. Maximum savings limit applies; patient out-of-pocket expenses may vary. This program is not health insurance. Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state health care programs. Please visit ZEPOSIA.com/copayterms for Program Terms, Conditions, and Eligibility Criteria. Medical co-pay benefit not available for residents of MA, MI, MN, and RI.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (Continued):

- 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

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ZEPOSIA—FOCUSED ON WHAT COUNTS

POWERFUL EFFICACY[1a]

Proven superior in reducing relapses vs Avonex[b]

Relative Reduction in ARR vs Avonex

48% at 1 year

38% at 2 years

PROVEN

SUPERIOR in reducing GdE and T2 lesions vs Avonex[1]

Relative Reduction in GdE Lesions

63% at 1 year

53% at 2 years

Relative Reduction in T2 Lesions

48% at 1 year

42% at 2 years

COMPARABLE SAFETY PROFILE VS AVONEX IN OVERALL INCIDENCE OF ADVERSE REACTIONS[1,9,10]

Overall Incidence of Adverse Reactions

At 1 Year:
Avonex **75.5%**
ZEPOSIA **59.8%**

At 2 Years:
Avonex **83.0%**
ZEPOSIA **74.7%**

THE FIRST AND ONLY S1P WITH NO FIRST-DOSE OBSERVATION REQUIRED[1,16,17c]

Full Prescribing Information for ZEPOSIA has

NO FIRST-DOSE OBSERVATION required

NO genetic testing required

NO ophthalmic testing required for most patients[18d]

[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:** ARR was assessed for ZEPOSIA and Avonex at 1 year and 2 years. **Secondary endpoints:** The number of new or enlarging T2 lesions and the number of GdE lesions were assessed for ZEPOSIA and Avonex at 1 year and 2 years. In addition, confirmed disability progression was prospectively evaluated for ZEPOSIA and Avonex in a pooled analysis from the 1-year and 2-year studies. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.[1,9,10]

[b] 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.[9,10]

[c] Before initiating treatment with ZEPOSIA, all patients require a recent CBC including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an ECG to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations.[1] Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation.[1] For patients with a history of uveitis or macular edema, an ophthalmic assessment is required.[1] An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.[1]

[d] 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. A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA.[1]

References (continued)**: 10.** 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 and Suppl 1-31. doi:10.1016/S1474-4422(19)30238-8 **11.** Ghione E, Bergsland N, Dwyer MG, et al. Brain atrophy is associated with disability progression in patients with MS followed in a clinical routine. *AJNR Am J Neuroradiol.* 2018;39(12):2237-2242. doi:10.3174/ajnr.A5876 **12.** Damasceno A, Damasceno BP, Cendes F. The clinical impact of cerebellar grey matter pathology in multiple sclerosis. *PLoS One.* 2014;9(5):e96193. doi:10.1371/journal.pone.0096193 **13.** Pontillo G, Cocozza S, Lanzillo R, et al. Determinants of deep gray matter atrophy in multiple sclerosis: a multimodal MRI study. *AJNR Am J Neuroradiol.* 2019;40(1):99-106. doi:10.3174/ajnr.A5915 **14.** Lymphocytopenia. National Heart, Lung, and Blood Institute (NHLBI). Accessed July 21, 2020. www.nhlbi.nih.gov/health-topics/lymphocytopenia **15.** Steinman L, Comi G, Bar-Or A, et al. P1031. Poster presented at: 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 11-13, 2019; Stockholm, Sweden. **16.** Gilenya. Prescribing information. Novartis Pharmaceuticals Corporation; 2019. **17.** Mayzent. Prescribing information. Novartis Pharmaceuticals Corporation; 2019. **18.** Marrie RA. Comorbidity in multiple sclerosis: implications for patient care. *Nat Rev Neurol.* 2017;13(6):375-382. doi:10.1038/nrneurol.2017.33 **19.** Cree BAC, Comi G, Mendzelevski B, et al; SUNBEAM and RADIANCE investigators. Cardiac safety profile of ozanimod in pooled phase 3 studies in relapsing multiple sclerosis (SUNBEAM and RADIANCE). Poster presented at: 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 10-12, 2018; Berlin, Germany.

Indication

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.

Please see Important Safety Information throughout and full Prescribing Information and Medication Guide.

Bristol Myers Squibb is committed to transparency. For information on the list price of ZEPOSIA as well as information regarding average out-of-pocket costs and assistance programs, please visit our pricing information page at ZEPOSIA.com/cost.

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