ZEPOSIA® (ozanimod) 0.92 mg capsules

DMT Naïve

MEET MIA

A Working Mother With an Active Lifestyle Looking for Her First DMT

- Works on her feet all day as a costume designer on Broadway
- Female, mid 30s
- Mother of a young child
- Evidence of disease activity

A real patient on ZEPOSIA since 2021.

Patient was compensated for her time. Individual results may vary.

> **Because I'm the main character in my life story—not MS.**

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. Women who become pregnant while taking ZEPOSIA for MS may enroll in the ZEPOSIA pregnancy registry by calling 1-877-301-9314 or visiting www.zeposiapregnancyregistry.com.

DMT=disease-modifying therapy; MS=multiple sclerosis.

INDICATIONS

ZEPOSIA® (ozanimod) is indicated for the treatment of:

1. Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
2. Moderately to severely active ulcerative colitis (UC) 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

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

Make ZEPOSIA Your 1ST Choice for Her 1ST DMT

Mia Is a Young Mother With an Active Lifestyle Who Started Taking ZEPOSIA as Her First DMT

DMT-Naïve Patient

Female, mid 30s | Mother of a young child | Evidence of disease activity

Medical History

- **Newly diagnosed** with RMS
- Had **no prior experience** with treatments
- Presented with numbness and tingling in her feet, which spread up to her waist within a day
- **Evidence of disease activity** on MRI (10-12 lesions)

Treatment Plan Considerations

- Wants a DMT that will **lower the chances of relapse**
- Prefers a **once-daily**[b] **oral option**

In ZEPOSIA Pivotal Trials[1,2a]

- **~70%** were **DMT naïve**
- **~67%** were **female**
- **~70%** were **≤40 years of age**

[a]In ZEPOSIA pivotal trials SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313): ~30% of participants had previous experience with disease-modifying therapy, ~33% of participants were male, and ~30% of participants were above the age of 40.[1,2]

[b]Patients with mild or moderate hepatic impairment (Child-Pugh class A or B), should initiate ZEPOSIA with a 7-day titration. After initial titration, the recommended dosage of ZEPOSIA in these patients is 0.92 mg taken orally once every other day, starting on Day 8. Use of ZEPOSIA in patients with severe hepatic impairment (Child-Pugh class C) is not recommended.[3]

MRI=magnetic resonance imaging; RMS=relapsing multiple sclerosis.

Why ZEPOSIA for DMT-naïve patients?

- **Visit ZeposiaHCP.com/MS to learn more**

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 or UC 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 and herpes simplex were seen in clinical trials of ZEPOSIA. 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.

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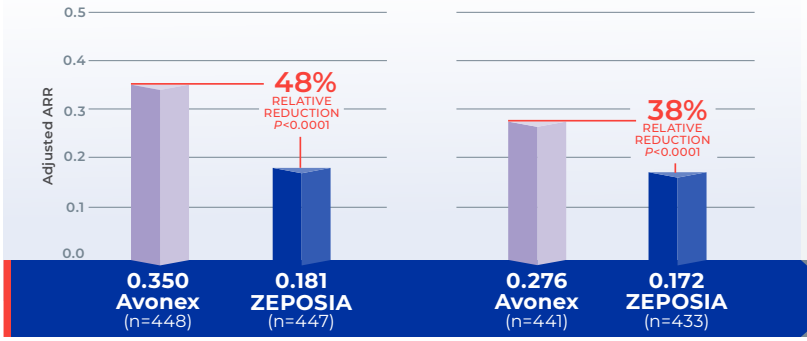
ZEPOSIA Delivered Powerful Efficacy in Reducing ARR vs Avonex® in Pivotal Trials[3]

In the open-label extension study, patients continuously treated with ZEPOSIA up to 7 years[a] had an ARR of 0.090[4]

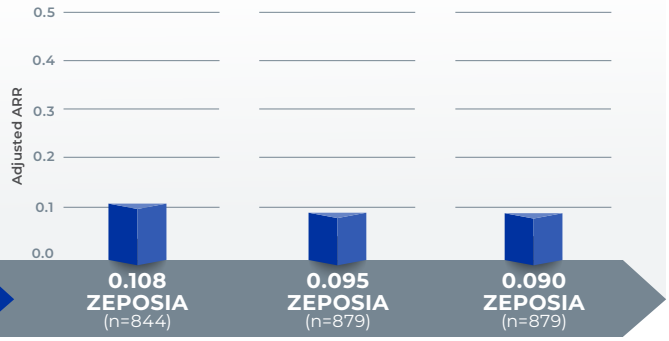
PRIMARY ENDPOINT — **ARR in Pivotal Trials[3]**

In pivotal trials, ZEPOSIA showed **48% relative reduction vs Avonex at 1 year and 38% at 2 years**



SUNBEAM 1 Year | RADIANCE 2 Years

SECONDARY ENDPOINT — **ARR in DAYBREAK* OLE[4-6]**



Up to 3 Years[5b] | Up to 5 Years[6c] | Up to 7 Years[4]

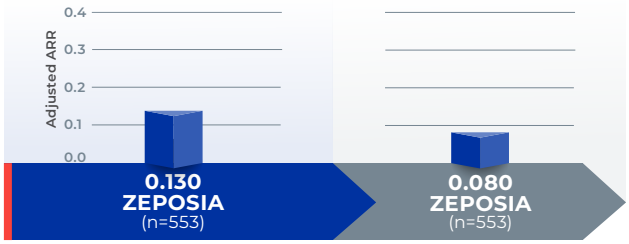
A relapse was defined as the occurrence of new or worsening neurological symptoms persisting for more than 24 hours attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.[1,2]

*DAYBREAK is an OLE trial that enrolled participants from multiple randomized phase 1, 2, or 3 studies, including SUNBEAM and RADIANCE, and is presented as a final analysis with a database lock of April 7, 2023. Endpoints were analyzed descriptively.[4-6]
[a]At database lock (April 7, 2023), mean (range) continuous ozanimod 0.92 mg oral daily dose exposure in DAYBREAK was 60.9 (0.03-81.5) months.[3,4]
[b]Study period includes DAYBREAK Day 1 through last treatment date or the data cutoff date of December 20, 2019.[5]
[c]At data cutoff date of February 2, 2021.[6]

Adjusted ARR for DMT-Naïve ZEPOSIA Patients in a Post Hoc Analysis[7d]

DMT Naïve at Baseline

ARR in Pivotal Trials[7] | **ARR in DAYBREAK OLE[7]**



Completion of Pivotal Trials | Up to 7 Years

~70%
of patients in ZEPOSIA pivotal trials were **DMT naïve**[2]

In ZEPOSIA pivotal trials SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313): ~30% of participants had previous experience with disease-modifying therapy.[1,2]

In SUNBEAM and RADIANCE, prior treatment status (treatment naïve vs previously treated) was pre-specified, but not powered to detect a difference in the treatment effect in these subgroups. In DAYBREAK, endpoints were analyzed descriptively.

[d]This analysis includes DMT-naïve patients who received the oral daily dose of ozanimod 0.92 mg in SUNBEAM (≥12 months) and RADIANCE (24 months). Phase 3 trial completers were eligible for enrollment in the OLE trial (DAYBREAK-NCT02576717) of ozanimod (April 7, 2023 database lock) 0.92 mg oral daily dose.[3,4,7]
Analyses were based on the negative binomial regression model with parent treatment group, adjusted for region (Eastern Europe vs rest of world), age at parent baseline, and the parent baseline number of gadolinium-enhancing lesions. The natural log transformation of time on treatment is used as an offset term to adjust for patients having different exposure times.[7]
DMT-experienced patients who received ZEPOSIA 0.92 mg oral daily dose (n=207) had ARR of 0.194 at the completion of the pivotal trials and ARR of 0.114 at April 7, 2023 database lock in DAYBREAK.[3,4,7]
ARR=annualized relapse rate; OLE=open-label extension.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (continued):

- Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with S1P receptor modulators. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

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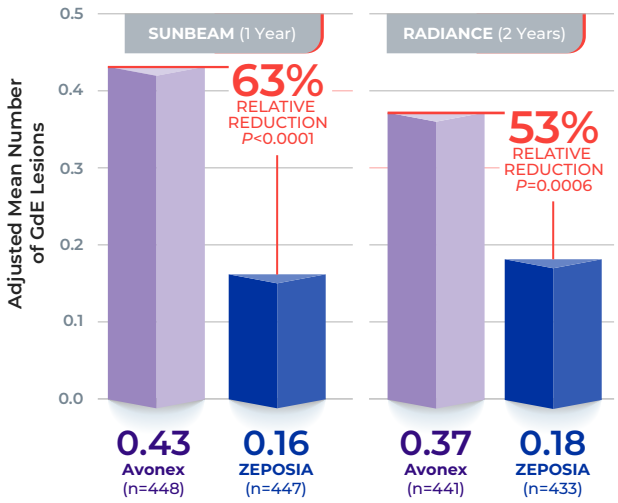
ZEPOSIA Reduced Lesions Across All Secondary Measures of MRI Activity[3]

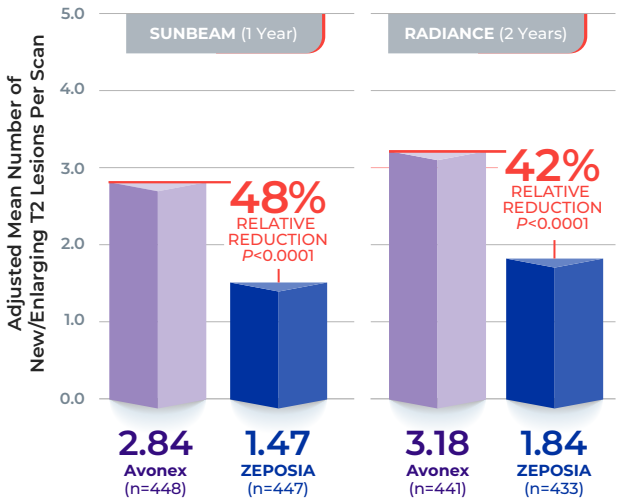
Number of GdE Lesions

SECONDARY ENDPOINT



Number of New/Enlarging T2 Lesions

SECONDARY ENDPOINT



In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12. In the 2-year RADIANCE study, brain MRIs were performed at baseline, Month 12, and Month 24.[1,2]

9 of 10 Patients Showed No 3-Month CDP in SUNBEAM and RADIANCE; Rate of CDP Measured Up to 7 Years[3,4]

SECONDARY ENDPOINT — **3-Month CDP at 2 Years (Pooled Analysis)**[2,3*†]

At 2 years,

92.4%

vs **92.2%** for Avonex showed no confirmed 3-month disability progression

Statistical significance was not reached for the pooled CDP

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)

POST HOC ANALYSIS — **3-Month CDP Up to 7 Years**[4*‡]

Up to 7 years,

77.9%

showed no confirmed 3-month disability progression (n=592/760)

22.1% of patients treated with ZEPOSIA (n=168/760) experienced **3-month CDP, as measured by EDSS**

Endpoints were analyzed descriptively.

*CDP was defined as a ≥1-point increase from baseline EDSS confirmed after 3 months and after 6 months.[3]
†This was a prospectively planned pooled analysis of SUNBEAM (≥12 months) and RADIANCE (24 months).[3]
‡This post hoc analysis includes patients who received ozanimod 0.92 mg oral daily dose in SUNBEAM (≥12 months) and RADIANCE (24 months). Phase 3 trial completers were eligible for enrollment in OLE DAYBREAK. The database lock for the OLE was April 7, 2023.[3,4]
CDP=confirmed disability progression; EDSS=Expanded Disability Status Scale; GdE=gadolinium enhancing; NS=not significant.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections (continued)**:**

- In the MS and UC 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 and UC. 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.

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Compelling Efficacy in Brain Volume Loss Data in Pivotal Trials[1,2]

Whole Brain Volume Loss[1,2]

SECONDARY ENDPOINT

Mean Percent Change From Baseline

SUNBEAM (1 Year)

31% RELATIVE REDUCTION

ZEPOSIA: –0.41 (n=397)
vs Avonex: –0.61 (n=406)

RADIANCE (2 Years)

26% RELATIVE REDUCTION

ZEPOSIA: –0.71 (n=390)
vs Avonex: –0.94 (n=397)

Thalamic Volume Loss[1,2]

EXPLORATORY ENDPOINT

Mean Percent Change From Baseline

SUNBEAM (1 Year)

32% RELATIVE REDUCTION

ZEPOSIA: –1.12 (n=393)
vs Avonex: –1.72 (n=406)

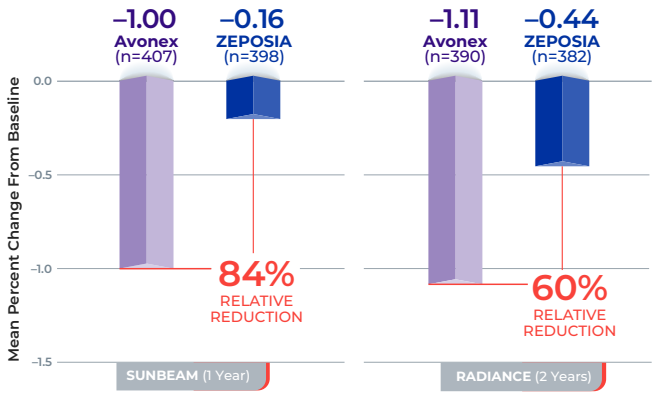
RADIANCE (2 Years)

27% RELATIVE REDUCTION

ZEPOSIA: –1.40 (n=385)
vs Avonex: –1.85 (n=391)

EXPLORATORY ENDPOINT

Cortical Grey Matter Volume Loss[1,2]



Volume loss endpoints were not part of the statistical analysis hierarchy.[1,2]

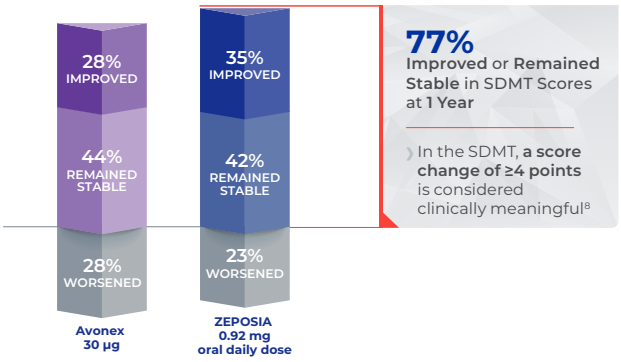
In the 1-year SUNBEAM study, brain MRIs were performed at baseline, Month 6, and Month 12.[1]

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

Post Hoc Analysis: Cognitive Processing Speed Data From SUNBEAM and DAYBREAK[8]

POST HOC ANALYSIS

SDMT Scores From SUNBEAM (1 Year)[3,8]



77%
Improved or **Remained Stable** in SDMT Scores at **1 Year**

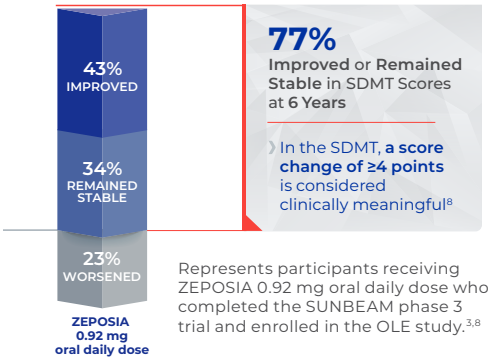
In the SDMT, **a score change of ≥4 points** is considered clinically meaningful[8]

ZEPOSIA: n=397 at Month 12 for SDMT; Avonex: n=395 at Month 12 for SDMT

POST HOC ANALYSIS

SDMT Scores From DAYBREAK (OLE)[3,8]

Categorical Analysis of Clinically Meaningful Change in SDMT Relative to SUNBEAM Baseline[a]



77%
Improved or **Remained Stable** in SDMT Scores at **6 Years**

In the SDMT, **a score change of ≥4 points** is considered clinically meaningful[8]

Represents participants receiving ZEPOSIA 0.92 mg oral daily dose who completed the SUNBEAM phase 3 trial and enrolled in the OLE study.[3,8]

ZEPOSIA: n=299 at 6 years for SDMT

Endpoint was not part of the statistical analysis hierarchy and was analyzed descriptively.[1,5]

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).[1,9] SDMT is a tool that measures cognitive processing speed.[1]

[a]The database lock for this analysis was April 7, 2023.[4]

MSFC=Multiple Sclerosis Functional Composite; SDMT=Symbol Digit Modalities Test.

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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Well-Established Safety Profile[3,4,10a]

10 YEARS

of experience across multiple indications[3,4,10b]

8

phase 2-3 clinical trials[3,10-19c]

across MS and UC

~56,000

patients

in clinical trials and the post-marketing setting[20,21]

~58,000

patient years

of total exposure in clinical trials and the post-marketing setting[20,21]

Overall ozanimod exposure in parent and extension trials (phase 1-3 MS, phase 2-3 UC) was 17,896.33 patient years (PY) and estimated to be 40,511 PY in the post-marketing setting. The cumulative number of patients exposed to ozanimod in parent and extension trials (all indications) was 4042 and estimated to be 51,736 in the post-marketing setting. Clinical trial data is current as of May 19, 2024, and post-marketing estimated data is current as of May 14, 2024.[20,21]

[a]ZEPOSIA has been studied across multiple indications in 4 clinical trials, including TRUE NORTH (phase 3); TOUCHSTONE (phase 2); and SUNBEAM (phase 3) and RADIANCE (phase 3). 496 patients receiving the orally once daily dose of ZEPOSIA during induction in TRUE NORTH or TOUCHSTONE and 882 patients receiving the 0.92 mg oral daily dose of ZEPOSIA in SUNBEAM or RADIANCE were assessed in the safety analysis.[3,10-12,14,15]

[b]In UC, from the start of the TOUCHSTONE phase 2 clinical trial (December 26, 2012) through TRUE NORTH OLE study data cutoff (June 30, 2023). In MS, from the start of the RADIANCE phase 2 clinical trial (September 18, 2012) through the DAYBREAK OLE database lock (April 7, 2023). From the first patient randomized (October 18, 2012) through the DAYBREAK database lock, the maximum continuous exposure was 117.2 months. The mean exposure to ZEPOSIA 0.92 mg in the parent trials and DAYBREAK was 74.8 months. Only includes patients receiving the 0.92 mg oral daily dose of ZEPOSIA.[3,4,10,13,22]

[c]ZEPOSIA has been studied across multiple indications in 8 phase 2-3 clinical trials.[3,10-19]

Moderate-to-severe UC: TRUE NORTH (NCT02435992), a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial; TRUE NORTH OLE (NCT02531126), an ongoing phase 3, multicenter, OLE trial; TOUCHSTONE (NCT01647516), a phase 2, multicenter, randomized, double-blind, placebo-controlled trial; and JAPAN TRUE NORTH, a phase 2/3, multicenter, randomized, double-blind, placebo-controlled, treat-through study.[10,14-16,18]

Relapsing MS: SUNBEAM (NCT02294058) and RADIANCE (NCT02047734), 2 phase 3, multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies; DAYBREAK (NCT02576717), a phase 3, multicenter, OLE trial; and ENLIGHTEN (NCT04140305), an ongoing phase 3b, multicenter, longitudinal, open-label, single-arm study.[3,4,11-13,17,19]

UC=ulcerative colitis.

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 and UC therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants, duration of use). Based on data from patients with MS, longer treatment duration increases the risk of PML in patients treated with S1P receptor modulators, and the majority of PML cases have occurred in patients treated with S1P receptor modulators for at least 18 months. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued.

Immune reconstitution inflammatory syndrome (IRIS) has been reported in MS patients treated with S1P receptor modulators who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within a few months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

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. 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

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Safety Comparable to Avonex in Overall Incidence of AEs, and Generally Similar Safety in Long-Term Extension Study; 10 Years of Experience[1-4*]

IN PIVOTAL TRIALS: Incidence of Adverse Reactions[1-3]

	SUNBEAM (1 Year)		RADIANCE (2 Years)	
Summary of Adverse Reactions	**Avonex (n=445)**	**ZEPOSIA (n=448)**	**Avonex (n=440)**	**ZEPOSIA (n=434)**
Overall incidence of adverse reactions	75.5%	59.8%	83.0%	74.7%
Severe adverse reactions	2.2%	1.6%	4.3%	3.5%
Serious adverse reactions	2.5%	2.9%	6.4%	6.5%

Adverse Reactions With an Incidence of at Least 2% in Patients Treated With ZEPOSIA and at Least 1% Greater Than Avonex[3a]

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%
Upper abdominal pain	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. 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.[1-3]

*From the first patient randomized (October 18, 2012) through the DAYBREAK database lock (April 7, 2023), the maximum continuous exposure was 117.2 months. The mean exposure to ZEPOSIA 0.92 mg oral daily dose in the parent trials and DAYBREAK was 74.8 months.[3,4]

[a]Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.[3]

[b]Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, viral respiratory tract infection, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis.[3]

[c]Includes the following terms: alanine aminotransferase increased, GGT increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased.[3]

[d]Includes hypertension, essential hypertension, and orthostatic hypertension.[3]

[e]ALC reductions are an expected pharmacodynamic effect related to the mechanism of ozanimod; although investigators were not required to report ALC reductions as TEAEs, lymphopenia and ALC decreases were reported as TEAEs according to investigator determination.[4]

[f]Includes preferred terms of hypertension, essential hypertension, labile hypertension, and systolic hypertension.[4]

[g]Includes preferred terms of depression, depressed mood, and depressive symptoms.[4]

AE=adverse event; ALC=absolute lymphocyte count; ALT=alanine aminotransferase; GGT=gamma-glutamyl transferase; IR=Incidence rate; TEAE=treatment-emergent adverse event; ULN=upper limit of normal.

DAYBREAK OLE: Incidence of Adverse Events[4]

Summary of TEAEs (PRIMARY ENDPOINT)	ZEPOSIA (N=2494)	IR/1000 PY
Any TEAE	89.0%	650.8
Severe TEAEs	9.6%	19.8
Serious TEAEs	15.3%	33.5
TEAEs leading to permanent treatment discontinuation	3.9%	7.7

TEAEs in ≥5% of Patients Treated With ZEPOSIA[4]

TEAEs	ZEPOSIA (N=2494)	IR/1000 PY
Nasopharyngitis	21.3%	49.6
Headache	17.1%	38.3
COVID-19	16.5%	33.5
Upper respiratory tract infection	12.4%	26.7
Lymphopenia[e]	10.3%	22.2
Back pain	9.6%	20.1
ALC decreased[e]	9.4%	20.0
Hypertension[f]	9.2%	19.3
GGT increased	8.0%	16.7
Urinary tract infection	6.8%	13.9
Respiratory tract infection	6.6%	13.6
Arthralgia	6.5%	13.3
Bronchitis	6.3%	12.9
Depression-related TEAE[g]	5.9%	12.0
Viral respiratory tract infection	5.8%	11.9
ALT increased	5.1%	10.2

Similar safety patterns were seen in the continuous ZEPOSIA 0.92 mg oral daily dose (n=881) population[3,4]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Liver Injury: Clinically significant liver injury, including acute liver failure requiring transplant, has occurred in patients treated with ZEPOSIA in the postmarketing setting. Signs of liver injury, including elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as ten days after the first dose. Obtain transaminase and bilirubin levels, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Obtain transaminase levels and total bilirubin levels periodically during treatment and until two months after ZEPOSIA discontinuation. Patients should be monitored for signs and symptoms of any hepatic injury. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes promptly checked, and ZEPOSIA should be interrupted. Treatment should not be resumed if a plausible alternative etiology for the signs and symptoms cannot be established, because these patients are at risk for severe drug-induced liver injury.

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Demonstrated Tolerability Profile With Low Discontinuation Rates Due to Adverse Events[1-4]

Low Discontinuation Rates Due to AEs[1,2]

SUNBEAM (1 Year)

2.9% for ZEPOSIA and **3.6%** for Avonex[1]

RADIANCE (2 Years)

3.0% for ZEPOSIA and **4.1%** for Avonex[2]

DAYBREAK (Up to 7 Years) N=2494

3.9% for ZEPOSIA in Long-Term Extension Study[4]

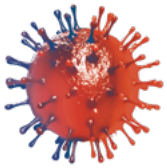
≥90%

of Patients Stayed on Therapy Through Completion of Pivotal Trials[1,2]*

*In the 1-year SUNBEAM trial, 94% of patients who received ZEPOSIA and 92% who received Avonex completed the study. In the 2-year RADIANCE trial, 87% of patients who received ZEPOSIA and 85% who received Avonex completed the study.[1,2]

Rates for Overall and Serious Infections and Malignancies Consistent vs Avonex[1-3]

In SUNBEAM and RADIANCE, the overall rate of infections with ZEPOSIA (35%) was similar to Avonex (34%).[3]



Serious Infections

The rate of serious infections at 1 year for ZEPOSIA was 1.1% vs 0.7% for Avonex, and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex.[1,2]

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 oral daily dose and in 0.2% of patients taking Avonex.[3]

ZEPOSIA causes a reduction in peripheral blood lymphocyte count and may increase the risk of infection.[3]

Controlled Lymphocyte Reductions

ALC was consistently maintained near the lower limit of normal across both pivotal trials, and the mean ALC for both SUNBEAM and RADIANCE was ≈0.8 x 10^9/L.[1,2,23]

The rate of malignancies at 1 year for ZEPOSIA was 0.2% vs 0% for Avonex, and the rate at 2 years for ZEPOSIA was 0.9% vs 0.5% for Avonex.[1,2]

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. Women who become pregnant while taking ZEPOSIA for MS may enroll in the ZEPOSIA pregnancy registry by calling 1-877-301-9314 or visiting www.zeposiapregnancyregistry.com.

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.

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. Obtain a baseline evaluation of the fundus, including a macula, near the start of treatment with ZEPOSIA. Perform an examination of the fundus, including the macula, periodically while on therapy and any time there is a change in vision. Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. Macular edema over an extended period of time (i.e. 6 months) can lead to permanent visual loss. Consider discontinuing ZEPOSIA if macular edema develops. The risk of recurrence after rechallenge has not been evaluated.

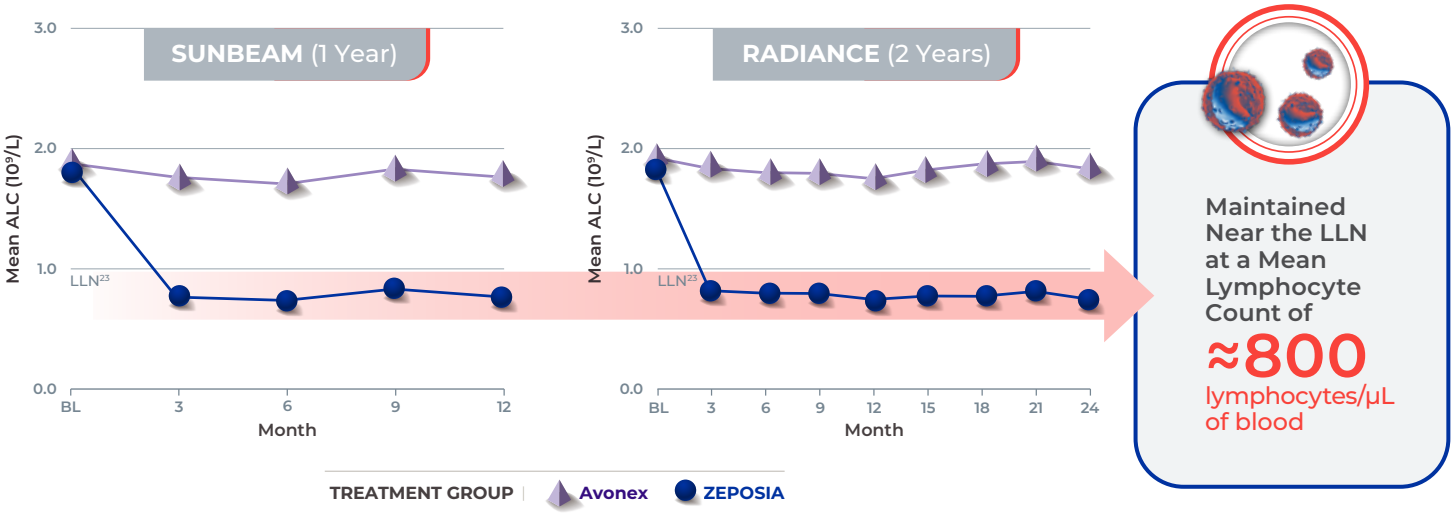
Patients with a history of uveitis and patients with a history of diabetes mellitus are at increased risk of macular edema during ZEPOSIA therapy.

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

ZEPOSIA® (ozanimod) | 0.92 mg capsules

ZEPOSIA Consistently Maintained ALC Near the Lower Limit of Normal[1,2,23]

ALC Consistently Maintained Near LLN at ≈0.8 x 10^9/L



Lymphocyte Numbers Can Be Restored to Normal Values by Discontinuing Therapy[1-3,24]

- **After discontinuing** ZEPOSIA 0.92 mg oral daily dose, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months
- **Mean ALC was approximately 0.8 x 10^9 cells/L** for both SUNBEAM and RADIANCE (at 1 year and 2 years, respectively)
- **ZEPOSIA causes a mean reduction** in peripheral blood lymphocyte count to approximately 45% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues; ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature

BL=baseline; LLN=lower limit of normal.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Cutaneous Malignancies: The risk of cutaneous malignancies (including basal cell carcinoma, squamous cell carcinoma, and melanoma) is increased in patients treated with S1P receptor modulators. Skin examinations are recommended prior to or shortly after the start of treatment and periodically thereafter for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using sunscreen with a high protection factor. Concomitant phototherapy with UV-B radiation or PUV-A photochemotherapy is not recommended in patients taking ZEPOSIA.

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® (ozanimod) | 0.92 mg capsules

One Capsule, Once a Day,* From the Start[3]

*For patients with hepatic impairment, refer to the dosing guidance below.

ZEPOSIA 7-Day Titration Schedule

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 & Thereafter
0.23 mg once daily				0.46 mg once daily			0.92 mg once daily*

The ZEPOSIA Starter Kit is designed to make titration instructions easier to follow[3]

- Initiate ZEPOSIA with a 7-day titration schedule as shown in the graphic above. After initial titration, the recommended dosage of ZEPOSIA is 0.92 mg taken orally, starting on Day 8
- 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
- If a dose is missed within the first 2 weeks of treatment, reinitiate treatment using the titration regimen
- If a dose is missed after the first 2 weeks of treatment, continue with the treatment as planned
- ZEPOSIA may be taken with or without food

Recommended dosage in patients with hepatic impairment[3]

- In patients with mild or moderate hepatic impairment (Child-Pugh class A or B), initiate ZEPOSIA with a 7-day titration. After initial titration, the recommended dosage of ZEPOSIA in these patients is 0.92 mg taken orally once every other day, starting on Day 8. Use of ZEPOSIA in patients with severe hepatic impairment (Child-Pugh class C) is not recommended

Getting Patients Started on ZEPOSIA[3]

NO Genetic Testing, NO First-Dose Observation Required

Assessments Prior to First Dose[3]

ECG to detect preexisting conduction abnormalities

Blood work (within the past 6 months)
- CBC, including lymphocyte count
- Transaminase and bilirubin levels

Determine VZV history and vaccination status† and evaluate medication history.

Initiate Patient on ZEPOSIA

Assessments Near the Start of Treatment[3]

Ophthalmic evaluation of the fundus, including the macula§

Skin examination¶

Check to see if your patients recently completed, or plan to have, an annual skin or eye exam to satisfy these requirements.

Periodically obtain transaminase and total bilirubin levels[3‡]

Periodically monitor for changes in vision§ and suspicious skin lesions[3¶]

Support provided by Bristol Myers Squibb to eligible commercial patients‖:

• Blood work • ECG • Ophthalmic evaluation • VZV antibody testing • Skin exam reimbursement

†VZV vaccination of antibody-negative patients is recommended prior to commencing treatment. Without documentation of VZV/chicken pox, or documentation of a full course of vaccination, test for antibodies. If live attenuated immunizations are required, administer at least 1 month prior to initiation.[3]
‡During treatment and until 2 months after discontinuation.[3]
§S1P receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. Perform an examination of the fundus, including the macula, periodically while on therapy and any time there is a change in vision.[3]
¶Also obtain a skin examination periodically during treatment, particularly for patients with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions, which should be promptly evaluated if observed.[3]
‖Home visits for initial routine medical tests are not available to people enrolled in Medicare, Medicaid, or other federal or state programs, or to people living in Rhode Island.

AV=atrioventricular; CBC=complete blood count; ECG=electrocardiogram; S1P=sphingosine 1-phosphate; VZV=varicella-zoster virus.

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.

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

ZEPOSIA® (ozanimod) | 0.92 mg capsules

Learn How to Get Your Patients Started on ZEPOSIA With the Start Form

ZEPOSIA® (ozanimod) | 0.92 mg capsules

Learn More About ZEPOSIA 360 Support™ Services

A real ZEPOSIA patient who was compensated for her time. Individual results may vary.

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. After stopping ZEPOSIA in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS).

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 80% to 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® (ozanimod) 0.92 mg capsules

For your patients with RMS[3]

PROTECT IT BEFORE IT'S GONE

With ZEPOSIA, You Have the Power to Help Preserve Their Most Valuable Resource[3]

POWERFUL EFFICACY in reducing ARR, GdE lesions, and new/enlarging T2 lesions vs Avonex[3a]

DATA ON BRAIN VOLUME AND COGNITIVE PROCESSING SPEED (SDMT) in secondary, exploratory endpoints and post hoc analysis[1,2]

SAFETY COMPARABLE TO AVONEX IN OVERALL INCIDENCE OF ADVERSE EVENTS,[2,3b] and generally similar safety in the long-term extension study; 10 years* of experience[4c]

*From the first patient randomized (October 18, 2012) through the DAYBREAK database lock (April 7, 2023), the maximum continuous exposure was 117.2 months. The mean exposure to ZEPOSIA 0.92 mg oral daily dose in the parent trials and DAYBREAK was 74.8 months.[3,4]

[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 oral daily dose vs weekly Avonex (interferon beta-1a), 30-µg intramuscular injection. **Primary endpoint:** ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.181 vs 0.350, respectively) and by 38% at 2 years (0.172 vs 0.276, 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]**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 upper abdominal pain, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. **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 the full Prescribing Information for additional SUNBEAM and RADIANCE data. See the IN PIVOTAL TRIALS table within this piece for definitions of these terms.

[c]**Study design: DAYBREAK** is an OLE trial that enrolled participants from multiple randomized phase 1 to 3 studies, including SUNBEAM and RADIANCE. These data are presented as a final analysis with a database lock of April 7, 2023. Patients evaluated in this analysis included those receiving an FDA-approved maintenance dose of 0.92 mg oral daily dose (n=881) who completed the randomized phase 1 to 3 trials (the "continuous" arm), and those who received ZEPOSIA 0.46 mg daily oral dose (n=877) or Avonex 30 µg (n=736) during phase 1 to 3 trials before receiving ZEPOSIA 0.92 mg oral daily dose at DAYBREAK baseline. The primary objective was to evaluate the long-term safety of ZEPOSIA. Secondary efficacy outcomes included ARR, new/enlarging T2 lesions, and GdE lesions. Endpoints were analyzed descriptively.[3,4]

Treatment-emergent adverse events (TEAEs): At the database lock (April 7, 2023), the overall incidence of TEAEs for ZEPOSIA in the DAYBREAK OLE trial was 89.0%. The most common TEAEs with an incidence of at least 5% in patients treated with ZEPOSIA, sorted by decreasing incidence, were as follows: nasopharyngitis, 21.3%; headache, 17.1%; COVID-19, 16.5%; upper respiratory tract infection, 12.4%; lymphopenia, 10.3%; back pain, 9.6%; ALC decreased, 9.4%; hypertension, 9.2%; gamma-glutamyl transferase increased, 8.0%; urinary tract infection, 6.8%; respiratory tract infection, 6.6%; arthralgia, 6.5%; bronchitis, 6.3%; depression-related TEAEs, 5.9%; viral respiratory tract infection, 5.8%; and ALT increased, 5.1%. The rate of TEAEs leading to permanent treatment discontinuation was 3.9%. **Severe TEAEs:** The rate of severe TEAEs was 9.6%. **Serious TEAEs:** The rate of serious TEAEs was 15.3%.[4]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Most Common Adverse Reactions that occurred in the MS clinical trials of ZEPOSIA-treated patients (≥4%): upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

In the UC clinical trials, the most common adverse reactions that occurred in ≥4% of ZEPOSIA-treated patients and greater than in patients who received placebo were upper respiratory infection, liver test increased, and headache.

Use in Specific Populations: Hepatic Impairment: Dosage adjustment in patients with mild or moderate hepatic impairment (Child-Pugh class A or B) is required, and use of ZEPOSIA in patients with severe hepatic impairment (Child-Pugh class C) is not recommended.

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

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