PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **ZEPOSIA®**

ozanimod capsules

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

Sphingosine 1-phosphate receptor modulator

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZEPOSIA® (ozanimod) is indicated for:

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

ZEPOSIA should only be prescribed by neurologists who are experienced in the treatment of multiple sclerosis, 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): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use. Physicians who choose to treat geriatric patients should consider 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 WARNINGS AND PRECAUTIONS, Special Populations).

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 Dosage Forms, Strengths, Composition and Packaging.

- 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 WARNINGS AND PRECAUTIONS, Cardiovascular).

- 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 WARNINGS AND PRECAUTIONS, Cardiovascular).

- 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).

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

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

- 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 WARNINGS AND PRECAUTIONS).

- Concomitant 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.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Prior to initiating treatment with ZEPOSIA the following assessments should be done to guide patient selection and treatment:

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 complete blood count (CBC) (i.e., within the last 6 months) (see WARNINGS AND PRECAUTIONS, Immune).
- 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.
- 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 WARNINGS AND PRECAUTIONS, Immune).
- Delay the start of ZEPOSIA in patients with severe active infection until resolved (see CONTRAINDICATIONS).

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 (see WARNINGS AND PRECAUTIONS, Cardiovascular - Treatment Initiation Recommendations).
- Determine whether patients are taking concomitant medications that reduce heart rate or atrioventricular conduction (see WARNINGS AND PRECAUTIONS, Cardiovascular - Treatment Initiation Recommendations; and DRUG INTERACTIONS).
- 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 WARNINGS AND PRECAUTIONS, Cardiovascular - Treatment Initiation Recommendations).

- 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 WARNINGS AND PRECAUTIONS, Cardiovascular - Treatment Initiation Recommendations).

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 WARNINGS AND PRECAUTIONS, Ophthalmologic; and ADVERSE REACTIONS, Macular edema).

Liver function tests

Prescribers should obtain recent (i.e., within last 6 months) transaminase and bilirubin levels (see WARNINGS AND PRECAUTIONS, Hepatic).

Current or prior medications

For patients taking antineoplastic, immunosuppressive, or immune-modulating therapies, including other disease modifying treatments for multiple sclerosis 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 WARNINGS AND PRECAUTIONS, Immune - Infections; and WARNINGS AND PRECAUTIONS, Immune - Prior and concomitant treatment with immunosuppressive or immune-modulating therapies).

3.2 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 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

Re-initiation of therapy following treatment interruption

Re-initiate treatment using the dose escalation regimen described in Table 1 if a dose of ZEPOSIA is missed during the first 2 weeks of treatment.

Maintenance treatment

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

Re-initiation of maintenance therapy after treatment interruption

The same dose escalation regimen described in Table 1 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, first-dose monitoring must be completed in patients for whom monitoring is recommended (see WARNINGS AND PRECAUTIONS, Cardiovascular – Treatment Initiation Recommendations).

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.

Special populations

Renal impairment

No ZEPOSIA dose adjustments are required in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of the major active metabolites of ozanimod has not been established. Use of ZEPOSIA in patients with hepatic impairment is not recommended.

Pediatric patients (below 18 years)

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

Geriatric patients (65 years or above)

Health Canada has not authorized an indication for geriatric use. Physicians who choose to treat geriatric patients should consider that treatment with ZEPOSIA, in the context of a greater frequency of other concomitant diseases and concomitant drug therapy, warrants caution.

3.3 Administration

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

3.4 Missed Dose

See above (Re-initiation of therapy following treatment interruption; Re-initiation of maintenance therapy after treatment interruption).

4 OVERDOSAGE

Patients should be managed by symptomatic and supportive care.

For management of a suspected drug overdose, contact your regional poison control centre.

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.

5 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, 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.

6 WARNINGS AND PRECAUTIONS

Cardiovascular

Bradyarrhythmia and Atrioventricular Conduction Delays

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

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 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 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.

Reduction in Heart Rate

In active-controlled MS clinical trials, after the initial dose of ZEPOSIA 0.23 mg, the greatest mean reduction from baseline in heart rate of 1.2 beats per minute (bpm) occurred at Hour 5 on Day 1, 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 DOSAGE AND ADMINISTRATION).

In the phase 3 clinical studies, bradycardia was reported on the day of treatment initiation in 0.6% 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.

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.

If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- With significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females).
- With arrhythmias requiring treatment with Class 1a or Class III antiarrhythmic drugs.

- With ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension.
- With a history of with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block.

Treatment initiation recommendations

Initiation of treatment with ZEPOSIA causes a transient decrease in heart rate and atrioventricular conduction delays. Use of a dose titration during treatment initiation helps to reduce these effects.

For all patients:

- Obtain an ECG prior to initiating treatment to determine whether pre-existing conduction abnormalities are present.
- Determine whether patients are taking concomitant medications that can reduce heart rate or atrioventricular conduction (see DOSAGE AND ADMINISTRATION, Dosing Considerations).
- Determine whether an evaluation by a cardiologist will be needed prior to initiating treatment.
- Use an up-titration scheme to help reduce cardiac effects when reaching the maintenance dose (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment; WARNINGS AND PRECAUTIONS, Cardiovascular - Bradyarrhthymia and Atrioventricular Conduction Delays; and ADVERSE REACTIONS, Bradyarrhythmia).

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:

- Administer the first dose of ZEPOSIA in a clinical setting where the patient can be monitored for a period of at least 6 hours after the first dose of ZEPOSIA for signs and symptoms of bradycardia, with hourly pulse and blood pressure measurements, and where symptomatic bradycardia can be managed.
- Obtain an ECG prior to dosing, and at the end of the 6-hour observation period.

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.

- Pre-existing significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females) (see WARNINGS AND PRECAUTIONS, Cardiovascular - QT Prolongation).
- A history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea. ZEPOSIA should not be used in these patients because significant bradycardia may be poorly tolerated.
- A history of recurrent syncope or symptomatic bradycardia.
- Concurrent treatment with heart rate lowering drugs.

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

If post-dose symptomatic bradycardia or bradyarrhythmia, or conduction related symptoms occur, or if ECG 6 hours post-dose shows new onset second degree or higher AV block or QTc > 450 msec in males, > 470 msec in females, appropriate management should be initiated and monitoring with continuous ECG should continue until the symptoms/findings have resolved, if no pharmacological intervention is required. If a patient requires pharmacological intervention during the first dose observation period, continuous overnight monitoring in a medical facility should be instituted and the first dose monitoring should be repeated when the second dose of ZEPOSIA is administered.

Experience with ZEPOSIA is limited in patients receiving concurrent therapy 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.

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.

<u>Increased Blood Pressure</u>

In the 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 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. Blood pressure should be monitored during treatment with ZEPOSIA and managed appropriately.

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 ADVERSE REACTIONS). Blood pressure should be regularly monitored during treatment with ozanimod.

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 aminotransferases may occur in patients receiving ZEPOSIA (see ADVERSE REACTIONS).

Obtain liver function tests if not recently available (i.e., within 6 months), before initiation of ZEPOSIA (see DOSAGE AND ADMINISTRATION).

In active-controlled MS clinical trials, 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 interferon (IFN) β-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients on ZEPOSIA and 3.1% of patients on 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.

In clinical trials, 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 patients on ZEPOSIA 0.92 mg and 0.8% of patients on IFN β-1a.

During treatment with ZEPOSIA, liver transaminases and bilirubin levels should be evaluated within the first 3 months after initiating treatment and periodically or as clinically indicated thereafter. For 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.

There are no data to establish whether patients with pre-existing liver disease are at increased risk to develop elevated liver function test (LFT) values when taking ZEPOSIA (See DOSAGE AND ADMINISTRATION – Special Populations).

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.

Before initiating, during treatment and after discontinuation with ZEPOSIA, the following

precautions should be taken:

- Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA (see DOSAGE AND ADMINISTRATION).
- Treatment initiation with ZEPOSIA should be delayed in patients with an active infection until resolution of the infection.
- Determine immunization status for VZV (see Vaccinations below).
- 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.
- Patients receiving ZEPOSIA should be instructed to promptly report symptoms of infections to their physician to facilitate early and effective diagnostic and therapeutic strategies.
- Suspension of treatment with ZEPOSIA, should be considered if a patient develops a serious infection.
- Because the elimination of ozanimod after discontinuation may take up to 3 months, monitoring for infections should be continued throughout this period.

In the pivotal clinical studies, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA 0.92 mg was similar to that in patients who received interferon (IFN) beta-1a (35.1% vs 34.5% and 1% vs 0.8%, respectively). ZEPOSIA increased the risk of viral upper respiratory tract infections, urinary tract infections, and herpes zoster (see ADVERSE REACTIONS).

The proportion of patients who experienced lymphocyte counts less than 0.2×10^9 /L was 3.3%. These values generally returned to greater than 0.2×10^9 /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 30 days, with approximately 90% of patients in the normal range within 3 months.

Herpetic Infections

In the 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. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (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.

Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA (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

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.

JCV infection resulting in PML has been observed in patients treated with MS therapies and has been associated with some risk factors (e.g., polytherapy with immunosuppressants, severely immunocompromised patients).

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.

Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ozanimod should be suspended until PML has been excluded. If confirmed, treatment with ZEPOSIA should be discontinued.

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 DOSAGE AND ADMINISTRATION).

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported 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. Cancer screening, including Pap test, is recommended as per standard of care.

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.

Varicella Zoster Virus (VZV) vaccination of patients without documented immunity to VZV is recommended at least 1 month prior to initiating treatment with ZEPOSIA (see DOSAGE AND ADMINISTRATION).

Prior and Concomitant Treatment with Antineoplastic, 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. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. 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 therapy lymphocyte counts typically return to the normal range within a median time of 30 days of stopping therapy, with approximately 90% of patients 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.

Neoplasm

Malignancies have been reported with ZEPOSIA in clinical trials.

For patients treated with immunosuppressive or immune modulating drugs, including S1P receptor modulators, there is potential for an increased risk of malignancies, particularly of the skin.

In the controlled Phase 3 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. 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.

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 clinical trials with ZEPOSIA, one case of PRES was reported in a patient with Guillain-Barré syndrome.

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

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 DRUG INTERACTIONS, Monoamine oxidase inhibitors). 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 DRUG INTERACTIONS, Adrenergic and serotonergic drugs). 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 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 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. 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.

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

Sexual Health

Reproduction

Fetal 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 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and NON-CLINICAL TOXICOLOGY).

Contraception

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 should use effective contraception (methods that result in less than 1% pregnancy rates) during ZEPOSIA treatment and for 3 months after stopping ZEPOSIA. ZEPOSIA is contraindicated in women (including female adolescents) who are pregnant or of childbearing potential and not using effective contraception (see CONTRAINDICATIONS; and see below Special Populations - Women of Childbearing Potential).

Fertility

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

6.1 Special Populations

6.1.1 Women of Childbearing Potential

ZEPOSIA is contraindicated in women (including female adolescents) who are pregnant or of childbearing potential not using effective contraception (see 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 of childbearing potential must use effective contraception 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). If a woman becomes pregnant while taking this drug, the patient must be informed of the risk to the fetus.

6.1.2 Pregnant Women

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

Pregnant women should be advised of a potential risk to the fetus if ZEPOSIA is used during pregnancy or if the patient becomes pregnant while taking this medicinal product (See WARNINGS AND PRECAUTIONS and NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). 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 considered in females discontinuing ZEPOSIA because of pregnancy or planned pregnancy (see WARNINGS AND PRECAUTIONS, Neurologic - Return of Disease Activity (Rebound) After ZEPOSIA Discontinuation).

6.1.3 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 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). There are no data on the presence of ozanimod in human milk, the effects on the breastfed 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.

6.1.4 Pediatrics

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

6.1.5 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 > 55 years of age, given the potential for an increased risk of adverse reactions in this population, especially with long-term treatment.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

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%).

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.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

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 Adverse Events with an Incidence of Greater Than or Equal to 1% for ZEPOSIA and at Equal or Higher Rates Than for IFN β-1a

SYSTEM ORGAN CLASS PREFERRED TERM[a]	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)

SYSTEM ORGAN CLASS PREFERRED TERM[a]	ZEPOSIA 0.92 mg n = 882 (%)	IFN β-1a 30 mcg n = 885 (%)
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)

SYSTEM ORGAN CLASS PREFERRED TERM[a]	ZEPOSIA 0.92 mg n = 882 (%)	IFN β-1a 30 mcg n = 885 (%)
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.

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 patients on ZEPOSIA 0.92 mg and 0.8% of patients on IFN β-1a.

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.

Bradyarrhythmia

In active-controlled MS clinical trials, after the initial dose of 0.23 mg, the greatest mean reduction from baseline in sitting/supine HR of 1.2 bpm occurred at Hour 5 on Day 1, 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.

Blood Lymphocyte Count Reduction

3.3% 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 was comparable between the patients treated with ZEPOSIA 0.92 mg and those treated with IFN β-1a (35.1% vs. 34.5 %, respectively). 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 on IFN β-1a.

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 WARNINGS AND PRECAUTIONS – Respiratory).

Neoplasm

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

Hypersensitivity

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

7.3 Less Common Clinical Trial Adverse Events (<1%)

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

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

Table 4 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		
Lymphopenia[a]	29 (3.3)	0

LABORATORY PARAMETER	ZEPOSIA 0.92 mg n = 882 (%)	IFN β-1a 30 mcg n = 885 (%)
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] Grade 4 lymphopenia

8 DRUG INTERACTIONS

8.1 Overview

Pharmacodynamic interactions

Anti-neoplastic, immune-modulating or immunosuppressive therapies

ZEPOSIA has not been studied in combination with anti-neoplastic, immune-modulating, or 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 WARNINGS AND PRECAUTIONS, Cardiovascular - Treatment initiation recommendations).

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 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 WARNINGS AND PRECAUTIONS, Immune – Vaccinations). 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 ACTION AND CLINICAL PHARMACOLOGY, 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.

8.2 Drug-Drug Interactions

Inhibitors of Breast Cancer Resistance Protein (BCRP)

Co-administration of BCRP inhibitors may increase exposure of the major active metabolites CC112273 and CC1084037, which may increase the risk of ZEPOSIA adverse reactions. Inhibitor of BCRP (cyclosporine) doubled the exposure of the minor active metabolites RP101988 and RP101075 (the direct precursor of the major active metabolite CC112273). Co-administration of inhibitors of BCRP (e.g., cyclosporine, eltrombopag) with ZEPOSIA is not recommended.

Effect of Strong Inhibitors of CYP2C8

Co-administration of gemfibrozil (a strong inhibitor of CYP2C8) 600 mg twice daily at steady state and a single dose of ozanimod 0.46 mg increased exposure (AUC) of active metabolites CC112273 and CC1084037 by approximately 47% and 69%, respectively. Therefore, co-administering ZEPOSIA with strong CYP2C8 inhibitors is not recommended.

Effect of Strong CYP2C8 Inducers

Co-administration of rifampin (a strong inducer of CYP2C8) 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, which may decrease the efficacy of ZEPOSIA. Therefore, the co-administration of strong CYP2C8 inducers (i.e., rifampin) with ZEPOSIA is not recommended.

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 CONTRAINDICATIONS; 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. ZEPOSIA increased the pseudoephedrine-induced heart rate response by approximately 3 bpm. 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 WARNINGS AND PRECAUTIONS, Cardiovascular).

8.3 Drug-Food Interactions

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

8.4 Drug-Herb Interactions

Interactions with herbal products have not been studied.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

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 is unknown but may involve reduction of lymphocyte migration into the central nervous system.

9.2 Pharmacodynamics

Immune System

Reduction in Blood Lymphocyte Counts

In active-controlled MS clinical trials, 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 90% of patients recovering within 3 months.

Reduction in Heart Rate

Ozanimod may cause a transient reduction in heart rate on initiation of dosing (see 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 DOSAGE AND ADMINISTRATION).

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.

9.3 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 5 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)	AUCτ (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 RP101509) 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 RP101509. 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 DOSAGE AND ADMINISTRATION).

Smokers: Population PK results showed that CC112273 steady-state exposure (AUC) was approximately 50% lower in smokers than in non-smokers. The clinical impact of smoking on ozanimod treatment for patients with RMS is not known.

10 STORAGE, STABILITY AND DISPOSAL

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

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

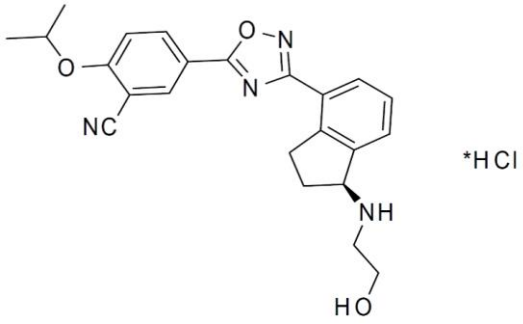
Drug Substance

Common 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.

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Table 6 Summary of Patient Demographics for Pivotal Clinical Trials in Relapsing Remitting Multiple Sclerosis

Study #	Trial 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 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 12+ months[a]	ozanimod 0.92 mg (N=447) ozanimod 0.46 mg (N=451) IFN β-1a 30 mcg IM (N=448)	34.8 years (18 – 55) 36.0 years (18 – 55) 35.9 years (18 – 55)	female = 63% female = 69% female = 67%

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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) ozanimod 0.46 mg (N=439) IFN β-1a 30 mcg IM (N=441)	36.0 years (18 – 55) 35.4 years (18 – 55) 35.1 years (18 – 55)	female = 67% female = 65% 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.

12.2 Study Results

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 7.

Table 7 Key Clinical and MRI Endpoints in RMS 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 Kaplan-Meier Estimate	78% 0.781 (p=0.0002)[1]	66% 0.663	76% 0.756 (p=0.0012)[1]	64% 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 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-enhancing lesions[5]	0.160	0.433	0.176	0.373
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).

13 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.

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.

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 at doses to rats 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.

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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]ZEPOSIA®
ozanimod (as ozanimod hydrochloride)

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).
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.

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 doctor 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:
  - 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 doctor 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 doctor 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 doctor 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.
- have never had chickenpox or have not been vaccinated against chickenpox (varicella zoster virus). Your doctor 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 doctor will decide if you need to be vaccinated against Human Papilloma Virus (HPV) before starting treatment. For female patients, your doctor 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.
  - Herpes Zoster Virus. Cases of herpes viral infections have been reported in patients

treated with similar medicines like 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

You should not take ZEPOSIA if you have any of these conditions.

- 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) or
  - have diabetes

The macula is a small area of the retina at the back of the eye. It allows you to see shapes, colors, 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 doctor 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 doctor about any changes in your vision.

- have liver problems. ZEPOSIA may affect your liver function. If you notice any of the following symptoms, tell your doctor **right away**:
  - yellowing of your skin or the whites of your eyes
  - abnormally dark urine
  - unexplained nausea or vomiting
  - tiredness

Your doctor 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 doctor if MS symptoms become worse after you stop taking ZEPOSIA.

Patients taking immunosuppressive or immune modulating medicines: you could be at an increased risk for developing cancer, particularly skin cancer. Basal cell carcinoma was reported with patients on ZEPOSIA therapy. Your doctor 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 doctor 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 doctor about options of effective birth control (see **Do not use ZEPOSIA if**).
- If you become pregnant or think you are pregnant, tell your doctor right away. You and your doctor will decide what is best for you and your baby.

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 doctor 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) 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 doctor 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. These may be the symptoms of **progressive multifocal leukoencephalopathy** (PML). This is a rare brain disorder caused by an infection.
- 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 **cryptococcal meningitis** caused by a fungal 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.
If any of these apply to you, tell your doctor or pharmacist before taking ZEPOSIA.

The following may interact with ZEPOSIA:
- **Medicines that treat an irregular heartbeat (medicines that cause QT prolongation)**
  - procainamide
  - amiodarone
  - sotalol

Your doctor 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 doctor 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:**
  - 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 doctor 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.

- **Vaccines**. If you need to receive a vaccine, talk to your doctor 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., rasagiline) may lead to increased blood pressure.

Serotonin Syndrome:
ZEPOSIA may cause serotonin syndrome, 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 syndrome if you take ZEPOSIA with certain antidepressants or migraine medications.

Serotonin syndrome 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 doctor 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 doctor'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.
- 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
  - a check 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

Your doctor 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

Usual dose:

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.
- 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 doctor tells you. Do not stop taking this medicine without talking to your doctor.

IMPORTANT – Missed Doses:

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

- Contact your doctor 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 doses after 14 days** of treatment:

- Continue with the treatment as planned

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

- Talk to your doctor 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 health care professional right away if any of these happen.
- Do not take a double dose to make up for a missed dose.

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

Overdose:

If you think you have taken too much ZEPOSIA contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using ZEPOSIA?

These are not all the possible side effects you may feel when taking ZEPOSIA. If you experience any side effects not listed here, contact 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			
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		✓	

Herpes zoster (chickenpox): rash of small fluid-filled blisters, appearing on reddened skin		✓	
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, colors may appear washed out or faded		✓	
Melanocytic nevus (a type of tumors - moles)		✓	
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.			✓
Cryptococcal infections (a type of fungal infection) including cryptococcal meningitis: headache accompanied by stiff neck, sensitivity to light, nausea, and/or confusion		✓	
Herpes zoster meningitis: headache, repeated vomiting			✓
Progressive multifocal leukoencephalopathy (PML), a rare brain infection (symptoms may include weakness on one		✓	

side of your body, problems thinking, or vision changes)			
Serotonin Syndrome: 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, talk to 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.celgene.ca or by calling 1-877-923-5436.

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