# PRODUCT MONOGRAPH

# INCLUDING PATIENT MEDICATION INFORMATION

**Pr ZEPOSIA®**

ozanimod capsules

capsules, 0.23 mg, 0.46 mg and 0.92 mg ozanimod (as ozanimod hydrochloride), oral

Sphingosine 1-phosphate receptor modulator

Bristol-Myers Squibb Canada

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## RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| 1 Indications | 04/2022 |
| 4 Dosage and administration | 12/2023 |
| 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic | 08/2024 |
| 7 Warnings and Precautions, Immune | 12/2023 |
| 7 Warnings and Precautions, Ophthalmologic | 04/2022 |
| 7 Warnings and Precautions, Respiratory | 04/2022 |
| 7.1.1 Pregnant Women | 04/2022 |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

ZEPOSIA® (ozanimod) is indicated for:

Multiple sclerosis (MS)

- the treatment of patients with relapsing remitting multiple sclerosis (RRMS) to decrease the frequency of clinical exacerbations.

Ulcerative colitis

- the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or a biologic agent.

ZEPOSIA should only be prescribed by physicians experienced in the treatment of multiple sclerosis or ulcerative colitis, are knowledgeable of the efficacy and safety profile of ZEPOSIA and are able to discuss benefits/harms with patients.

#### 1.1 Pediatrics

**Pediatrics (<18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (≥ 65 years of age):**

Multiple Sclerosis

Clinical studies of ZEPOSIA did not include patients over 65 years old. Therefore, it is not known whether the safety and efficacy differ in elderly patients compared to younger patients with multiple sclerosis.

Ulcerative Colitis

A limited number of patients ≥ 65 years of age were enrolled in the clinical trials. Within this population, compared to placebo efficacy was observed during induction treatment only. Therefore, Health Canada has not authorized ZEPOSIA for maintenance treatment of ulcerative colitis in patients ≥ 65 years of age.

Physicians who choose to treat geriatric patients should consider that treatment with ZEPOSIA in the context of greater frequency of reduced hepatic, renal, immune, pulmonary and cardiovascular function, other concomitant diseases and concomitant drug therapy, warrants caution and may necessitate additional or more frequent monitoring (see 7.1.4 Geriatrics).

## 2 CONTRAINDICATIONS

ZEPOSIA is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- In 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 (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

- In patients with a history or presence of second-degree atrioventricular (AV) block Type II or third-degree AV block, sick sinus syndrome, or sinoatrial block unless the patient has a functioning pacemaker (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

- In patients with increased risk of opportunistic infections, including those who are immunocompromised due to treatment (e.g., antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g., immunodeficiency syndrome) (see 7 WARNINGS AND PRECAUTIONS, Immune).

- In patients with severe active infections including active bacterial, fungal or viral infections (e.g., hepatitis, tuberculosis), until resolution of the infection (see 7 WARNINGS AND PRECAUTIONS, Immune).

- In patients with known active malignancies, except localized basal cell carcinoma of the skin (see 7 WARNINGS AND PRECAUTIONS, Neoplasm).

- In women (including female adolescents) who are pregnant or of childbearing potential not using effective contraception. Pregnancy must be excluded before start of treatment as ZEPOSIA may cause fetal harm (see 4.1 Dosing Considerations, 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, and 7.1.1 Pregnant Women).

- With concomitant use of MAO inhibitors. ZEPOSIA should not be administered with other MAO inhibitors because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. At least 3 months should elapse between discontinuation of ZEPOSIA and initiation of treatment with MAO inhibitors (see 7 WARNINGS AND PRECAUTIONS, Neurologic and 9.4 Drug-Drug Interactions).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

Prior to initiating treatment with ZEPOSIA the following assessments should be done to guide

patient selection and treatment.

Refer to 7.1.1 Pregnant Women and 9 DRUG INTERACTIONS for more complete information.

Immune system effects

ZEPOSIA causes a reduction in circulating lymphocyte counts to approximately 43% to 47% of baseline values at the 0.92 mg ozanimod dose via reversible retention in lymphoid organs and may increase the risk of infections. Prescribers should:

- Review a recent (i.e., within the last 6 months or after discontinuation of prior MS therapy) complete blood count (CBC), including lymphocyte count, before initiation of ZEPOSIA (see 7 WARNINGS AND PRECAUTIONS, Immune).

- Check varicella zoster virus (VZV) antibody status if there is no healthcare professional confirmed history of chickenpox or vaccination with varicella vaccine; VZV vaccination of antibody-negative patients is recommended, with a delay in treatment initiation for 1 month after vaccination (see 7 WARNINGS AND PRECAUTIONS, Immune).

- Vaccination against human papilloma virus (HPV) should be considered before initiating treatment with ZEPOSIA (see 7 WARNINGS AND PRECAUTIONS, Immune).

- Delay the start of ZEPOSIA in patients with severe active infection until resolved (see 2 CONTRAINDICATIONS).

- In patients that are switched from previous MS therapies with a known association to progressive multifocal leukoencephalopathy (PML), a recent cerebral MRI should be considered before initiating treatment with ZEPOSIA to evaluate for findings suggestive of PML (see 7 WARNINGS AND PRECAUTIONS, Immune).

Cardiac effects

Initiation of treatment with ZEPOSIA causes a transient decrease in heart rate and atrioventricular conduction delays. Prescribers should:

- Obtain an electrocardiogram (ECG) for all patients to determine whether pre-existing conduction abnormalities are present.

- Determine whether patients are taking concomitant medications that reduce heart rate or atrioventricular conduction (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9.2 Drug Interactions Overview).

- For patients with sinus bradycardia (heart rate (HR) <55 bpm), first or second-degree [Mobitz type I] atrioventricular block (AV block), or a history of myocardial infarction or heart failure, prepare to administer the first dose of ZEPOSIA in a clinical setting where they can be monitored for signs and symptoms of bradycardia, with hourly pulse and blood pressure measurements for at least 6 hours, and where symptomatic bradycardia

can be managed (see 4.4 Administration).

- For patients with certain other pre-existing cardiac conditions, seek an evaluation from a cardiologist prior to initiating treatment, to assess suitability of treatment and to determine the most appropriate strategy for monitoring cardiac effects (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

- Use an up-titration scheme to help reduce cardiac effects when reaching the maintenance dose (see 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.2 Clinical Trial Adverse Reactions).

See 2 CONTRAINDICATIONS AND 7 WARNINGS AND PRECAUTIONS, Cardiovascular for more complete information regarding patients with certain cardiovascular conditions in which ZEPOSIA should not be used or may require additional monitoring.

Ophthalmologic evaluation

Patients with a history of diabetes mellitus, uveitis and underlying/co-existing retinal diseases are at increased risk of macular edema. It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disorders undergo an ophthalmic evaluation prior to initiating ZEPOSIA therapy and during treatment (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

Liver function tests and hepatic impairment

Prescribers should obtain recent (i.e., within last 6 months) liver function test including transaminase and bilirubin levels prior to initiating treatment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Exposure to active metabolites of ozanimod, CC112273 and CC1084037, is higher in patients with mild or moderate hepatic impairment (see 10.3 Pharmacokinetics), which may increase the risk of adverse reactions. Therefore, dosage adjustment is required in this patient population (see 4.2 Recommended Dose and Dosage Adjustment). Use of ZEPOSIA is not recommended in patients with severe hepatic impairment.

Skin cancer

Skin cancers have been reported in patients treated with S1P modulators, including ZEPOSIA. Monitor for suspicious skin lesions before initiating treatment with ZEPOSIA, particularly in patients with risk factors for skin cancer (see 7 WARNINGS AND PRECAUTIONS, Neoplasm).

Pregnancy

ZEPOSIA is contraindicated in women (including female adolescents) who are pregnant or of childbearing potential not using effective contraception (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential and 7.1.1 Pregnant Women).

- A negative pregnancy test must be obtained before initiation of treatment in women of childbearing potential.

Current or prior medications

For patients taking antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies, including other disease modifying treatments and corticosteroids, or if there is a history of prior use of such drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ZEPOSIA (see 7 WARNINGS AND PRECAUTIONS, Immune).

### 4.2 Recommended Dose and Dosage Adjustment

**Treatment initiation**

Treatment has to be initiated in all patients with an initiation pack that lasts for 7 days. The initial dose escalation regimen of ZEPOSIA from Day 1 to Day 7 is shown below in Table 1. Following the 7-day dose escalation, the maintenance dosage is 0.92 mg once daily taken orally starting on Day 8.

Initiation of ZEPOSIA without dose escalation may result in greater reductions in heart rate (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

**Table 1 Dose Escalation Regimen**

| | |
|---|---|
| Days 1-4 | 0.23 mg once daily |
| Days 5-7 | 0.46 mg once daily |
| Days 8 and thereafter | 0.92 mg once daily |

**Maintenance treatment**

The recommended dose of ZEPOSIA is 0.92 mg once daily taken orally.

**Special populations**

Renal impairment

No ZEPOSIA dose adjustments are required in patients with renal impairment (see 10.3 Pharmacokinetics).

Hepatic impairment

In patients with mild or moderate hepatic impairment (Child-Pugh class A or B), initiate ZEPOSIA with the 7-day dose escalation regimen, as shown in Table 1 above. After initial dose escalation, the recommended dosage of ZEPOSIA in these patients is 0.92 mg taken orally once every other day, starting on Day 8 (see 10.3 Pharmacokinetics).

The effect of hepatic impairment on the pharmacokinetics of the major active metabolites of ozanimod has not been established with severe hepatic impairment. Use of ZEPOSIA in patients with severe hepatic impairment (Child-Pugh class C) is not recommended.

Pediatric patients (below 18 years)

Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

Geriatric patients (65 years or above)

No dose adjustment is needed in patients over 65 years of age. Caution should be used in patients over 65 years of age, given the potential for an increased risk of adverse reactions in this population, especially with long-term treatment (see 7.1.4 Geriatrics;10.3 Pharmacokinetics).

### 4.4 Administration

ZEPOSIA capsules should be swallowed whole and can be administered with or without food.

Patients should be advised that ZEPOSIA and its active metabolites remain in the blood and continues to have effects, including decreased blood lymphocyte counts, for up to 3 months following the last dose.

See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests for recommendations regarding monitoring that should be performed during therapy with ZEPOSIA.

First-dose monitoring of ozanimod

For patients with sinus bradycardia (heart rate < 55 bpm), first or second-degree [Mobitz type I] atrioventricular block (AV block), or a history of myocardial infarction or heart failure:

- Obtain an ECG prior to dosing, and at the end of the 6-hour observation period
- Monitor patients for signs and symptoms of bradycardia, with hourly pulse and blood pressure measurements
- If symptoms of bradyarrhythmia or atrioventricular (AV) block occur, initiate appropriate management, with continuous monitoring (e.g. continuous ECG monitoring) until the symptoms have resolved.
- Should a patient require pharmacological intervention during the first-dose observation period, continuous overnight monitoring (e.g. continuous ECG monitoring) in a medical facility should be instituted and the first-dose monitoring strategy should be repeated when the second dose of ozanimod is administered.

*Extended monitoring beyond 6 hours*

Continued monitoring is required if any of the following abnormalities are present after 6 hours (in the presence or absence of symptoms), until the abnormality resolves:

- Heart rate at 6 hours post-dose is < 45 bpm;
- Heart rate at 6 hours post-dose is the lowest value post-dose, suggesting the maximum reduction in heart rate may not have occurred;
- ECG at 6 hours post-dose shows new onset second degree or higher AV block.
- QTc interval > 450 msec in males, > 470 msec in females

### 4.5 Missed Dose

Re-initiation of therapy following treatment interruption during the dose escalation phase

Re-initiate treatment using the dose escalation regimen described in Table 1 above (see 4.2 Recommended Dose and Dosage Adjustment) if a dose of ZEPOSIA is missed during the first 2 weeks of treatment.

Re-initiation of therapy following treatment interruption during the maintenance phase

The same dose escalation regimen described in Table 1 above (see 4.2 Recommended Dose and Dosage Adjustment) must be followed when ZEPOSIA maintenance treatment is interrupted for:

- More than 7 consecutive days between Day 15 and Day 28 of treatment.
- More than 14 consecutive days after Day 28 of treatment.

If ZEPOSIA maintenance treatment is interrupted for a duration mentioned above, first-dose monitoring must be completed in patients for whom monitoring is recommended (see 4.4 Administration).

If the dose of ZEPOSIA missed after the first 2 weeks of treatment is of shorter duration than the above, continue with the treatment as planned.

## 5 OVERDOSAGE

Patients should be managed by symptomatic and supportive care.

In patients with overdosage of ZEPOSIA, it is important to observe for signs and symptoms of bradycardia, which may include overnight monitoring in a medical facility. Regular measurements of pulse rate and blood pressure are required, and continuous ECG monitoring should be performed. The decrease in HR induced by ozanimod can be reversed by parenteral atropine or isoprenaline.

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|---|
| For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669). |

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 2 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral | capsule 0.23 mg, 0.46 mg, 0.92 mg | colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose,<br>Capsule shell: black iron oxide (E172), gelatin, pharmaceutical ink, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172) |

0.23 mg: Size 4 opaque hard gelatin capsules with light grey body and light grey cap. Imprinted in black ink with “OZA” on cap and “0.23 mg” on the body.

0.46 mg: Size 4 opaque hard gelatin capsules with light grey body and orange cap. Imprinted in black ink with “OZA” on cap and “0.46 mg” on the body.

0.92 mg: Size 4 opaque hard gelatin capsules with orange body and orange cap. Imprinted in black ink with “OZA” on cap and “0.92 mg” on the body.

The ‘initiation pack’ is a folding wallet containing 7 hard gelatin capsules in blisters: 4 x 0.23 mg capsules and 3 x 0.46 mg capsules.

The one-month standard pack contains 28 x 0.92 mg hard gelatin capsules in blisters.

## 7 WARNINGS AND PRECAUTIONS

### Cardiovascular

Bradyarrhythmia and Atrioventricular Conduction Delays

Initiation of ZEPOSIA may result in transient reductions in heart rate and atrioventricular delays (see 8 ADVERSE REACTIONS).

See 4.1 Dosing Considerations for the cardiac assessments that should be performed before initiating treatment with ZEPOSIA.

In patient with certain cardiac conditions, first-dose monitoring is recommended and ZEPOSIA should therefore be administered in a clinical setting (see 4.4. Administration).

*Reduction in Heart Rate*

After the initial dose of ZEPOSIA 0.23 mg, the greatest mean reduction from baseline in heart rate occurred at Hour 5 on Day 1 (decrease of 1.2 bpm in the MS clinical trials, and 0.7bpm in the UC studies), returning to near baseline at Hour 6. With continued up-titration, the maximal heart rate effect of ozanimod occurred on Day 8.

Heart rates below 40 bpm were not observed. Initiation of ZEPOSIA without dose escalation may result in greater reductions in heart rate. (see 4.2 Recommended Dose and Dosage Adjustment).

In the MS phase 3 clinical studies, bradycardia was reported on the day of treatment initiation in 0.5% of patients treated with ZEPOSIA compared to no patients who received IFN beta-1a. After Day 1, the incidence of bradycardia was 0.8% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a.

In UC clinical studies, during induction in TRUENORTH-I and TOUCHSTONE-I studies, bradycardia was reported on the day of treatment initiation (Day 1), in 0.2% of patients treated with ozanimod and none in patients treated with placebo. After Day 1 bradycardia was reported in 0.2% of patients treated with ozanimod. During the maintenance in TRUENORTH-M, bradycardia was not reported. See 8.2 Clinical Trial Adverse Reactions, under Description of selected treatment emergent adverse events, for bradycardia events observed in MS and UC studies.

*Atrioventricular Conduction Delays*

Initiation of ZEPOSIA may result in transient atrioventricular conduction delays. At ZEPOSIA exposures higher than the recommended dosage without dose titration, first- and second-degree type 1 atrioventricular blocks were observed in healthy volunteers; however, in the phase 3 clinical studies with dose titration, second- or third-degree atrioventricular blocks were not reported in patients treated with ZEPOSIA.

<u>Treatment initiation recommendations in patients with certain cardiovascular conditions</u>

ZEPOSIA was not studied in patients who had:

- Myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure (see 2 CONTRAINDICATIONS).

- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second degree AV block or higher grade AV block (either history or observed at screening), unless patient had a functioning pacemaker (see 2 CONTRAINDICATIONS).

- Cardiac arrhythmias requiring treatment with Class Ia or III antiarrhythmic drugs.

- Significant QT prolongation (QTcF >450 msec males, >470 msec females).
- Severe untreated sleep apnea.
- A resting heart rate less than 55 beats per minute (bpm) at baseline.

If treatment with ZEPOSIA is considered in the context of the following cardiac conditions, an evaluation from a cardiologist should be sought prior to initiating treatment, to assess suitability of treatment and to determine the most appropriate strategy for monitoring cardiac effects.

- Patients with a pre-existing significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females).
- Patients with ischemic heart disease, heart failure, a history of cardiac arrest or myocardial infarction, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea. ZEPOSIA should not be used in these patients because significant bradycardia may be poorly tolerated.
- Patients with a history of with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block.
- A history of recurrent syncope or symptomatic bradycardia.
- With arrhythmias requiring treatment with Class 1a or Class III antiarrhythmic drugs.
- There is limited experience with ZEPOSIA in patients receiving concurrent treatment with heart-rate lowering drugs, including but not limited to, beta blockers, calcium channel blockers (such as verapamil or diltiazem), cholinomimetics or other substances that may decrease heart rate (e.g. ivabradine or digoxin). Concomitant use of these substances during ZEPOSIA initiation may be associated with severe bradycardia and heart block (see 9.2 Drug Interactions Overview).

  If concomitant treatment with a drug that reduces heart rate is considered during initiation of treatment with ZEPOSIA, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

Increased Blood Pressure

In the MS pivotal clinical studies, patients treated with ZEPOSIA had an average increase of approximately 1 to 2 mm Hg in systolic pressure over patients who received interferon (IFN) β-1a, and no effect on diastolic pressure. The increase in systolic pressure was first detected after approximately 3 months of treatment and persisted throughout treatment. Hypertension (hypertension, essential hypertension and blood pressure increased) was reported as an adverse reaction in 4.5% of patients treated with ZEPOSIA 0.92 mg and in 2.3% of patients who received IFN β-1a. Two patients treated for MS with ZEPOSIA 0.92 mg and one patient treated

with IFN β-1a experienced a hypertensive crisis that was not clearly influenced by a concomitant medication.

The mean increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in UC patients treated with ZEPOSIA was similar to patients with MS. See 8.2 Clinical Trial Adverse Reactions, under Description of selected treatment emergent adverse events, for Increased blood pressure events observed in UC trials. Hypertensive crisis was reported in the maintenance period in one patient receiving ozanimod and one patient receiving placebo.

Certain foods that may contain very high amounts (i.e., more than 150 mg) of tyramine could cause severe hypertension because of potential tyramine interaction in patients taking ZEPOSIA, even at the recommended doses. Because of an increased sensitivity to tyramine, patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

In MS clinical studies, hypertension was more frequently reported in patients treated with ZEPOSIA than in patients treated with IFN β-1a IM and in patients receiving concomitant ZEPOSIA and SSRIs or SNRIs (see 9.4 Drug-Drug Interactions).

Blood pressure should be regularly monitored during treatment with ozanimod and managed appropriately.

**Driving and Operating Machinery**

No studies on the effects on the ability to drive and the use of machines have been performed.

**Hepatic/Biliary/Pancreatic**

Elevated Hepatic Enzymes

Elevations of transaminases and total bilirubin have been reported in patients receiving ZEPOSIA during clinical trials and in the post marketing setting (see 8.1 Adverse Reaction Overview; 8.2 Clinical Trial Adverse Reactions; 8.5 Post-Market Adverse Reactions).

Clinically significant liver injury and acute liver failure requiring liver transplant, has occurred in patients treated with ZEPOSIA in the post marketing setting. Signs of liver injury, including elevated serum hepatic enzymes and elevated total bilirubin, with or without clinical symptoms, have occurred as early as ten days after the first dose.

Obtain liver function tests including aminotransferase and bilirubin levels if not recently available (i.e., within 6 months), before initiation of ZEPOSIA (see 4.1 Dosing Considerations).

During treatment with ZEPOSIA, in the absence of clinical symptoms, liver transaminase and total bilirubin levels should be evaluated at months 1, 3, 6, 9, 12 after initiating treatment and at regular intervals thereafter. For patients who develop liver transaminase levels above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase measurement. Treatment with ZEPOSIA should be interrupted with repeated confirmation of liver transaminases above 5 times the ULN and should only be re-initiated once

liver transaminase levels have normalized.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed.

Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ZEPOSIA and caution should be exercised with these patients. Dosage adjustments are required in patients with mild or moderate hepatic impairment and, use of ZEPOSIA in patients with severe hepatic impairment is not recommended (see 4.1 Dosing Considerations; 4.2 Recommended Dose and Dosage Adjustment; 10.3 Pharmacokinetics).

Use in patients with hepatic impairment

Exposure to active metabolites of ozanimod, CC112273 and CC1084037, is higher in patients with mild or moderate hepatic impairment (see 10.3 Pharmacokinetics), which may increase the risk of adverse reactions. Therefore, dosage adjustment in this patient population is required (see 4.2 Recommended Dose and Dosage Adjustment). Use of ZEPOSIA is not recommended in patients with severe hepatic impairment.

**Immune**

Infections

ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to 43% to 47% of baseline values at the 0.92 mg ozanimod dose because of reversible retention of lymphocytes in lymphoid tissues. ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA.

Patients receiving ZEPOSIA should be instructed to promptly report symptoms of infections to their physician to facilitate early and effective diagnostic and therapeutic strategies. Because the elimination of ozanimod after discontinuation may take up to 3 months, monitoring for infections should be continued throughout this period. Suspension of treatment with ZEPOSIA should be considered if a patient develops a serious infection (see 2 CONTRAINDICATIONS).

Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2 \times 10^9$/L, if confirmed on repeat testing, should lead to interruption of ozanimod therapy until the level reaches $>0.5 \times 10^9$/L when re-initiation of ozanimod can be considered.

See 8.2 Clinical Trial Adverse Reactions under description of selected treatment emergent adverse events, for infections reported in MS and UC trials. The proportion of patients who experienced lymphocyte counts less than $0.2 \times 10^9$ /L was 3.3% in MS studies and less than or equal to 3% in the controlled UC studies. These values generally returned to greater than $0.2 \times 10^9$ /L while patients remained on treatment with ZEPOSIA. After discontinuing ZEPOSIA 0.92

mg, the median time for peripheral blood lymphocytes to return to the normal range was approximately 30 days, with approximately 80 to 90% of patients in the normal range within 3 months.

*Herpetic Infections*

In the MS pivotal clinical studies, 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 who received IFN beta-1a. In UC clinical studies, herpes zoster was reported in 0.4% of patients who received ozanimod 0.92 mg and none in patients who received placebo in the induction period, in the maintenance period, herpes zoster was reported in 2.2% of patients who received ozanimod 0.92 mg and 0.4% of patients who received placebo. None were serious or disseminated in the UC trials (see 8.2 Clinical Trial Adverse Reactions, under description of selected treatment emergent adverse events, for herpetic infection events in MS and UC clinical trials. Herpes simplex encephalitis and varicella zoster meningitis have been reported with S1P receptor modulators.

Physicians should be vigilant for clinical symptoms that may be suggestive of serious herpetic infections. For cases of disseminated herpes infection, treatment should follow current relevant guidelines (see Vaccinations below).

*Cryptococcal Infection*

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with S1P receptor modulators. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. ZEPOSIA treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

*Progressive Multifocal Leukoencephalopathy*

Progressive multifocal leukoencephalopathy (PML) has been reported with ZEPOSIA in patients with MS. PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised and may lead to death or severe disability. With another S1P modulator, the estimated risk of PML appears to increase with cumulative exposure over time. Cases of PML have been reported after approximately 2-3 years of treatment in patients who had not been previously treated with other MS therapies with a known association with PML or in patients who had not previously received or were not concomitantly taking any suppressive or immunomodulatory medications.

Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, treatment with ozanimod should be suspended until PML has been excluded. If confirmed, treatment with ZEPOSIA should be discontinued.

MRI findings may be apparent before clinical signs or symptoms. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Before initiating treatment with ZEPOSIA, a recent MRI should be considered for patients switched from other MS agents that have a risk of PML (see 4.1 Dosing Considerations). During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions.

Human papilloma virus

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in patients under treatment with another S1P receptor modulator during postmarketing experience. Due to the immunosuppressive properties of ozanimod, vaccination against HPV should be considered prior to treatment initiation with ZEPOSIA taking into account vaccination recommendations (see 4.1 Dosing Considerations). Cancer screening, including Pap test, is recommended as per standard of care.

Vaccinations

- Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for VZV antibodies before initiating treatment with ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA, following which initiation of treatment with ZEPOSIA should be postponed for 1 month (see 4.1 Dosing Considerations).

- As with other drugs impacting the immune system, immunization recommendations for adults (routine and specific risk groups) from the Canadian Immunization Guide (https://www.canada.ca/en/public-health/services/publications/healthy-living/canadianimmunization-guide-part-3-vaccination-specific-populations.html) and local infectious disease experts should be considered when evaluating the need for other vaccinations, before commencing and during treatment with ZEPOSIA.

- No clinical data are available on the efficacy and safety of vaccinations in patients taking ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA.

Prior and Concomitant Treatment with Antineoplastic, Non-Corticosteroid Immunosuppressive, or Immune-modulating Therapies

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 and UC. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression.

In UC clinical studies, concomitant use of corticosteroids was allowed and did not appear to influence the safety or efficacy of ozanimod.

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy.

When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

ZEPOSIA can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

Immune System Effects Following Discontinuation of ZEPOSIA

After stopping ZEPOSIA the median time to recovery of peripheral blood lymphocyte to the normal range was approximately 30 days, with approximately 80% to 90% of patients with peripheral blood lymphocyte in the normal range within 3 months. However, use of immunosuppressants within this period may lead to an additive effect on the immune system. Physicians who choose to start a new immunosuppressant within 1-3 months after the last ZEPOSIA dose should consider that the major active metabolites of ozanimod may still remain in the blood.

*PML and IRIS (Immune Reconstitution Inflammatory Syndrome)*

No cases of IRIS after discontinuation of ZEPOSIA in the presence of PML have been reported; however, IRIS has been reported in patients treated with other S1P receptor modulators who developed PML and subsequently discontinued treatment. The time to onset of IRIS in patients with PML was generally within weeks to a few months after S1P receptor modulator discontinuation. IRIS presents as a worsening in neurological status that may be rapid, as a result of the sudden reconstitution of immune function. It can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS and appropriate treatment of the associated inflammatory reaction involving the brain should be undertaken.

**Monitoring and Laboratory Tests**

The following assessments should be done during treatment with ZEPOSIA

- Monitor for signs and symptoms of infections regularly during treatment. Complete blood count should also be periodically monitored (see 7 WARNINGS AND PRECAUTIONS, Immune).
- Monitor for signs and symptoms of liver injury. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic for detailed monitoring recommendations.
- Monitor for suspicious skin lesions regularly during treatment with ZEPOSIA, particularly in patients with risk factors for skin cancer (see 7 WARNINGS AND PRECAUTIONS, Neoplasm).
- An ophthalmic evaluation should be performed at any time in any patient complaining of

visual disturbances. Patients with diabetes mellitus or a history of uveitis are at increased risk for macula edema and should have regular ophthalmic evaluations while receiving ZEPOSIA (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).
- Monitor blood pressure regularly in all patients (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

**Neoplasm**

Malignancies have been reported with ZEPOSIA in clinical trials (see 8.2 Clinical Trial Adverse Reactions).

For patients treated with immunosuppressive or immune modulating drugs, including sphingosine 1-phosphate (S1P) receptor modulators, there is potential for an increased risk of malignancies, particularly of the skin. Since there is a potential risk of malignant skin growths, patients treated with ZEPOSIA should be cautioned against exposure to sunlight and ultraviolet light by wearing protective clothing and using sunscreen with a high protection factor. Patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy.

In the controlled Phase 3 MS studies, basal cell carcinoma was reported with a similar incidence in patients treated with ZEPOSIA (0.2%, 3 patients) and patients that received IFN beta-1a (0.1%, 1 patient). Other skin malignancies, including malignant melanoma in situ (<0.1%, 1 patient) and keratoacanthoma (<0.1%, 1 patient) were reported only in patients treated with ZEPOSIA. Vigilance for cutaneous neoplasms is recommended in patients treated with ZEPOSIA. Health care professionals and patients are advised to monitor for suspicious skin lesions before initiating treatment with ZEPOSIA and regularly during treatment, particularly for patients with risk factors for skin cancer. If a suspicious lesion is observed, it should be evaluated promptly.

In patients treated with ozanimod in UC controlled clinical studies one patient (0.2%) had squamous cell carcinoma of the skin, in the induction period, and one patient (0.4%) had basal cell carcinoma, in the maintenance period. One patient (0.4%) re-randomized to the maintenance placebo arm had breast cancer. There were no cases in patients who did not receive ozanimod.

**Neurologic**

Posterior Reversible Encephalopathy Syndrome (PRES)

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. In controlled MS clinical trials with ZEPOSIA, one case of PRES was reported in a patient with Guillain-Barré syndrome.

PRES is a syndrome characterized by sudden onset of severe headache, confusion, seizure and visual loss. Should a patient on ZEPOSIA treatment develop any unexpected neurological or psychiatric symptoms/signs (e.g. cognitive deficits, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/signs) or any symptom/sign suggestive of an increase of intracranial pressure or accelerated neurological deterioration, the

physician should promptly schedule a complete physical and neurological examination and should consider a magnetic resonance imaging (MRI). 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.

Increase in Disease Activity After ZEPOSIA Discontinuation

In MS, severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator. The possibility of severe exacerbation of disease after stopping ZEPOSIA treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon ZEPOSIA discontinuation and appropriate treatment should be instituted as required.

Serotonin Toxicity/Serotonin Syndrome

In vitro investigations showed that CC112273 and CC1084037, the active metabolites of ozanimod, were selective inhibitors of the monoamine oxidase B (MAO-B) (see 9.4 Drug-Drug Interactions).The concomitant use of MAO inhibitors, including selective MAO-B inhibitors, and serotonergic or opioid drugs has been associated with the occurrence of serotonin toxicity, also known as serotonin syndrome (see 9.4 Drug-Drug Interactions). In clinical trials, a small number of patients treated with ZEPOSIA were concomitantly exposed to serotonergic or opioid drugs with no reports of serotonin toxicity. However, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration.

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

Therefore, the concomitant use of ZEPOSIA with serotonin-norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), opioid drugs (e.g. meperidine and its derivatives, methadone, propoxyphene, tramadol, tapentadol), tricyclic, tetracyclic or triazolopyridine antidepressants, cyclobenzaprine or St John's wort is not recommended (see 9 DRUG INTERACTIONS). If co-administration of ZEPOSIA and a serotonergic or opioid drug is clinically warranted, a careful observation of the patient is advised, particularly during treatment initiation and doses increases (see 9 DRUG INTERACTIONS).

If serotonin toxicity is suspected, discontinuation of the serotonin agents should be considered.

**Ophthalmologic**

Macular Edema

In the active-controlled MS clinical trials with ZEPOSIA, macular edema was observed in one (0.1%) patient with ZEPOSIA 0.92 mg and 3 (0.3%) patients with ZEPOSIA 0.46 mg and none with IFN β-1a. Patients observed to have macular edema had pre-existing risk factors.

Macular edema was reported in a total of 1 (0.2%) patient in the TRUENORTH-I and TOUCHSTONE-I studies, and in 1 (0.4%) patient in the TRUENORTH-M study treated with ZEPOSIA, and in no patients who received placebo.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA. Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA should be discontinued needs to take into account the potential benefits and risks for the individual patient.

*Macular edema in patients with a history of uveitis or diabetes mellitus*

Patients with a history of diabetes mellitus, uveitis and underlying/co-existing retinal diseases are at increased risk of macular edema and require careful assessment before initiating treatment and during treatment with ZEPOSIA. The incidence of macular edema is also increased in MS patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

**Psychiatric**

Depression and Suicide

Depression and suicidal ideation are known to occur at an increased frequency in the MS population. A relationship between the occurrence of depression and/or suicidal ideation and the use of ZEPOSIA has not been established. A similar incidence of depression was seen in the IFN β-1a treated patients and the patients treated with ZEPOSIA in the active-controlled MS clinical trials (2.8% vs 2.6%, respectively). Patients treated with ZEPOSIA should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, antidepressant therapy or cessation of ZEPOSIA therapy should be considered.

**Reproductive Health: Female and Male Potential**

Women of childbearing potential/Contraception

ZEPOSIA is contraindicated in women (including female adolescents) who are pregnant or of

childbearing potential not using effective contraception (see 7.1.1 Pregnant Women and 2 CONTRAINDICATIONS). Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the fetus. Women (including female adolescents) of child-bearing potential should be advised that animal studies have shown that ozanimod is harmful to the developing fetus. Women of childbearing potential must use effective contraception (methods that result in less than 1% pregnancy rates) during treatment and for at least 3 months after discontinuation of ZEPOSIA, since it takes approximately 3 months for the active metabolites CC112273 and CC1084037 to be eliminated from the body after stopping treatment and potential risks to the fetus may persist during this time (see 10.3 Pharmacokinetics). If a woman becomes pregnant while taking this drug, the patient must be informed of the risk to the fetus.

- **Fertility**

  No fertility data are available in humans. In animal studies, no adverse effects on fertility were observed (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- **Teratogenic Risk**

  There are no adequate and well-controlled studies in pregnant women. In rats and rabbits, administration of ozanimod during organogenesis was well tolerated by the dams, but resulted in embryo- fetal death, abnormal/delayed ossification, and abnormalities of the viscera and large blood vessels of the offspring. Systemic exposure at the NOAEL for embryo fetal toxicity was 3.5 times (rat) and below (rabbit) systemic exposure of total active drug (combined ozanimod and the major pharmacologically active human metabolites CC112273 and CC1084037) at the maximum recommended human dose (see 7.1.1 Pregnant Women and 16 NON-CLINICAL TOXICOLOGY).

**Respiratory**

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in patients treated with ZEPOSIA as early as 3 months after treatment initiation. In pooled analyses of the pivotal studies (SUNBEAM and RADIANCE), the decline in absolute FEV1 from baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV1 at 12 months between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute value and % predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN β-1a (60 mL, 95% CI (-110, -10); 1.4%, 95% CI: (-2.6, -0.2)), though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after drug discontinuation. One patient discontinued ZEPOSIA because of dyspnea.

Similar to MS clinical studies, small mean reductions in pulmonary function tests were observed with ZEPOSIA relative to placebo ($FEV_1$ and FVC) during UC clinical studies in the induction

period. There were no further reductions with longer term treatment with ZEPOSIA, in the maintenance period and these small changes in pulmonary function tests were reversible in patients re-randomized to placebo.

Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA, if clinically indicated.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

ZEPOSIA is contraindicated in women (including female adolescents) who are pregnant or of childbearing potential not using effective contraception (see 2 CONTRAINDICATIONS).

There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women. The receptor affected by ozanimod (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development. Clinical experience (post-marketing data and pregnancy registry information) suggests that use of another S1P receptor modulator is associated with an increased risk of overall major congenital malformation when administered during pregnancy in comparison with the prevalence observed in the general population. The pattern of malformation reported with the other S1P receptor modulator is similar to that observed in the general population, with an increase in the prevalence of congenital heart disease (e.g., atrial septal defects), renal abnormalities, and musculoskeletal abnormalities.

Based on animal data and its mechanism of action ZEPOSIA can cause fetal harm when administered to a pregnant woman. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated ozanimod induced embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits (see 16 NON-CLINICAL TOXICOLOGY). In embryo foetal toxicity studies, adverse maternal effects or fetal toxicity during embryogenesis were observed at doses above 1 mg/kg/day in the rat and above 0.2 mg/kg/day in the rabbit. These doses in rats and rabbits yielded teratogenic effects in both. The fetal toxicity manifestations included embryo-fetal death, abnormal/delayed ossification, visceral abnormalities, and malformed great vessels. Systemic exposure at the NOAEL for embryo fetal toxicity was 3.5 times (rat) and below (rabbit) systemic exposure of total active drug (combined ozanimod and the major pharmacologically active human metabolites CC112273 and CC1084037) at the maximum recommended human dose.

Women of child bearing age should be advised of the potential risk to the fetus if the patient becomes pregnant while taking ZEPOSIA. Because it takes approximately 3 months for the active metabolites of ozanimod to be eliminated from the body after stopping treatment, ZEPOSIA must be discontinued at least 3 months before planning a pregnancy. Medical advice should be given regarding the risk of harmful effects on the fetus associated with treatment and medical follow-up examination should be performed (e.g. ultrasonography examination). The possibility of severe exacerbation of disease should be discussed with females discontinuing ZEPOSIA because of pregnancy or planned pregnancy (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ZEPOSIA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients on-line at www.Zeposiapregnancyregistry.com or by calling 1-877-301-9314.

### 7.1.2 Breast-feeding

A study in lactating rats treated with ozanimod showed excretion of ozanimod and its metabolites in the milk, at levels higher than those of maternal plasma (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). There are no data on the presence of ozanimod in human milk, the effects on the breast-fed infant, or the effects of the drug on milk production. Since many drugs are excreted in human milk and because of the potential for adverse reactions to ozanimod and its metabolites in nursing infants, women receiving ZEPOSIA should not breast-feed.

### 7.1.3 Pediatrics

**Pediatrics (<18 years of age)**: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics

The safety and effectiveness of ZEPOSIA in patients aged 65 years and over have not been studied. There are limited data available on RRMS patients > 55 years of age. Patients enrolled in the ongoing clinical trials continue to be dosed with 0.92 mg ozanimod daily after they become 55 and older. Caution should be used in patients > 65 years of age, given the potential for an increased risk of adverse reactions in this population, especially with long-term treatment.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

Multiple Sclerosis

The adverse drug reactions were determined based on data from the ozanimod clinical development programme. In 2 active-controlled MS clinical studies, 882 patients received ZEPOSIA 0.92 mg with an overall exposure of 1323 person-years. The adverse reactions presented in Table 3 below are based on safety information from 882 patients treated with ZEPOSIA 0.92 mg and 885 IFN β 1a-treated patients.

The most commonly reported adverse reactions in Phase III clinical studies were nasopharyngitis (11%), alanine aminotransferase increased (5%), and gamma-glutamyltransferase increased (5%). Overall the incidence of adverse reactions leading to discontinuation was 2.9% in patients treated with ZEPOSIA 0.2mg and 4.1% in patients treated with IFN.

The most common adverse reactions leading to discontinuation were related to liver enzyme elevations (1.1%).

The overall incidence of serious adverse reactions in the 1- and 2-year studies was 0.8% and did not indicate any specific system organ class.

Ulcerative Colitis

The safety of ZEPOSIA was evaluated in two randomized, double-blind, placebo-controlled clinical studies (TRUENORTH-Induction [I], n=429) and TRUENORTH-Maintenance [M], n =230) in adult subjects with moderately to severely active ulcerative colitis. Data from the induction period of a Phase 2 randomized, double-blind, placebo-controlled study (TOUCHSTONE-Induction [I], n=67), in adult subjects with moderately to severely active ulcerative colitis, is also included in Table 4.

Treatment induction was studied in a total of 496 patients who received ZEPOSIA 0.92 mg with an overall exposure of 97.5 person years. The overall exposure of the 230 patients in TRUENORTH-M was 165.5 person-years.

Additional safety information, provided in 8.2 Clinical Trial Adverse Reactions - Description of selected treatment emergent adverse events includes data from the maintenance period of the TOUCHSTONE study and uncontrolled studies. In the randomized and uncontrolled studies, 1158 patients received ZEPOSIA 0.92 mg with an overall exposure of 1841.7 person-years.

The most commonly reported adverse reactions in the TRUENORTH-I and TOUCHSTONE-I studies were liver function test increased (4.8%) and nasopharyngitis (3.0%). The most commonly reported adverse reactions in the TRUENORTH-M study was liver function test increased (10.9%), alanine aminotransferase increased (4.8%) and headache (3.9%).

The most common adverse reactions leading to discontinuation during the TRUENORTH-I and TOUCHSTONE-I studies were related to GI disorders (0.8%). Overall the incidence of adverse reactions leading to discontinuation was 3% of subjects treated with ZEPOSIA 0.92 mg versus 2.8% of subject treated with placebo. The most common adverse reactions leading to discontinuation during the TRUENORTH-M study was related to eye disorder (0.4%), ovarian cyst (0.4%) and liver function test increased (0.4%). Overall, the incidence of adverse reactions leading to discontinuation was 1.3% of subjects treated with ZEPOSIA 0.92 mg in the TRUENORTH-M study versus 2.6% of subjects treated with placebo.

The overall safety profile was similar for patients with RRMS and UC.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Multiple Sclerosis

Treatment-Emergent Table 3 lists treatment emergent adverse events that occurred in greater than or equal to 1% of ZEPOSIA-treated patients and at a similar or higher rate than for IFN β-1a.

The most common adverse reaction was nasopharyngitis.

**Table 3 - Treatment-Emergent Adverse Events[a] with an Incidence of Greater Than or Equal to 1% for ZEPOSIA and at Equal or Higher Rates Than for IFN β-1a**

| | ZEPOSIA 0.92 mg n = 882 (%) | IFN β-1a 30 mcg n = 885 (%) |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Abdominal pain upper | 20 (2.3) | 9 (1.0) |
| Nausea | 15 (1.7) | 10 (1.1) |
| Diarrhea | 12 (1.4) | 12 (1.4) |
| **General Disorders and Administration Site Conditions** | | |
| Fatigue | 20 (2.3) | 16 (1.8) |
| Asthenia | 12 (1.4) | 10 (1.1) |
| **Infections and Infestations** | | |
| Nasopharyngitis | 98 (11.1) | 84 (9.5) |
| Urinary tract infection[b] | 36 (4.1) | 27 (3.1) |
| Pharyngitis | 28 (3.2) | 20 (2.3) |
| Bronchitis | 23 (2.6) | 17 (1.9) |
| Respiratory tract infection viral | 21 (2.4) | 11 (1.2) |
| Rhinitis | 19 (2.2) | 13 (1.5) |
| Cystitis | 10 (1.1) | 9 (1.0) |
| **Injury, Poisoning and Procedural Complications** | | |
| Contusion | 10 (1.1) | 7 (0.8) |
| **Investigations** | | |
| Liver function test increased[c] | 93 (10.5) | 49 (5.5) |

| | | |
|---|---|---|
| Pulmonary function test decreased[d] | 15 (1.7) | 7 (0.8) |
| **Metabolism and Nutrition Disorders** | | |
| Hypercholesterolemia | 17 (1.9) | 14 (1.6) |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Back pain | 35 (4.0) | 23 (2.6) |
| Arthralgia | 28 (3.2) | 14 (1.6) |
| **Nervous System Disorders** | | |
| Headache[e] | 82 (9.3) | 80 (9.0) |
| Vertigo | 11 (1.2) | 7 (0.8) |
| Dizziness | 10 (1.1) | 10 (1.1) |
| Migraine | 9 (1.0) | 6 (0.7) |
| **Psychiatric Disorders** | | |
| Insomnia | 21 (2.4) | 20 (2.3) |
| **Vascular Disorders** | | |
| Hypertension[f] | 41 (4.6) | 21 (2.4) |
| Orthostatic hypotension | 38 (4.3) | 28 (3.2) |

[a] Preferred Terms are coded using the MedDRA (Version 18.1)

[b] At least one of these adverse reactions was reported as serious

[c] Includes the following terms: ALT increased, AST increased, GGT increased, liver function test abnormal, blood bilirubin increased, blood alkaline phosphatase increased, hepatic enzyme increased, bilirubin conjugated increased, transaminases increased.

[d] Includes the following terms: forced vital capacity decreased, carbon monoxide diffusing capacity decreased, forced expiratory volume decreased, spirometry abnormal, pulmonary function test abnormal, pulmonary function test decreased.

[e] Includes the following terms: headache, tension headache, cluster headache.

[f] Includes the following terms: hypertension, orthostatic hypertension, essential hypertension, hypertensive crisis, blood pressure increased.

Ulcerative Colitis

**Table 4 - Treatment- Emergent Adverse Events Reported by ≥1% of Patients Treated with ZEPOSIA during induction period (TRUENORTH-I and TOUCHSTONE-I) and ≥1% higher than placebo**

| | Induction Period (TRUENORTH-I; TOUCHSTONE-I) | |
|---|---|---|
| | **ZEPOSIA 0.92 mg n = 496 (%)** | **Placebo (n = 281) %** |
| **Gastrointestinal Disorders** | | |
| Nausea | 14 (2.8) | 5 (1.8) |
| Vomiting | 7 (1.4) | 1 (0.4) |
| **General Disorders and Administration Site Conditions** | | |
| Pyrexia | 14 (2.8) | 3 (1.1) |
| **Infections and Infestations** | | |
| Nasopharyngitis | 15 (3.0) | 3 (1.1) |
| **Investigations** | | |
| Liver function test increased[a] | 24 (4.8) | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Arthralgia | 12 (2.4) | 3 (1.1) |
| **Vascular Disorders** | | |
| Hypertension | 6 (1.2) | 0 |

[a] Includes the following terms: ALT increased, AST increased, GGT increased

**Table 5- Treatment- Emergent Adverse Events Reported by ≥1% of Patients Treated with ZEPOSIA during maintenance period (TRUENORTH-M) and ≥1% higher than placebo**

| | Maintenance Period (TRUENORTH-M) | |
|---|---|---|
| | **ZEPOSIA 0.92 mg n = 230 (%)** | **Placebo (n = 227) %** |
| **Gastrointestinal Disorders** | | |
| Dyspepsia | 3 (1.3) | 0 |
| **General Disorders and Administration Site Conditions** | | |
| Oedema peripheral | 6 (2.6) | 0 |
| **Infections and Infestations** | | |
| Nasopharyngitis | 7 (3.0) | 4 (1.8) |
| Herpes zoster | 5 (2.2) | 1 (0.4) |
| Gastroenteritis | 3 (1.3) | 0 |
| Oral herpes | 3 (1.3) | 0 |
| **Investigations** | | |
| Liver function test increased[a] | 25 (10.9) | 3 (1.3) |
| **Nervous System Disorders** | | |
| Headache | 9 (3.9) | 1 (0.4) |

[a] Includes the following terms: ALT increased, GGT increased and Liver function test increased

### Description of selected treatment emergent adverse events

Elevated Hepatic Enzymes

In active-controlled MS clinical trials, elevations of 3-fold the ULN or greater occurred in 5.5% of patients on ZEPOSIA and 3.1% of patients on interferon (IFN) β-1a. The median time to elevation 3-fold the ULN was 6 months. The majority (79%) continued treatment with ZEPOSIA with values returning to < 3 times the ULN within approximately 2-4 weeks. Elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ZEPOSIA 0.92 mg and 1.3% of patients on IFN β-1a. In MS clinical studies, ZEPOSIA was

discontinued for a confirmed elevation greater than 5-fold the ULN.

Overall, the discontinuation rate due to elevations in hepatic enzymes was 1.1% of MS patients on ZEPOSIA 0.92 mg and 0.8% of patients on IFN β-1a.

In UC studies, elevations of ALT to 3-fold the ULN or greater occurred in the TRUENORTH-I study in 2.6% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo, and in TRUENORTH-M elevations occurred in 2.3% and no patients, respectively. In controlled and uncontrolled UC clinical studies, the majority (96%) of patients with ALT greater than 3-fold the ULN continued treatment with ozanimod with values returning to less than 3 fold the ULN within approximately 2 to 4 weeks.

In the TRUENORTH-I study, elevations of ALT to 5-fold the ULN or greater occurred in 0.9% of patients treated with ZEPOSIA 0.92 mg and 0.5% of patients who received placebo, and in the TRUENORTH-M study elevations occurred in 0.9% and no patients, respectively.

Overall, the discontinuation rate because of elevations in hepatic enzymes was 0.4% of patients treated with ozanimod 0.92 mg, and none in patients who received placebo in the controlled UC clinical studies.

Increased Blood Pressure

In active-controlled MS clinical trials, patients treated with ZEPOSIA had an average increase of approximately 1 to 2 mm Hg in systolic pressure over IFN β-1a, and no effect on diastolic pressure. The increase in systolic pressure was first detected after approximately 3 months of treatment initiation and persisted throughout treatment. Hypertension (hypertension, essential hypertension, and blood pressure increased) was reported as an adverse reaction in 4.5% of patients treated with ZEPOSIA 0.92 mg and in 2.3% of patients who received IFN β-1a.

The mean increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in UC patients treated with ozanimod is similar to patients with MS. In UC clinical studies [TRUENORTH and TOUCHSTONE], during the induction period, the average increase from baseline in SBP was 3.7 mm Hg in patients treated with ozanimod and 2.3 mm Hg in patients treated with placebo. During the maintenance period, the average increase from baseline in SBP was 5.1 mm Hg in patients treated with ozanimod and 1.5 mm Hg in patients treated with placebo. There was no effect on DBP.

Hypertension was reported as an adverse reaction in 1.2% of patients treated with ozanimod 0.92 mg and none in patients treated with placebo in the induction period, and in 2.2% and 2.2% of patients in the maintenance period, respectively. Hypertensive crisis was reported in one patients receiving ozanimod and one patient receiving placebo.

Bradyarrhythmia

After the initial dose of 0.23 mg, the greatest mean reduction from baseline in sitting/supine HR occurred at Hour 5 on Day 1 (decrease of 1.2 bpm in active-controlled MS clinical studies and 0.7 bpm in controlled UC induction studies), returning to near baseline at Hour 6.

Bradycardia was reported in 0.5% of patients on ZEPOSIA versus 0% on IFN β-1a on the day of treatment initiation. After Day 1, the incidence of bradycardia was 0.8% on ZEPOSIA versus 0.7% on IFN β-1a. Patients who experienced bradycardia were generally asymptomatic. Heart rates below 40 beats per minute were not observed.

In active-controlled MS clinical trials with dose escalation, clinically relevant abnormalities with >2% higher incidence in the ozanimod treatment group on Day 1, Hour 6 were atrial premature complexes, sinus arrhythmia, ventricular premature complexes, short PR interval (no delta wave), and first-degree atrioventricular block; second-or third-degree atrioventricular blocks were not reported with continuous ZEPOSIA 0.92 mg treatment.

In UC clinical studies, during the induction period, bradycardia was reported on the day of treatment initiation (Day 1), in 0.2% of patients treated with ozanimod and none in patients treated with placebo. After Day 1 bradycardia was reported in 0.2% of patients treated with ozanimod. During the maintenance period, bradycardia was not reported.

Blood Lymphocyte Count Reduction

In MS clinical studies, 3.3% of patients and in UC controlled clinical studies, less than 3% of patients experienced lymphocyte counts less than 0.2 x $10^9$/L, with values generally resolving to greater than 0.2 x $10^9$/L while remaining on treatment with ZEPOSIA.

After discontinuing ZEPOSIA 0.92 mg, the median time to recovery of peripheral blood lymphocytes to the normal range was 30 days, with approximately 90% of patients recovering within 3 months.

Infections

In active-controlled MS trials, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA 0.92 mg was comparable with patients treated with IFN β-1a (35.1% vs. 34.5 % and 1% vs 0.8%, respectively).

Progressive multifocal leukoencephalopathy was reported with ZEPOSIA (see 7 WARNINGS AND PRECAUTIONS, Immune).

In UC clinical studies, during the induction period, the overall rate of infections and rate of serious infections in patients treated with ozanimod were similar to that in patients who received placebo. (9.9% vs. 10.7% and 0.8% vs. 0.4%, respectively). During the maintenance period, the overall rate of infections in patients treated with ozanimod was higher than in patients treated with placebo (23% vs. 12%) and the rate of serious infections was similar (0.9% vs. 1.8%).

ZEPOSIA increased the risk of upper respiratory tract infections, urinary tract infection, and herpes infections.

*Herpetic infections*

In MS clinical studies, herpes zoster was reported in 0,6% of patients treated with ZEPOSIA

0.92 mg and in 0.2% of patients on IFN β-1a.

In UC clinical studies, herpes zoster was reported in 0.4% of patients who received ozanimod 0.92 mg and none in patients who received placebo in the induction period. In the maintenance period, herpes zoster was reported in 2.2% of patients who received ozanimod 0.92 mg and in 0.4% of patients who received placebo. None were serious or disseminated.

Respiratory system

Dose-dependent reductions in absolute forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were observed in patients treated with ZEPOSIA (see 7 WARNINGS AND PRECAUTIONS, Respiratory). These small changes were not progressive and were reversible with discontinuation of ZEPOSIA.

Neoplasm

Malignancies, such as melanoma, basal cell carcinoma, squamous cell carcinoma of the skin, breast cancer, and seminoma, were reported with ZEPOSIA in the active-controlled trials in MS and UC. An increased risk of cutaneous malignancies has been reported with another S1P receptor modulator.

Cervical squamous cell carcinoma, dermatofibrosarcoma protuberans and ovarian cancer have also been reported in the open-label extension trial with ZEPOSIA in multiple sclerosis.

Hypersensitivity

Hypersensitivity, including rash and urticaria, has been reported with ZEPOSIA in active-controlled MS clinical trials.

### 8.3 Less Common Clinical Trial Adverse Reactions

Multiple Sclerosis

The following is a list of treatment-emergent adverse events reported by patients treated with ZEPOSIA at any dose in MS-controlled trials (n=1944) at an incidence of < 1% in any treatment group but at an incidence of ≥ 0.3% higher in the ZEPOSIA group than IFN β-1a or placebo. Although the events reported occurred during treatment with ZEPOSIA, they were not necessarily caused by ZEPOSIA.

**Blood and lymphatic system disorders:** iron deficiency anemia

**Cardiac disorders:** palpitations, AV block first degree, sinus bradycardia

**Endocrine disorders:** autoimmune thyroiditis

**Eye disorders:** eye pain, vision blurred, retinal disorder, cataract, blepharospasm, macular degeneration, optic atrophy

**Gastrointestinal disorders:** gastritis, GERD, dyspepsia, dental caries, chronic gastritis, aphthous ulcer

**General disorders and administration site conditions:** peripheral swelling, chest discomfort

**Hepatobiliary disorders:** hyperbilirubinemia

**Immune system disorders:** seasonal allergy

**Infections and Infestations:** tonsillitis, cystitis, gastroenteritis, vaginal infection, viral infection, tracheitis, herpes zoster, ear infection, tooth abscess, viral upper respiratory tract infection, conjunctivitis, vulvovaginal mycotic infection, appendicitis

**Injury, poisoning and procedural complications:** joint injury, muscle strain

**Investigations:** activated partial thromboplastin time prolonged, weight increased, blood triglycerides increased

**Metabolism and nutrition disorders:** hyperlipidemia, decreased appetite, dyslipidemia

**Musculoskeletal and connective tissue disorders:** muscular weakness, spinal pain, neck pain, intervertebral disc disorder, joint swelling

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** melanocytic nevus, uterine leiomyoma, lipoma

**Nervous system disorders:** muscle spasticity, neuralgia, tension headache, trigeminal neuralgia

**Psychiatric disorders:** anxiety disorder

**Renal and urinary disorders:** urinary incontinence

**Reproductive system and breast disorders:** menstruation irregular, ovarian cyst, menstrual disorder, metrorrhagia, breast cyst

**Respiratory, thoracic and mediastinal disorders:** oropharyngeal pain, catarrh, rhinorrhea, epistaxis, dyspnea, nasal congestion, nasal septum deviation, paranasal cyst

**Skin and Subcutaneous Tissue Disorders:** alopecia, pruritus, urticaria, seborrheic dermatitis, skin disorder, skin lesion

**Vascular disorders:** hypotension, phlebitis

Ulcerative Colitis

The following is a list of treatment-emergent adverse events reported by patients treated with

ZEPOSIA 0.92 mg during the Induction and Maintenance periods at an incidence of < 1% but at an incidence of ≥ 0.5% higher in the ZEPOSIA group than placebo. Although the events reported occurred during treatment with ZEPOSIA, they were not necessarily caused by ZEPOSIA.

**Blood and lymphatic system:** lymphopenia

**Eye disorders:** cataract

**Ear and labyrinth disorders:** tinnitus

**Gastrointestinal disorders:** abdominal pain upper, dyspepsia, flatulence, gastritis, gastroesophageal reflux disease

**General disorders and administration site conditions:** non-cardiac chest pain

**Infections and Infestations:** bronchitis gastroenteritis viral

**Investigations:** hepatic enzyme increased

**Metabolism and nutrition disorders:** decreased appetite

**Psychiatric disorders:** insomnia

**Renal and urinary disorders:** nephrolithiasis

**Respiratory, thoracic and mediastinal disorders:** oropharyngeal pain

**Skin and Subcutaneous Tissue Disorders:** acne, erythema nodosum, ingrowing nail, pruritus, psoriasis

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

**Clinical Trial Findings**

Multiple Sclerosis

**Table 6 - Abnormal Laboratory Findings with an Incidence of Greater Than or Equal to 1% for ZEPOSIA**

| Laboratory Parameter | ZEPOSIA 0.92 mg n = 882 (%) | IFN β-1a 30 mcg n = 885 (%) |
|---|---|---|
| **Blood & Lymphatic System Disorders** | | |
| Grade 4 lymphopenia[a] | 29 (3.3) | 0 |
| **Investigations** | | |
| Alanine aminotransferase increased | 47 (5.3) | 28 (3.2) |
| Gamma-glutamyltransferase increased | 40 (4.5) | 11 (1.2) |
| Hypercholesterolemia | 17 (1.9) | 14 (1.6) |
| Aspartate aminotransferase increased | 16 (1.8) | 17 (1.9) |
| Hepatic enzyme increased | 12 (1.4) | 6 (0.7) |

[a] Absolute lymphocyte count < 0.2 x $10^9$/L

Ulcerative Colitis

**Table 7 - Abnormal Laboratory Findings with an Incidence of Greater Than or Equal to 1% for ZEPOSIA in the induction period (TRUENORTH-I and TOUCHSTONE-I) and ≥1% higher than placebo**

| | Induction Period (TRUENORTH-I; TOUCHSTONE-I) | |
|---|---|---|
| **Laboratory Parameter** | **ZEPOSIA 0.92 mg n = 496 (%)** | **Placebo n = 281 (%)** |
| **Investigations** | | |
| Alanine aminotransferase increased | 12 (2.4) | 0 |

| | | |
|---|---|---|
| Aspartate aminotransferase increased | 6 (1.2) | 0 |
| Gamma-glutamyltransferase increased | 6 (1.2) | 0 |

**Table 8 - Abnormal Laboratory Findings with an Incidence of Greater Than or Equal to 1% for ZEPOSIA in maintenance period (TRUENORTH-M) and ≥1% higher than placebo**

| | **Maintenance Period (TRUENORTH-M)** | |
|---|---|---|
| **Laboratory Parameter** | **ZEPOSIA 0.92 mg n = 230 (%)** | **Placebo n = 227 (%)** |
| **Investigations** | | |
| Alanine aminotransferase increased | 11 (4.8) | 1 (0.4) |
| Gamma-glutamyltransferase increased | 7 (3.0) | 1 (0.4) |
| Liver function test increased | 3 (1.3) | 0 |

At week 10 in the induction period, 1.1% of patients treated with ZEPOSIA had grade 4 lymphopenia and no patients on placebo. Overall, of patients who entered the maintenance period, 3% of patients treated with ZEPOSIA developed grade 4 lymphopenia during study treatment.

### 8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during postapproval use of ZEPOSIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Hepatobiliary Disorders:** Liver injury.

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

**Serious Drug Interactions**

- Monoamine oxidase (MAO) inhibitors (e.g. selegiline, phenelzine, rasagiline, safinamide, the antibiotic linezolid and the dye methylene blue)
  See 9.4 Drug-Drug Interactions

## 9.2 Drug Interactions Overview

**Pharmacodynamic interactions**

Anti-neoplastic, immune-modulating or Non-Corticosteroid immunosuppressive therapies

ZEPOSIA has not been studied in combination with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies. Co-administration of anti-neoplastic, immune-modulating or immunosuppressive therapies is not recommended due to the risk of additive immune effects during such therapy and in the weeks following discontinuation of any of these drugs.

When switching to or from other disease modifying therapies with immunosuppressive or immune-modulating effects, the half-life and mode of action of ZEPOSIA and the other therapy must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation.

ZEPOSIA can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

Anti-arrhythmic Drugs and QTc-Prolonging Drugs

ZEPOSIA has not been studied in patients taking QTc-prolonging drugs. ZEPOSIA has been shown to not meaningfully prolong the QTc interval. Because of potential additive effects of QTc prolonging drugs with known arrhythmogenic properties on heart rate reductions, treatment with ZEPOSIA should generally not be initiated in patients who are concurrently receiving Class Ia (e.g., disopyramide, procainamide) or Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs or other QTc-prolonging drugs. Class Ia and Class III antiarrhythmics were excluded from use in the multiple sclerosis clinical trials of ZEPOSIA. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought regarding the switch to non-QTc-prolonging drugs or appropriate monitoring (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

In addition to the Class Ia and Class III antiarrhythmic drugs, other drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples found below. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes: Class 1c antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, haloperidol); antidepressants (e.g., fluoxetine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone);

macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, ciprofloxacin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole); domperidone; 5-HT3 receptor antagonists (e.g., ondansetron); kinase inhibitors (e.g., sunitinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol). Current information sources should be consulted for more comprehensive lists of QTc-prolonging drugs.

Heart Rate-Lowering Drugs

The effect of co-administration of the maintenance dosage of ZEPOSIA, propranolol, or diltiazem, or administration with both a beta blocker and a calcium channel blocker taken together has not been studied.

ZEPOSIA has not been studied with Class Ia or III antiarrhythmics, or other substances that may decrease heart rate, including, but not limited to, digoxin, cholinesterase inhibitors, pilocarpine, or ivabradine. Due to potential additive effects on reduction of heart rate or cardiac conduction, ZEPOSIA should not be initiated in patients receiving these classes of medication. If treatment with ZEPOSIA is considered necessary, advice from a cardiologist should be sought regarding the switch to a non-heart-rate lowering drug or for appropriate monitoring (e.g., at least overnight monitoring) during treatment initiation, if the heart-rate-lowering drugs cannot be discontinued (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Vaccination

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ZEPOSIA treatment and for up to 3 months after discontinuation of treatment with ZEPOSIA (see 7 WARNINGS AND PRECAUTIONS, Immune). During, and for up to three months after discontinuation of treatment with ZEPOSIA, vaccinations may be less effective.

**Pharmacokinetic interactions**

Ozanimod is extensively metabolized in humans to form a number of circulating active metabolites, including two major active metabolites, CC112273 and CC1084037 and several minor active metabolites including RP101988 and RP101075 (see 10.3 Pharmacokinetics).

Effect of ozanimod on MAO Activity

In vitro, CC112273 and CC1084037 inhibited MAO-B with more than 1000-fold selectivity over monoamine oxidase A (MAO-A) ($IC_{50}$ > 10000 nM) with $IC_{50}$ values of 5.72 nM and 58 nM, respectively. Free concentrations of CC112273 and CC1084037 are less than 8% of these in vitro $IC_{50}$ values.

## 9.4 Drug-Drug Interactions

***The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).***

**Table 9 - Established or Potential Drug-Drug Interactions**

| [Proper/Common name] | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| BCRP inhibitors (e.g. cyclosporine, eltrombopag) | T | Coadministration of ozanimod with cyclosporine, a strong BCRP inhibitor, had no effect on the exposure of ozanimod and its major active metabolites (CC112273 and CC1084037) | |
| Strong CYP2C8 Inhibitors (e.g. gemfibrozil) | CT | Co-administration of gemfibrozil 600 mg twice daily at steady state and a single dose of ozanimod 0.46 mg increased exposure (AUC) of major active metabolites CC112273 and CC1084037 by approximately 47% and 69%, respectively. | Co-administering ZEPOSIA with strong CYP2C8 inhibitors is not recommended. |
| Strong CYP2C8 Inducers (e.g. rifampin) | CT | Co-administration of rifampin 600 mg once daily at steady state and a single dose of ZEPOSIA 0.92 mg resulted in reduced exposure (AUC) for CC112273 and CC1084037 by approximately 60% and 55%, respectively. | Co-administration of strong CYP2C8 inducers with ZEPOSIA is not recommended as this may lead to a decrease in the efficacy of ZEPOSIA. |

Legend: CT = Clinical Trial; T = Theoretical

Monoamine Oxidase (MAO) Inhibitors

The potential for clinical interaction with MAO inhibitors has not been studied. However, the co-administration with MAO-B inhibitors may decrease exposure of the major active metabolites CC112273 and consequently CC1084037. In addition, CC112273 and CC1084037 inhibited MAO-B in vitro ($IC_{50}$ values of 5.72 nM and 58 nM, respectively) with more than 1000-fold selectivity over MAO-A. Therefore, the concomitant use of drugs in the MAO inhibitor class (e.g. selegiline, phenelzine, rasagiline, safinamide) or other drugs that are potent inhibitors of MAO (including the antibiotic linezolid and the dye methylene blue), is contraindicated due to the likely reduction in active metabolite concentration leading to reduced therapeutic effect and risk of non-selective MAO inhibition, which may lead to hypertensive crisis (See 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

At least 3 months should elapse between discontinuation of ZEPOSIA and initiation of treatment with MAO inhibitors.

Tyramine

MAO in the gastrointestinal tract and liver (primarily type A) provides protection from exogenous amines (e.g., tyramine). If tyramine were absorbed intact, it could lead to severe hypertension, including hypertensive crisis. Aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines (e.g., aged cheese, pickled herring) may cause release of norepinephrine resulting in a rise in blood pressure (tyramine reaction). Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of ZEPOSIA.

Adrenergic and Serotonergic Agents

*Opioid and serotonergic medications*

Serious, sometimes fatal reactions, including serotonin toxicity (also known as serotonin syndrome) have been precipitated by concomitant use of MAO inhibitors (including selective MAO-B inhibitors) with opioid drugs (e.g., meperidine and its derivatives, methadone, propoxyphene, tramadol or tapentadol) and/or serotonin medications. In clinical trials, a small number of patients treated with ZEPOSIA were concomitantly exposed to opioids and/or serotonergic medications with no events of serotonin toxicity/serotonin syndrome. However, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration. Therefore, the co-administration of ZEPOSIA with opioid drugs and/or serotonergic medications, including serotonin-norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), tricyclic, tetracyclic or triazolopyridine antidepressants, cyclobenzaprine or St John's wort, is not recommended. If concomitant treatment with ZEPOSIA and opioid drugs or serotonergic medications is clinically warranted, a careful observation of the patient is advised, particularly during treatment initiation and dose increases.

*Sympathomimetic medications*

A placebo-controlled crossover study was conducted to assess the potential of ZEPOSIA to enhance pressor responses to pseudoephedrine in healthy subjects. Co-administration of ZEPOSIA with pseudoephedrine did not potentiate the pseudoephedrine-induced blood pressure response. No clinically significant differences in heart rate or blood pressure was observed when ZEPOSIA 1.84 mg daily (two times the recommended dosage) for 28 days was co-administered with a single dose of 60 mg pseudoephedrine (a sympathomimetic agent) compared to pseudoephedrine alone. However, hypertensive crisis has occurred with administration of ZEPOSIA 0.92 mg alone and hypertensive crisis has been reported with co-administration of other selective and nonselective MAO inhibitors (e.g., rasagiline) with sympathomimetic medications (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

### 9.5 Drug-Food Interactions

Food (high- and low-fat meals) intake had no effect on ozanimod exposure ($C_{max}$ and AUC).

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

MS and UC are autoimmune diseases characterized by the trafficking and accumulation of autoimmune-driven T and B lymphocytes in inflamed tissues.

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator. In humans, approximately 94% of circulating total active drug exposure is represented by ozanimod (6%) and the two major active metabolites CC112273 (73%), and CC1084037 (15%), all binding with high affinity to S1P1 and S1P5 subtypes. The binding of ozanimod and its metabolites to S1P1 receptors on lymphocytes prevents lymphocyte egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which ozanimod and its active metabolites exert their therapeutic effects in multiple sclerosis and ulcerative colitis is unknown but may involve reduction of lymphocyte migration into the central nervous system and intestine.

The ozanimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Ozanimod has minimal impact on cells involved in innate immune response.

### 10.2 Pharmacodynamics

Immune System

*Reduction in Blood Lymphocyte Counts*

In active-controlled MS clinical trials and controlled UC studies, mean lymphocyte counts decreased to approximately 43% to 47% of baseline at 3 months (approximate mean blood lymphocyte counts 0.8 x $10^9$/L) and remained stable during treatment with ZEPOSIA.

After discontinuing ZEPOSIA 0.92 mg, the median time to recovery of peripheral blood lymphocytes to the normal range was 30 days, with approximately 80 to 90% of patients with peripheral blood lymphocyte in the normal range within 3 months.

Reduction in faecal calprotectin (FCP)

In patients with UC, treatment with ozanimod resulted in a decrease in the inflammatory marker, faecal calprotectin (FCP) during the induction period (TRUENORTH-I and TOUCHSTONE-I), which was then maintained throughout the maintenance period. Ozanimod produced a

nominally significantly greater reduction in mean serum FCP at Week 10 compared with placebo (TRUENORTH-I: -470.231 versus 21.115 µg/g; p = 0.002); this effect was maintained at Week 52 among subjects continuously treated with ozanimod compared with those re-randomized to placebo (TRUENORTH-M: -1575.136 versus -463.285 µg/g; nominal p = 0.019).

Reduction in Heart Rate

Ozanimod may cause a transient reduction in heart rate on initiation of dosing (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). A dose escalation schedule of ZEPOSIA 0.23 mg followed by doses of 0.46 mg, and 0.92 mg attenuates the magnitude of heart rate reductions (see 4.2 Recommended Dose and Dosage Adjustment).

Cardiac Electrophysiology

In a randomized, double-blind, positive- and placebo-controlled, parallel group thorough QT study using a 14-day dose-escalation regimen of 0.23 mg QD on Days 1-4, 0.46 mg QD on Days 5-7, 0.92 mg QD (target therapeutic dose) on Days 8-10, and 1.84 mg QD (supratherapeutic dose) on Days 11-14 in healthy subjects (62/group), there was no evidence of any clinically relevant effect on the QTcF interval. The duration of treatment in this study was not sufficient to achieve steady-state plasma concentrations of the major metabolites, CC112273 and CC1084037.

### 10.3 Pharmacokinetics

Ozanimod is extensively metabolized in humans to form a number of circulating active metabolites, including two major active metabolites, CC112273 and CC1084037, with similar activity and selectivity for $S1P_1$ and $S1P_5$ to the parent drug. The maximum plasma concentration ($C_{max}$) and area under the curve (AUC) for ozanimod, CC112273, and CC1084037 increased proportionally over the dose range of ZEPOSIA 0.46 mg to 0.92 mg (0.5 to 1 time the recommended dose). Following multiple dosing, approximately 94% of circulating total active drug exposure are represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%). At a dose of 0.92 mg orally once daily in RRMS, the geometric mean [coefficient of variation (CV%)] $C_{max}$ and $AUC_{0\text{-}24h}$ at steady state were 231.6 pg/mL (37.2%) and 4223 pg*h/mL (37.7%), respectively, for ozanimod and 6378 pg/mL (48.4%) and 132861 pg*h/mL (45.6%), respectively, for CC112273. $C_{max}$ and $AUC_{0\text{-}24h}$ for CC1084037 are approximately 20% of that for CC112273. Factors affecting CC112273 are applicable for CC1084037 as they are interconverting metabolites.

**Table 10 - Mean (SD) Pharmacokinetic Parameters for Ozanimod and Its Most Predominant Active Metabolite CC112273 in Patients with RMS Following Oral Dosing of ZEPOSIA 0.92 mg Once Daily for 12 Weeks**

| Analyte | $C_{max}$ (pg/mL) | $T_{max}$ (h)[a] | $C_{min}$ (pg/mL) | $AUC_T$ (pg*h/mL) |
|---|---|---|---|---|
| **ozanimod** | 244 (77.6) | 7.92 (4.00, 10.0) | 111 (48.2) | 4460 (1419) |
| **CC112273** | 6977 (2978) | 6.00 (0.00, 24.0) | 4617 (2234) | 143765 (56290) |

[a] $T_{max}$ is presented as median (minimum – maximum)

## Absorption

The $T_{max}$ of ozanimod, and the major active metabolites CC112273 and CC1084037 were approximately 6-8 hours, 10 hours and 16 hours, respectively. The extent of human absorption appears to be high, based on high permeability of ozanimod and low recovery of total radioactivity (0.06% of the dose) or intact ozanimod in feces over 24 hours following administration of a single dose of radio-labeled ozanimod.

Food effect:

Administration of ozanimod with a high-fat, high-calorie meal (approximately 900 to 1100 calories with 150, 250 to 360, and 500 to 600 calories from protein, carbohydrate, and fat, respectively) had no effect on ozanimod exposure ($C_{max}$ and AUC).

## Distribution:

The mean (CV%) apparent volume of distribution of ozanimod (Vz/F) was 5590 L (27%), indicating extensive tissue distribution. Binding of ozanimod to human plasma proteins is approximately 98.2%. Binding of CC112273 and CC1084037 to human plasma proteins is approximately 99.8% and 99.3%, respectively.

## Metabolism:

Ozanimod is metabolized by multiple enzymes to form circulating major active metabolites (e.g., CC112273 and CC1084037) and minor active metabolites (e.g., RP101988, RP101075, and RP112509) with similar activity and selectivity for S1P1 and S1P5. The oxidative pathway to formation of carboxylate metabolite RP101988 is mediated by ALDH/ADH while formation of RP101075 by dealkylation is predominantly carried out by CYP3A4. RP101075 is N-acetylated by NAT-2 to form RP101442 or deaminated by MAO-B to form the major metabolite CC112273.

CC112273 is either reduced to form CC1084037 or undergoes CYP2C8 mediated oxidation to form RP112509. CC1084037 is oxidized rapidly to form CC112273 by AKR 1C1/1C2, and/or 3β- and 11β-HSD and undergoes reversible metabolism to CC112273. The oxido-reduction interconversion between CC112273 and CC1084037 favors CC112273 and there are no direct metabolites of CC1084037 other than its metabolism to CC112273 and subsequent elimination via that pathway. Approximately 94% of circulating total active drug exposure is represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%), in humans.

## Elimination

The mean (CV%) apparent oral clearance for ozanimod was approximately 192 L/h (37%). The mean (CV%) plasma half-life ($t_{1/2}$) of ozanimod was approximately 21 hours (15%). Steady state for ozanimod was achieved within 7 days, with the estimated accumulation ratio following repeated oral administration of 0.92 mg once daily of approximately 2.

The model-based mean (CV%) effective half-life ($t_{1/2}$) of CC112273 was approximately 11 days (104%) in RMS patients, with mean (CV%) time to steady state of approximately 45 days (45%) and accumulation ratio of approximately 16 (101%). Plasma levels of CC112273 and its direct, interconverting metabolite CC1084037 declined in parallel in the terminal phase, yielding similar $t_{1/2}$ for both metabolites. Steady state attainment and accumulation ratio for CC1084037 are expected to be similar to CC112273.

Following a single oral 0.92 mg dose of [$^{14}$C]-ozanimod, approximately 26% and 37% of the radioactivity was recovered from urine and feces, respectively, primarily composed of inactive metabolites. Ozanimod, CC112273, and CC1084037 concentrations in urine were negligible.

**Special Populations and Conditions**

- **Pediatrics:** No data are available on administration of ZEPOSIA to pediatric or adolescent patients (< 18 years of age).

- **Geriatrics:** No PK data are available on administration of ZEPOSIA to patients aged 65 years and over. The safety and efficacy of ZEPOSIA in patients aged 55 years and over have not been established.

- **Sex:** While population PK of ozanimod are not affected by gender, CC112273 steady-state exposure (AUC) was about 35% lower in males than in females.

- **Ethnic Origin:** In a dedicated Japanese PK bridging study, following repeated dosing of 0.92 mg ZEPOSIA, ozanimod exposure ($C_{max}$ and $AUC_{tau}$) were unchanged and CC112273 exposure ($C_{max}$ and $AUC_{tau}$) were approximately 28% and 43% higher, respectively, in Japanese subjects (N=10) compared to Caucasian subjects (N=12).

- **Renal Insufficiency:** In a dedicated renal impairment trial, following a single oral dose of 0.23 mg ZEPOSIA, exposures ($AUC_{last}$) for ozanimod and CC112273 were approximately 27% higher and 23% lower, respectively, in subjects with end stage renal disease (N=8) compared to subjects with normal renal function (N=8).

  No dose adjustment is needed in patients with renal impairment (see 4.2 Recommended Dose and Dosage Adjustment).

- **Hepatic Insufficiency:** In a study with participants with mild (Child-Pugh class A, N=8) or moderate (Child-Pugh class B, N=8) hepatic impairment, following an 8-day dose escalation regimen of once daily doses of ZEPOSIA 0.23 mg on Days 1 to 4, 0.46 mg on Days 5 to 7, and 0.92 mg on Day 8, there was no meaningful impact of mild or moderate hepatic impairment on pharmacokinetics of ozanimod and its major active metabolites CC112273 and CC1084037 on Day 1, Day 5, or Day 8 of dosing. Mean unbound exposures ($AUC_{0\text{-last}}$, measured up to 64 days post-dose) of CC112273 and CC1084037 increased by approximately 2-fold compared to healthy controls (N=8). It is recommended that patients with mild or moderate hepatic impairment (Child-Pugh class A or B) complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day, starting on Day 8 (see 4.2 Recommended Dose and Dosage Adjustment).

No PK data are available on administration of ZEPOSIA to patients with severe hepatic impairment. The safety and efficacy of ZEPOSIA in patients with severe hepatic impairment have not been established. Administration of ZEPOSIA in this patient population is not recommended.

- **Smokers:** Population PK results showed that CC112273 steady-state exposure (AUC) was approximately 50% lower in smokers than in non-smokers, although for smokers this reduction in exposure did not result in meaningful differences in ALC reduction or an apparent impact on clinical safety.

## 11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 25°C. Do not store above 25°C.

## 12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

**PART II: SCIENTIFIC INFORMATION**

# 13 PHARMACEUTICAL INFORMATION

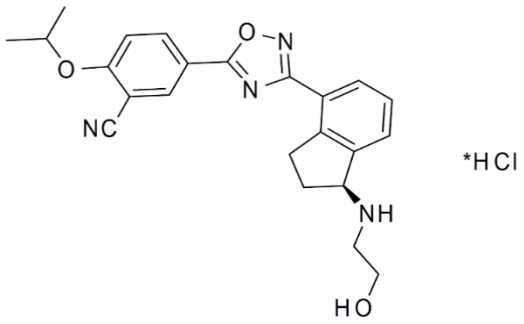
## Drug Substance

Proper name: ozanimod hydrochloride

Chemical name: 5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile, monohydrochloride

Molecular formula and molecular mass: $C_{23}H_{24}N_4O_3$•HCl; 440.92

Structural formula:




Physicochemical properties: Ozanimod is a white to off-white powder with a pKa value of 7.90. Ozanimod has pH dependent solubility in aqueous media across the physiological pH range. The melting point is 240°C.

# 14 CLINICAL TRIALS

## 14.1 Clinical Trials by Indication

### Relapsing-Remitting Multiple Sclerosis

**Table 11 - Summary of patient demographics for pivotal clinical trials in Relapsing Remitting Multiple Sclerosis**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| SUNBEAM (RPC01-301) | Randomized, double-blind, double-dummy, active-controlled parallel-group | Once daily oral dosing with ozanimod 0.92 mg or ozanimod 0.46 mg, or IFN β-1a 30 mg IM weekly | ozanimod 0.92 mg (N=447)<br><br>ozanimod | 34.8 years (18 – 55) | female = 63% |

| | | | | | |
|---|---|---|---|---|---|
| | study | injection for 12+ months[a] | 0.46 mg (N=451)<br><br>IFN β-1a 30 mcg IM (N=448) | 36.0 years (18 – 55)<br><br>35.9 years (18 – 55) | female = 69%<br><br>female = 67% |
| RADIANCE (RPC01-201B) | Randomized, double-blind, double-dummy, active-controlled parallel-group study | Once daily oral dosing with ozanimod 0.92 mg or ozanimod 0.46 mg, or IFN β-1a 30 mg IM weekly injection for 24 months | ozanimod 0.92 mg (N=433)<br><br>ozanimod 0.46 mg (N=439)<br><br>IFN β-1a 30 mcg IM (N=441) | 36.0 years (18 – 55)<br><br>35.4 years (18 – 55)<br><br>35.1 years (18 – 55) | female = 67%<br><br>female = 65%<br><br>female = 69% |

[a] Treatment was continued until all subjects received a minimum of 12 months of investigational product

ZEPOSIA was evaluated in two randomized, double-blind, double-dummy, parallel-group, active controlled clinical trials of similar design and endpoints, in patients with relapse-remitting MS (RRMS) treated for at least 1 year (SUNBEAM - Treatment continued for all patients until the last enrolled patient completed 1 year) and 2 years (RADIANCE).

The dose of ZEPOSIA was 0.92 mg and 0.46 mg given orally once daily, with a starting dose of 0.23 mg on Days 1-4, followed by an escalation to 0.46 mg on Days 5-7, and followed by the assigned dose on Day 8 and thereafter. The dose of IFN β-1a, the active comparator, was 30 mcg given intramuscularly once weekly. Both studies included patients who had experienced at least one relapse within the prior year, or one relapse within the prior two years with evidence of at least a gadolinium-enhancing (GdE) lesion in the prior year and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.0. Neurological evaluations were performed at baseline, every 3 months, and at the time of a suspected relapse. MRIs were performed at baseline (SUNBEAM and RADIANCE), 6 months (SUNBEAM), 1 year (SUNBEAM and RADIANCE), and 2 years (RADIANCE).

The primary endpoint of both SUNBEAM and RADIANCE was the annualized relapse rate (ARR) over 12 months for SUNBEAM and 24 months for RADIANCE. The key secondary outcome measures included: 1) the number of new or enlarging MRI T2 hyperintense lesions over 12 and 24 months 2) the number of MRI T1 GdE lesions at 12 and 24 months, and 3) the time to confirmed disability progression, defined as at least a 1-point increase from baseline EDSS sustained for 12 weeks. Confirmed disability progression was prospectively evaluated in a pooled analysis of SUNBEAM and RADIANCE. An additional MRI outcome measure was the mean percentage change from baseline in normalized brain volume.

In SUNBEAM, 1346 patients were randomized to receive ZEPOSIA 0.92 mg (n = 447), ZEPOSIA 0.46 mg (n= 451), or IFN β-1a (n = 448); 94% of ZEPOSIA-treated 0.92 mg, 94% of

ZEPOSIA-treated 0.46 mg, and 92% of IFN β-1a -treated patients completed the study. Mean (median) age was 35.6 (35) years, 66% were female, mean (median) time since MS symptom onset was 7 (5.2) years, and mean (SD) time since MS diagnosis was 3.7 (4.4) years. The mean (median) EDSS score at baseline was 2.62 (2.5); 70% had not been treated with a disease-modifying therapy. At baseline, the mean number of relapses in the prior year was 1.3 and 47% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The median duration of treatment was 13.6 months.

In RADIANCE, 1313 patients were randomized to receive ZEPOSIA 0.92 mg (n = 433), ZEPOSIA 0.46 mg (n = 439), or IFN β-1a (n = 441); 90% of ZEPOSIA-treated 0.92 mg, 85% of ZEPOSIA-treated 0.46 mg, and 85% of IFN β-1a-treated patients completed the study. Mean (median) age was 35.5 (35) years, 67% were female, mean (median) time since MS symptom onset was 6.5 (4.8) years, and mean (SD) time since MS diagnosis was 3.7 (4.7) years. Mean (median) EDSS score at baseline was 2.51 (2.5); 71% had not been treated with a disease-modifying therapy. At baseline, the mean number of relapses in the prior year was 1.3 and 43% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The median duration of treatment was 24 months.

The ARR was significantly lower in patients treated with ozanimod 0.92 mg than in patients who received IFN β-1a 30 mcg IM. The number of new or enlarging T2 lesions and the number of GdE lesions was significantly lower in patients treated with ZEPOSIA than in patients who received IFN β-1a.

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

The results for SUNBEAM and RADIANCE are shown in Table 12.

**Table 12- Key Clinical and MRI Endpoints in RRMS Patients from SUNBEAM and RADIANCE**

| Endpoints | SUNBEAM (≥ 1 year) | | RADIANCE (2 year) | |
|---|---|---|---|---|
| | ZEPOSIA 0.92 mg (n=447) % | IFN β-1a 30 mcg (n=448) % | ZEPOSIA 0.92 mg (n=433) % | IFN β-1a 30 mcg (n=441) % |

| | | | | |
|---|---|---|---|---|
| **Clinical Endpoints** | | | | |
| **Annualized Relapse Rate (Primary Endpoint)** | 0.181 | 0.350 | 0.172 | 0.276 |
| **Relative Reduction** | 48% (p<0.0001) | | 38% (p<0.0001) | |
| **Proportion Relapse-free** | 78% | 66% | 76% | 64% |
| **Kaplan-Meier Estimate** | 0.781 (p=0.0002)[1] | 0.663 | 0.756 (p=0.0012)[1] | 0.642 |
| **Proportion of Patients with 3-Month Confirmed Disability Progression[2]** | 7.6% ZEPOSIA vs. 7.8% IFN β-1a | | | |
| **Hazard Ratio** | 0.95<br>p=0.7651 | | | |
| **Relative Risk Reduction (Pooled Analysis[2])** | 5%; p = NS[3] | | | |
| **MRI Endpoints** | | | | |
| **Mean number of new or enlarging T2 hyperintense lesions per MRI[4]** | 1.465 | 2.836 | 1.835 | 3.183 |
| **Relative Reduction** | 48% (p<0.0001) | | 42% (p<0.0001) | |
| **Mean number of T1 Gd-** | 0.160 | 0.433 | 0.176 | 0.373 |

| | | |
|---|---|---|
| **enhancing lesions[5]**<br><br>**Relative Reduction** | 63% (p<0.0001) | 53% (p=0.0006) |

[1] Log-rank test

[2] Prospectively planned pooled analysis of SUNBEAM and RADIANCE

[3] NS = Not Significant

[4] Through the treatment period

[5] At the end of the treatment period for each study

In SUNBEAM at 12 months and RADIANCE at 24 months, treatment with ozanimod 0.92 mg resulted in reductions in mean percent change from baseline in normalised whole brain volume compared to IFN β-1a IM (-0.41% versus -0.61%, and -0.71% versus -0.94%, respectively, nominal p-value <0.0001 for both studies).

**Ulcerative Colitis**

**Table 13 - Summary of patient demographics for pivotal clinical trials in Ulcerative Colitis**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| TRUENORTH-I | Randomized, double-blind, placebo-controlled | 7-day dose escalation, followed by once daily oral dosing with ozanimod 0.92 mg or placebo up to week 10 | ozanimod 0.92 mg (N=429)<br><br>placebo (N=216) | 41.4 years (18 - 72)<br><br>41.9 years (19 - 74) | female = 42.9%<br><br>female = 33.8% |
| TRUENORTH-M | Randomized, double-blind, placebo-controlled with randomized withdrawal | Once daily oral dosing with ozanimod 0.92 mg for 42 weeks | ozanimod 0.92 mg (N=230)<br><br>placebo (N=227) | 42.4 years (18 - 72)<br><br>43.0 years (18 - 74) | female = 49.1%<br><br>female = 46.3% |

The efficacy and safety of ozanimod were evaluated in two multicenter, randomised, double-blind, placebo-controlled clinical studies [TRUENORTH-I and TRUENORTH-M ] in adult patients with moderately to severely active ulcerative colitis. TRUENORTH-I included patients who were randomised 2:1 to ozanimod 0.92 mg or placebo. Patients could have had an inadequate response, loss of response, or intolerance to a biologic (e.g., TNF blocker and/or vedolizumab), corticosteroids, and/or immunomodulators (e.g. 6-mercaptopurine and azathioprine) therapy.

Patients were to be receiving treatment with oral aminosalicylates and/or corticosteroids. In both studies, randomization was stratified according to prior anti-TNF therapy experience (yes or no).

The 10-week induction period (TRUENORTH-I) was followed by a 42-week, randomised, withdrawal maintenance period (TRUENORTH-M) for a total of 52 weeks of therapy.

Disease assessment was based on the Mayo score, which ranges from 0 to 12 and has four subscores from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on centrally-reviewed endoscopy, and physician global assessment. Moderately to severely active ulcerative colitis was defined at baseline (Week 0) as a Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥2. An endoscopy score of 2 was defined by marked erythema, lack of vascular pattern, friability, erosions; and a score of 3 was defined by spontaneous bleeding, ulceration.

TRUENORTH-I

In TRUENORTH-I, patients were randomized to either ZEPOSIA 0.92 mg given orally once daily (n=429) or placebo (n=216) beginning with a dose escalation, s*ee* 4.2 Recommended Dose and Dosage Adjustment. Patients received concomitant aminosalicylates (e.g., mesalazine 71%; sulfasalazine 13%) and/or oral corticosteroids (33%) at a stable dose prior to and during the induction period.

There were 30% of patients who had an inadequate response, loss of response or are intolerant to TNF blockers. Of these patients, 63% received at least two or more biologics including TNF blockers; 47% received an integrin receptor blocker (e.g. vedolizumab); 36% failed to ever respond to at least one TNF blocker; 65% lost response to a TNF blocker. There were 41% of patients who failed and/or were intolerant to immunomodulators. At baseline, patients had a median Mayo score of 9, with 65% of patients less than or equal to 9 and 35% having greater than 9.

The primary endpoint was clinical remission at week 10, defined as a Three-component Mayo: rectal bleeding subscore = 0 and stool frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the Baseline Stool Frequency subscore) and endoscopy subscore ≤ 1.

Key secondary endpoints at week 10 were clinical response, endoscopic improvement, and mucosal healing. Clinical response with a definition of (Three-component Mayo: A reduction from Baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from Baseline in the Rectal Bleeding subscore of ≥ 1 point or an absolute Rectal Bleeding subscore of ≤ 1 point), endoscopic improvement with a definition of Endoscopy subscore of ≤ 1 point), and mucosal healing defined as Endoscopy subscore of ≤ 1 point and a Geboes index score < 2.0.

The results of the efficacy endpoints in TRUENORTH-I are shown in

Table 14.

TRUENORTH-M

Patients in TRUENORTH M could have come from either TRUENORTH-I or from a group who received ZEPOSIA 0.92 mg open- label. In order to be randomized to treatment in TRUENORTH-M, patients had to have received ZEPOSIA 0.92 mg and be in clinical response at week 10. Responders from both groups (457/796=57%) were re-randomized in a double-blinded fashion (1:1) to receive either ZEPOSIA 0.92 mg (n=230) or placebo (n=227) for 42 weeks.The total study duration was 52 weeks, including both studies. Efficacy assessments were at week 52. Concomitant aminosalicylates were required to remain stable through week 52. Patients on concomitant corticosteroids were to taper their dose upon entering the maintenance study.

At study entry, 35% of patients were in clinical remission, 29% of patients were on corticosteroids and 31% of patients who were previously treated with TNF blockers.

The primary endpoint was the proportion of patients in clinical remission at Week 52. Key secondary endpoints at Week 52 were the proportion of patients with clinical response, endoscopic improvement, mucosal healing, corticosteroid-free clinical remission, and the proportion of patients maintaining clinical remission at Week 52 among patients who achieved clinical remission at 10 weeks of TRUENORTH-I.

A significantly greater proportion of patients treated with ozanimod achieved clinical remission, clinical response, endoscopic improvement, and mucosal healing compared to placebo at week 10 as shown in

Table 14.

**Table 14-Proportion of patients meeting efficacy endpoints in the induction period from TRUENORTH-I (at week 10)**

| | ZEPOSIA 0.92 mg (N=429) | | Placebo (N=216) | | Treatment Difference %[a] (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| **Clinical remission[b]** | **79** | **18%** | **13** | **6%** | **12% (7.5, 17.2)** | p=<0.0001 |
| Without prior TNF blocker exposure | 66/299 | 22% | 10/151 | 7% | | |
| Prior TNF blocker exposure | 13/130 | 10% | 3/65 | 5% | | |
| **Clinical response[c]** | **205** | **48%** | **56** | **26%** | **22% (14.4, 29.3)** | p=<0.0001 |
| Without prior TNF blocker exposure | 157/299 | 53% | 44/151 | 29% | | |
| Prior TNF blocker exposure | 48/130 | 37% | 12/65 | 19% | | |
| **Endoscopic improvement[d]** | **117** | **27%** | **25** | **12%** | **16% (9.7, 21.7)** | p=<0.0001 |
| Without prior TNF blocker exposure | 97/299 | 32% | 18/151 | 12% | | |
| Prior TNF blocker exposure | 20/130 | 15% | 7/65 | 11% | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Mucosal healing[e]** | **54** | **13%** | **8** | **4%** | **9% (4.9, 12.9)** | p=<0.001 |
| Without prior TNF blocker exposure | 47/299 | 16% | 6/151 | 4% | | |
| Prior TNF blocker exposure | 7/130 | 5% | 2/65 | 3% | | |

CI = confidence interval; TNF = tumor necrosis factor.

[a] Treatment difference (adjusted for stratification factors of prior TNF blocker exposure and corticosteroid use at baseline).
[b] Clinical remission is defined as: RBS = 0, SFS ≤ 1 (and a decrease of ≥ 1 point from the baseline SFS), and endoscopy subscore ≤ 1 without friability.
[c] Clinical response is defined as: A reduction from baseline in the 3-component Mayo score of ≥ 2 and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 or an absolute RBS of ≤ 1.
[d] Endoscopic improvement is defined as: Endoscopy subscore of ≤ 1 point without friability
[e] Mucosal healing is defined as both Mayo endoscopic score ≤ 1 without friability and histological improvement (defined as no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation Geboes index score < 2.0).

*Rectal bleeding and stool frequency subscores*

Decreases in rectal bleeding and stool frequency subscores were observed as early as week 2 (ie, 1 week after completing the required 7-day dose titration); the separation in improvements from placebo in patients treated with ozanimod increased from Week 4 through Week 10.

Of those patients treated with ZEPOSIA who achieved clinical response during the 10-week induction period from TRUENORTH-I (48% and 26% on ZEPOSIA and placebo, respectively), a significantly greater proportion of patients treated with ZEPOSIA achieved clinical remission, clinical response, endoscopic improvement and mucosal healing, corticosteroid-free clinical remission, as well as durable clinical remission and maintenance of remission compared to placebo at Week 52 as shown in Table 15.

**Table 15- Proportion of induction period responders meeting efficacy endpoints in the maintenance period in TRUENORTH-M (at week 52)**

| | **ZEPOSIA 0.92 mg (N=230)** | **Placebo (N=227)** | **Treatment difference %[a] (95% CI)** | **P-value** |
|---|---|---|---|---|

| | n | % | n | % | | |
|---|---|---|---|---|---|---|
| **Clinical remission[b]** | **85** | **37%** | **42** | **19%** | **19% (10.8, 26.4)** | p=<0.0001 |
| Without prior TNF blocker exposure | 63/154 | 41% | 35/158 | 22% | | |
| Prior TNF blocker exposure | 22/76 | 29% | 7/69 | 10% | | |
| **Clinical response[c]** | **138** | **60%** | **93** | **41%** | **19% (10.4, 28.0)** | p=<0.0001 |
| Without prior TNF blocker exposure | 96/154 | 62% | 76/158 | 48% | | |
| Prior TNF blocker exposure | 42/76 | 55% | 17/69 | 25% | | |
| **Endoscopic improvement[d]** | **105** | **46%** | **60** | **26%** | **19% (11.0, 27.7)** | p=<0.001 |
| Without prior TNF blocker exposure | 77/154 | 50% | 48/158 | 30% | | |
| Prior TNF blocker exposure | 28/76 | 37% | 12/69 | 17% | | |
| **Mucosal healing[e]** | **68** | **30%** | **32** | **14%** | **16% (8.2, 22.9)** | p=<0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Without prior TNF blocker exposure | 51/154 | 33% | 28/158 | 18% | | |
| Prior TNF blocker exposure | 17/76 | 22% | 4/69 | 6% | | |
| **Corticosteroid-free clinical remission[f]** | **73** | **32%** | **38** | **17%** | **15% (7.8, 22.6)** | p=<0.001 |
| Without prior TNF blocker exposure | 55/154 | 36% | 31/158 | 20% | | |
| Prior TNF blocker exposure | 18/76 | 24% | 7/69 | 10% | | |
| **Maintenance of clinical remission at week 52 in the subset of patients in remission at week 10[g]** | **41/79** | **52%** | **22/75** | **29%** | **24% (9.1, 38.6)** | p=0.0025 |
| Without prior TNF blocker exposure | **37/64** | 58% | 19/58 | 33% | | |
| Prior TNF blocker exposure | 4/15 | 27% | 3/17 | 18% | | |

CI = confidence interval; TNF = tumor necrosis factor.

[a] Treatment difference (adjusted for stratification factors of clinical remission and concomitant corticosteroid use at week 10).

[b] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the baseline SFS) and endoscopy subscore ≤ 1 point without friability.

[c] Clinical response is defined as: A reduction from baseline in the 3-component Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

[d] Endoscopic improvement is defined as: Endoscopy subscore of ≤ 1 point without friability.

[e] Mucosal healing is defined as both Mayo endoscopic score ≤ 1 without friability and histological improvement (defined as no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation Geboes index score < 2.0)

[f] Corticosteroid-free remission is defined as clinical remission at week 52 while off corticosteroids for ≥ 12 weeks.

[g] Maintenance of improvement defined as clinical remission at week 52 in the subset of patients in clinical remission at week 10.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:** In rat and monkey repeated dose general toxicology studies, oral ozanimod administration resulted in lymphopenia, decreased thymic cortical lymphocytes, and decreased splenic marginal zone lymphocytes. These findings represent the expected effects of an $S1P_1$ agonist. Ozanimod also increased lung weights and increased the incidence of mononuclear alveolar infiltrates at the mid and high dose levels in the rat and monkey studies. The no-adverse effect dose level in the 39-week monkey study was 0.1 mg/kg/day at which systemic exposure to ozanimod was 3.7 times that at maximum recommended human dose (MRHD), while exposure to major human metabolites was subtherapeutic. The pulmonary changes were not associated with any observable clinical signs in the rats or monkeys, did not increase in severity with long term dosing, and were reversible. In addition to lymphopenia, ozanimod had an inhibitory effect on T-cell-dependent IgG and IgM antibody responses in rats. No in vitro phototoxicity potential was observed with ozanimod or its metabolites.

**Genotoxicity:** Ozanimod and multiple metabolites were negative in bacterial mutagenicity assays. In mammalian *in vitro* genotoxicity assays, ozanimod and CC112273 were not genotoxic while CC1084037 was clastogenic. However, CC1084037 administered by oral gavage once daily to rats at doses up to 1000 mg/kg/day was negative for the induction of micronucleated polychromatic erythrocytes and negative for the induction of DNA damage in liver in both male and female rats. After oral dosing in the rat, ozanimod was negative for induction of micronucleated polychromatic erythrocytes. Overall, ozanimod and metabolites do not exhibit any *in vitro* or *in vivo* genotoxic potential.

**Carcinogenicity:** Ozanimod administered orally was evaluated for carcinogenicity in a 6-month Tg.rasH2 mouse bioassay (8, 25 and 80 mg/kg/day) and a two-year rat bioassay. In the 6-month Tg.rasH2 mouse study, statistically significant increased incidences of hemangiosarcomas were seen in males at all dose levels and in the females at the mid and high dose across multiple organs. Systemic exposure at the 8 mg/kg/day dose was about 1680x, 106x, and 97x that at the MRHD for ozanimod, its major inactive human metabolite, and total $S1P_1$ agonists (ozanimod plus its major active human metabolites), respectively.

Based on published data, hemangiosarcomas induced by the pharmacologically similar drug siponimod in mice have been postulated to result from chronic stimulation of endothelial cells through the $S1P_1$ receptor (also known as the endothelial differentiation gene (EDG) 1 receptor) resulting in sustained production of placental growth factor 2 (PlGF2) and subsequently, persistent vascular endothelial cell mitoses. This receptor is abundant on vascular endothelial cells and is important in endothelial cell migration, differentiation, and survival. In contrast, rat and human vascular endothelial cells did not release PlGF2 or only transiently released PlGF2 in response to siponimod, and subsequently, sustained stimulation and hemangiosarcoma formation were not observed in rats. Whether the same phenomena occur after ozanimod is not known.

In the two-year rat bioassay, no incidence of any tumor type was increased at ozanimod dose levels up to 2 mg/kg/day at which systemic exposure was 126x, 212x, and 7.6x that at the MRHD for ozanimod, its major inactive human metabolite, and total S1P agonists (ozanimod plus its major active metabolites), respectively.

**Reproductive and Developmental Toxicology:** Oral administration of ozanimod at 0.2, 2, and 30 mg/kg/day to male and female rats prior to and over mating and until gestation day (GD) 7 (in females) or necropsy (in males after 7 weeks of dosing) had no effect on mating, fertility, and reproductive indices (sperm quality and caesarean data). Thus, the ozanimod NOEL for gonadal function, mating behavior, reproductive performance, and early gestation effects in rat was 30 mg/kg/day. At this dose, estimated systemic exposure to total active drug and metabolites (ozanimod, CC112273 and CC1084037), is approximately 150 times that at the MRHD.

Sphingosine 1-phosphate signaling has been shown to regulate crucial events during embryogenesis, such as angiogenesis, cardiogenesis, limb development and neurogenesis and the sphingosine 1-phosphate receptor is known to be involved in vascular formation during embryogenesis. Adverse effects on embryo fetal development of ozanimod in rats and rabbits appear, or at least the vascular findings, related to the pharmacology of ozanimod and its pharmacologically active metabolites. In rats, ozanimod at 0.2, 1 and 5 mg/kg/day administered by oral gavage during organogenesis was well tolerated by the dams with only slight effects on maternal body weight gain and food consumption at the high dose. At 5 mg/kg/day, there was clear embryo-toxicity with a high incidence of embryo-fetal death, slightly reduced mean fetal weight, retarded ossification and malformations with three fetuses with anasarca and two others with malpositioned testes. The embryo fetal toxicity NOAEL in rat is 1 mg/kg/day at which is systemic exposure to total active drug and metabolites (ozanimod, CC112273 and CC1084037), is 3.5 times that at the MRHD. In pregnant rabbits, ozanimod at 0.2, 0.6 and 2 mg/kg/day was well tolerated at 0.2 and 0.6 mg/kg/day but resulted in an abortion at 2 mg/kg/day. At 2 mg/kg/day, there was increased incidence of embryo-fetal death, a single abortion, abnormal and retarded ossification, and eight fetuses with malformed great blood vessels or absent inominate artery, and while there were no effects on embryo-fetal survival at 0.6 mg/kg/day, there were visceral and skeletal morphological changes which were similar to those observed at the high dose. The NOAEL for embryo fetal toxicity was 0.2 mg/kg/day. Exposure to total active drug and metabolites (ozanimod, CC112273 and CC1084037) in rabbit was subtherapeutic compared to exposure at the MRHD. CC112273 and CC1084037 data were derived from pharmacokinetic bridging studies.

In a pre and postnatal developmental toxicity study, pregnant rats (F0 generation) were dosed by oral gavage with ozanimod at 0.2, 0.7 and 2 mg/kg/day from GD 6 through parturition and lactation (up to day 20 of lactation). Ozanimod at doses up to and including 2 mg/kg/day was well tolerated by the dams. Administration of ozanimod to F0 dams at 2.0 mg/kg/day resulted in the following effects in the F1 offspring; decreased body weight in males and females (5%-7% lower than control) during lactation and after weaning, increased motor activity, and increased estrous cycle length in the F1 females (5.2 days compared to 4.2 days seen in controls). Due to the percentage changes of <10%, or the lack of a dose response, or other correlative effects, all of these effects were considered non-adverse. However, given the importance of sphingosine 1-phosphate signaling in neurogenesis during embryogenesis, a more thorough assessment of CNS morphology and more complex learning and memory tasks than the passive avoidance

test would have been appropriate. For the parameters evaluated in this study, a NOAEL for maternal, pre- and postnatal toxicity was 2.0 mg/kg/day at which total active drug and metabolite exposure (ozanimod + CC112273 + CC1084037) in rats is 5.6 times that at the MRHD.

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrZEPOSIA®**

**ozanimod capsules**

Read this carefully before you start taking **ZEPOSIA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ZEPOSIA**.

**What is ZEPOSIA used for?**

ZEPOSIA is used to treat:

- Adult patients with the relapsing and remitting form of multiple sclerosis (RRMS).
- Adult patients with moderately to severely active ulcerative colitis (UC) when other medicines do not work or cannot be used.

ZEPOSIA is not authorized for use in children.

**How does ZEPOSIA work?**

Ozanimod, the medicinal ingredient in ZEPOSIA, binds to selective receptors on your white blood cells. This keeps the white blood cells in your body's lymph nodes and lowers the number of white blood cells circulating in your body. How ZEPOSIA works is not known, but it may be due to less white blood cells entering your central nervous system where they could cause inflammation and damage to the nerves protective coating. ZEPOSIA helps reduce the inflammation in ulcerative colitis. It works by stopping certain white blood cells from reaching the lining of the intestine.

**What are the ingredients in ZEPOSIA?**

Medicinal ingredients: ozanimod (as ozanimod hydrochloride)

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose. The capsule is made of black iron oxide (E172), gelatin, pharmaceutical ink, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172).

**ZEPOSIA comes in the following dosage forms:**

capsules, 0.23 mg, 0.46 mg, 0.92 mg

**Do not use ZEPOSIA if:**

- you are allergic to ozanimod or any of the other ingredients of ZEPOSIA (see **What are the ingredients in ZEPOSIA?** above)
- you are at an increased risk of opportunistic infection, i.e. if you have a weakened immune system due to:
    - treatments that suppress the immune system (cancer treatments, immunosuppressive or immune modulating therapies, total lymphoid irradiation or bone marrow transplantation)

- disease (immunodeficiency syndrome)

- you have had in the last 6 months:
  - heart attack
  - unstable angina
  - stroke or warning signs of a stroke
  - a sudden worsening of the signs and symptoms of heart failure that required treatment or have been diagnosed with Class III or IV heart failure, or certain types of heart failure in the last 6 months.
- you have or have had a history of certain types of irregular or abnormal heartbeat (arrhythmia) that is not corrected by a pacemaker.
- you currently have an infection, such as hepatitis or tuberculosis.
- you currently have cancer (except for a type of skin cancer called basal cell carcinoma).
- you take certain medicines called monoamine oxidase (MAO) inhibitors (e.g. selegiline, phenelzine, linezolid).
- you are pregnant, think you may be pregnant or plan to get pregnant.
- you are of childbearing age and not using an effective method of birth control.
- you are of childbearing age and your healthcare professional has not performed a pregnancy test to confirm you are pregnant before you start treatment.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZEPOSIA. Talk about any health conditions or problems you may have, including if you:**

- have or have had problems with your heart, such as:
  - an irregular or abnormal heartbeat (arrhythmia)
  - a heart attack
  - severe heart disease
  - uncontrolled high blood pressure
  - a history of stroke or other diseases related to blood vessels in the brain
  - a slow heart rate or you are taking or have recently taken medicines that slow your heart rate (such as beta blockers or calcium channel blockers)

- have untreated severe breathing problems when you sleep (severe sleep apnea)

Your healthcare professional may decide not to use ZEPOSIA if you have or have had one of the above conditions, or may refer you to a cardiologist before you start treatment

- are taking medications:
    - to lower your blood pressure
    - to treat an irregular heartbeat (medicines that cause QT prolongation)
    - that slow your heart rate

Depending on the medications you are taking, your healthcare professional may decide not to use ZEPOSIA or refer you to a cardiologist to change your medication (see **The following may interact with ZEPOSIA** below for more information)

- have an infection. ZEPOSIA lowers your white blood cell count. This may increase your risk of infections including serious and life-threatening infections. This can occur while you are being treated with ZEPOSIA and up to 3 months after you stop treatment. Your healthcare professional should do a complete blood test to check your white blood cell count before you start treatment if you have not had one done within the last 6 months, during treatment and after you stop treatment. Tell your healthcare professional **right away** if you suspect you have an infection while taking ZEPOSIA.

- have never had chickenpox or have not been vaccinated against chickenpox (varicella zoster virus). You may develop an infection with the varicella zoster virus while taking ZEPOSIA. This may cause herpes viral infections, such as herpes zoster (shingles) and other serious complications including an infection of the membranes covering your brain (meningitis). Your healthcare professional will check your antibody levels and may decide to vaccinate you if you do not have enough antibodies against the virus. If you get the vaccine, you will start treatment 1 month after the full course of the vaccination is completed.

- have not been vaccinated against:
    - Human Papilloma Virus (HPV). Your healthcare professional will decide if you need to be vaccinated against Human Papilloma Virus (HPV) before starting treatment. For female patients, your healthcare professional may recommend HPV screening. HPV infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in patients treated with medicines similar to ZEPOSIA.

- plan to receive a vaccine:
    - you should not receive certain types of vaccines (called “live attenuated vaccines”) while you are being treated with ZEPOSIA and for up to 3 months after stopping treatment.

- have a weakened immune system due to a disease or from medicines that suppress the immune system. You may get infections more easily or an infection you already have may get worse. ZEPOSIA lowers your white blood cell count during treatment and for up 3 month after you stop taking it.

- have not had a test to check your liver function within the last 6 months

- have breathing problems. ZEPOSIA can have a slight effect on your lung function
- have or have had:
    - changes in your vision or other signs of swelling in the central vision area at the back of the eye - a condition known as macular edema
    - disease of the retina
    - inflammation or infection of the eye (uveitis).

The macula is a small area of the retina at the back of the eye. It allows you to see shapes, colours, and details clearly and sharply. ZEPOSIA may cause swelling in the macula and it can happen anytime during treatment.

Your chance of developing macular edema is higher if you have diabetes, have had an inflammation or infection of the eye or are on long-term treatment with ZEPOSIA.

Your healthcare professional may want you to undergo an eye examination:

- before you start ZEPOSIA
- during treatment and
- at anytime throughout your treatment if you notice changes in your vision. Tell your healthcare professional **right away** about any changes in your vision, which include:
    - blurry vision
    - blurry or wavy vision near or in the center of you field of vision
    - a blind spot in the center of your vision
    - sensitivity to light
    - colours may appear washed out or faded
    - unusually coloured vision
- have liver problems. ZEPOSIA may affect your liver function. If you notice any of the following symptoms, tell your healthcare professional **right away**:
    - yellowing of your skin or the whites of your eyes
    - abnormally dark urine
    - unexplained nausea or vomiting

- tiredness
- upper abdominal pain
- loss of appetite

Your healthcare professional may carry out blood tests to check your liver function and may consider stopping ZEPOSIA treatment if your liver problem is serious.

**Other warnings you should know about:**

**AFTER YOU STOP TREATMENT**

- ZEPOSIA will stay in your body for about 3 months after you stop taking it. Your white blood cell count may remain low during this time. The side effects described in this leaflet may still occur.
- your symptoms of MS can return and may become worse compared to before you started treatment or during treatment. Tell your healthcare professional if MS symptoms become worse after you stop taking ZEPOSIA.

**Cancer risk:** you could be at an increased risk for developing cancer, particularly skin cancer. Basal cell carcinoma was reported with patients on ZEPOSIA therapy. Your healthcare professional should check for any abnormal skin growths before you start treatment and regularly during your treatment with ZEPOSIA especially if you are at a higher risk for skin cancer. During treatment you should:

- check your skin regularly for unusual changes
- limit how much time you are exposed to the sun and UV rays. Wear protective clothes and regularly apply sunscreen with a high degree of UV protection.

**Depression, thoughts of suicide and suicidal behaviour:** are known to occur in patients with MS. Thoughts of suicide and suicidal behaviour have been reported with patients taking ZEPOSIA. Tell your family you are taking this medicine. If you, your caregiver or family members notice changes in your mood, or you start to have thoughts about hurting yourself, **contact your healthcare professional right away**.

**Pregnancy: You should avoid becoming pregnant while taking ZEPOSIA and for at least 3 months after you stop taking it before planning a pregnancy.** ZEPOSIA may harm your unborn baby. Female patients who might become pregnant should use effective birth control methods during treatment and for at least 3 MONTHS after stopping ZEPOSIA. Ask your healthcare professional about options of effective birth control (see **Do not use ZEPOSIA if**).

- If you become pregnant or think you are pregnant, tell your healthcare professional right away. You and your healthcare professional will decide what is best for you and your baby.

**Pregnancy Registry**: Information is being collected on use of ZEPOSIA in pregnant women. This is done in order to track effects of ZEPOSIA treatment on pregnant women and their offspring. Talk to your healthcare professional for more information.

**Breast-feeding: You should not breast-feed while you are taking ZEPOSIA.** ZEPOSIA can pass into breast milk and there is a risk of serious side effects for a breast-fed baby. Talk with your healthcare

professional before breast-feeding while you take ZEPOSIA.

**Laboratory Tests:**

- Abnormal liver function test results: a high level of an enzymes called alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and aspartate aminotransferase (AST) and bilirubin have been reported in MS patients taking ZEPOSIA.

- Lower lung function test results: decreases in lung function (breathing) tests were have been reported in MS patients taking ZEPOSIA.

Tell your healthcare professional right away, if you get any of the following symptoms during your treatment with ZEPOSIA. It could be serious:

- if you believe your MS is getting worse (e.g. weakness or visual changes) or if you notice any new or unusual symptoms ( e.g. problems thinking, memory problems, confusion, sudden inability to walk, severe imbalance, weakness on one side of your body or vision changes). These may be the symptoms of **progressive multifocal leukoencephalopathy** (PML). This is a rare brain disorder caused by an infection. Your healthcare professional may consider an MRI scan to check for this condition. Your healthcare professional will decide whether you need to stop taking ZEPOSIA.

- if you have fever, feel like you have a flu, or have a headache accompanied by stiff neck, sensitivity to light, nausea, and/or confusion. These may be symptoms of meningitis (inflammation of the membranes covering the brain) and/or encephalitis (inflammation of the brain) caused by a fungal (Cryptococcus) or viral (chicken pox) infection.

- if you have symptoms such as the sudden start of a severe headache, confusion, seizures, changes in your behaviour and changes to your vision. These may be symptoms of a condition called **posterior reversible encephalopathy syndrome** (PRES).

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with ZEPOSIA:**

**Serious Drug Interactions**

**Do not take ZEPOSIA if you:**

- are taking or have recently taken any monoamine oxidase inhibitors (MAOIs) such as selegiline, phenelzine, rasagiline, safinamide, linezolid, methylene blue as you may have serious side effects. Ask your healthcare professional if you are unsure.

- **Medicines that treat an irregular heartbeat (medicines that cause QT prolongation)**

- procainamide
- amiodarone
- sotalol

Your healthcare professional may decide to refer you to a cardiologist to change your medicine before you start treatment with ZEPOSIA.

- **Medicines that slow down your heartbeat such as:**
  - beta-blockers (such as atenolol or propranolol)
  - calcium channel blockers (such as verapamil or diltiazem)
  - cholinomimetics
  - other substances that can decrease your heart rate (ivabradine or digoxin)

ZEPOSIA can slow your heartbeat when you first start treatment. Your healthcare professional may decide to refer you to a cardiologist to change your medicine before you start treatment.

- **Medicines that suppress or modulate the immune system, including other medicines used to treat MS and medicines used to treat cancer:**
  - cyclosporine
  - beta-interferons
  - glatiramer acetate
  - natalizumab
  - mitoxantrone
  - dimethyl fumarate
  - terifunomide
  - alemtuzumab
  - corticosteroids
  - ocrelizumab

ZEPOSIA should not be started while you are taking these medicines or you are switching to or from other therapies used to treat MS with immunosuppressive or immune modulating effects. Your healthcare professional may want to wait for several weeks after you stop taking these medicines before starting you on ZEPOSIA to reduce the possible additive effect on your immune system. ZEPOSIA can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

- **Eltrombopag**, a medicine used to treat abnormally low platelet levels in the blood
- **Gemfibrozil**, a medicine used to help lower fats and raise “good” cholesterol in the blood
- **Rifampin**, a medicine used to treat bacterial infections, including tuberculosis
- **Vaccines:** If you need to receive a vaccine, talk to your healthcare professional first. For more information about vaccines see **To help avoid side effects and ensure proper use** above.
- **Tyramine:** Certain foods that may contain very high amounts of tyramine [aged, fermented, cured, smoked, and pickled foods (e.g., aged cheese, pickled herring)] could cause (tyramine reaction) severe hypertension (rise in blood pressure) in patients taking ZEPOSIA, even at the recommended doses. You should avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

There is a potential for serious adverse reactions, including a sudden, severe increase in blood pressure (hypertensive crisis) and serotonin toxicity, with co-administration of ZEPOSIA and the following medications:

- treatment with opioid medications (e.g., meperidine and its derivatives, methadone, propoxyphene, tramadol or tapentadol) is not recommended.
- treatment with serotonergic medications (e.g., serotonin-norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), tricyclic, tetracyclic or triazolopyridine antidepressants, cyclobenzaprine or St John’s wort) is not recommended.
- treatment with sympathomimetic medications (e.g., pseudoephedrine) may lead to increased blood pressure or heart rate.

Your healthcare professional will regularly monitor your blood pressure while you take ZEPOSIA.

Serotonin Toxicity:

ZEPOSIA may cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take ZEPOSIA with certain antidepressants or migraine medications.

Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

**How to take ZEPOSIA:**

**Before you start treatment:**

Your healthcare professional will:

- conduct an electrocardiogram (ECG) to check for any pre-existing heart conditions. If you have certain heart conditions or risk factors the first dose ZEPOSIA will have to be taken in your healthcare professional's office or hospital where your heart rate and blood pressure can be monitored (hourly blood pressure and pulse measurements, ECG monitoring) for at least 6 hours. The same process may apply if you are starting treatment again after a break from ozanimod therapy.

- perform:

    - liver tests if you have not had one within the last 6 months

    - a complete blood test if you have not had one in the last 6 months or have recently stopped previous treatment for MS.

    - a check of your antibody levels for the chickenpox virus (varicella zoster virus)

    - a pregnancy test if you are a woman of childbearing potential

- check if you currently have a severe infection

- check your medication history

- check your skin for suspicious moles

Your healthcare professional may also:

- have you go for an eye exam if you have or had uveitis (a swelling in the middle layer of tissue in the eye wall) a history of retinal disorders or diabetes

- consider a Magnetic Resonance Imaging (MRI) scan of your brain, if you have received certain previous treatment for MS.

- check that you are vaccinated against the human papilloma virus (HPV). Your healthcare professional will tell you if you need to get vaccinated against HPV before starting treatment.

- recommend that you get screened for HPV if you are a female

**Usual dose:**

ZEPOSIA capsules are to be taken by mouth once daily according to the following schedules.

**On Days 1 to 7 (Initiation Pack):**

- When you start treatment with ZEPOSIA you will be given an Initiation Pack. The Initiation Pack contains 7 capsules. Over a period of 7 days you will slowly increase (titrate) your dose. Follow the directions on the Initiation Pack and the table below.

- Take your Initiation doses once a day at about the same time each day with or without food. Swallow the capsules whole with water. Do not open, break, or chew your capsules.

Starter pack dosing schedule:

| Day | Daily Dose | Capsule Colour |
|---|---|---|
| Day 1 to Day 4 | 0.23 mg (1 time per day) | Light grey |
| Day 5 to Day 7 | 0.46 mg (1 time per day) | Light grey and orange |

**On Day 8 and after (Maintenance dose):**

- Switch to your maintenance dose.
- The recommended dose is 0.92 mg (orange capsule) once a day.
- If you have mild to moderate liver problems (assessed by your healthcare professional), the recommended dose, after completing the 7-day Initiation Pack, is 0.92 mg **once every other day**.
- Take ZEPOSIA exactly as your healthcare professional tells you to take it.
- Take your maintenance dose once a day **at about the same time each day** with or without food. Swallow the capsules whole with water. Do not open, break, or chew your capsules.
- Continue taking ZEPOSIA every day for as long as your healthcare professional tells you. Do not stop taking this medicine without talking to your healthcare professional.

If you have questions about how long to take ZEPOSIA, talk to your healthcare professional.

**Overdose:**

If you think you, or a person you are caring for, have taken too much ZEPOSIA, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

**Missed Dose:**

**IMPORTANT**

If you **miss 1 day between day 1 and day 14** of treatment:

- Contact your healthcare professional right away before you take the next dose.
- You will have to re-start treatment (from Day 1) using a new initiation pack.
- Do not take a double dose to make up for a missed dose.

If you **miss 1 to 7 days after 14 days** of treatment:

- Continue with the treatment as planned

If you miss **more than 7 days after 14 days** of treatment:

- Talk to your healthcare professional about how to re-start your treatment (from day 1) if you have stopped taking ZEPOSIA:
    - for more than 7 consecutive days between day 15 and day 28 of treatment
    - for more than 14 consecutive days after day 28 of treatment.
- Contact your healthcare professional right away if any of these happen so he or she can tell you how to re-start your treatment.
- Do not take a double dose to make up for a missed dose.

**What are possible side effects from using ZEPOSIA?**

These are not all the possible side effects you may have when taking ZEPOSIA. If you experience any side effects not listed here, tell your healthcare professional.

- headache
- back pain
- infections of the
    - nose or nostrils
    - nasal cavity
    - mouth
    - throat (pharynx), or
    - voice box (larynx)
- respiratory infection
- low blood pressure when you stand up (orthostatic hypotension)

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **COMMON** | | | |

| | | | |
|---|---|---|---|
| **Herpes simplex (oral herpes):** pain, heat, and itching in area of infection, small red or tiny fluid-filled blisters or sores | | ✓ | |
| **Herpes zoster** (chickenpox): rash of small fluid-filled blisters, appearing on reddened skin | | ✓ | |
| **Hypertension** (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations | | ✓ | |
| **Lymphopenia** (low white blood cells - lymphocytes): get infections more easily, fever, sore throat or mouth ulcers due to infections | | ✓ | |
| **Urinary tract infection:** pain or burning when urinating, bloody or cloudy or foul smelling urine | | ✓ | |
| **UNCOMMON** | | | |
| **Allergic reaction:** rash, red, itchy skin, hives | ✓ | | |
| **Atrioventricular block** (irregular heartbeat) | | ✓ | |
| **Bradycardia** (low heart rate): feeling dizzy, tired, fainting, chest pain | | ✓ | |
| **Macular edema** (swelling and build-up of fluid in the center of the retina): blurry vision, blurry or wavy vision near or in the center of your field of vision, a blind spot in the center of your vision, sensitivity to light, colours may appear | | ✓ | |

| | | | |
|---|---|---|---|
| washed out or faded, unusually coloured vision | | | |
| **Melanocytic nevus** (a type of tumors - moles) | | ✓ | |
| **Skin Cancer:** shiny pearly nodules, moles, patches or open sores that changes in size, shape or colour or do not heal, red or brown blotches or tumours usually on the skin of the legs or face | | ✓ | |
| **RARE** | | | |
| **Posterior reversible Encephalopathy syndrome (PRES)** (symptoms may include sudden severe headache, feeling nauseous or throwing up confusion, drowsiness, personality change, paralysis, abnormal speech, convulsions and vision changes) | | | ✓ |
| **FREQUENCY NOT KNOWN** | | | |
| **Cerebrovascular accident, ischemic stroke, transient ischemic attack** (stroke): Sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause. | | | ✓ |
| **Liver problems:** yellowing of your skin or the whites of your eyes, abnormally dark urine, unexplained nausea or vomiting, tiredness, upper abdominal pain, loss of appetite | | ✓ | |
| **Meningitis** (inflammation of the membranes covering the brain) **and/or encephalitis** (inflammation of the brain)**, caused by fungal (Cryptococcus) or viral (chickenpox)** | | ✓ | |

| | | | |
|---|---|---|---|
| **infections:** headache accompanied by stiff neck, sensitivity to light, nausea, repeated vomiting, confusion, and/or seizures (fits) | | | |
| **Progressive multifocal leukoencephalopathy (PML)** (a rare brain infection): (progressive weakness on one side of your body, sudden inability to walk, severe imbalance, problems thinking, memory problems, confusion, or vision changes) | | ✓ | |
| **Serotonin Toxicity:** agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea | | | ✓ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store between 15°C and 25°C. Do not store above 25°C.

Keep out of reach and sight of children.

Do not take this medicine after the expiry date, which is stated on the box.

Keep in the original package.

Ask your pharmacist how to dispose of medicines you no longer use.

**If you want more information about ZEPOSIA:**

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.bms.com/ca, or by calling number 1-866-463-6267.

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