▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ZEPOSIA (ozanimod) Capsules

1. NAME OF THE MEDICINE

Australian Approved Name: ozanimod

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 230 microgram capsule contains 230 micrograms ozanimod (equivalent to 250 micrograms ozanimod hydrochloride).

Each 460 microgram capsule contains 460 micrograms ozanimod (equivalent to 500 micrograms ozanimod hydrochloride).

Each 920 microgram capsule contains 920 micrograms ozanimod (equivalent to 1.00 mg ozanimod hydrochloride).

For the full list of excipients, see section 6.1 (List of excipients).

Description

Ozanimod hydrochloride is a white to off-white solid with a melting point of ~240°C. Ozanimod hydrochloride is poorly hygroscopic. The solubility of ozanimod hydrochloride in ethanol and methanol is 1.43 and 2.41 mg/mL and in a pH 5.1 aqueous medium is 3.51 mg/mL. The pKa for ozanimod hydrochloride is 7.90 and the partition coefficient (logP) is 3.28.

Ozanimod hydrochloride exists as the (S) configuration with an enantiomeric purity of not less than 99.0%.

3. PHARMACEUTICAL FORM

Capsule.

Zeposia 230 microgram capsules:

Light grey opaque capsule, size 4, imprinted in black ink with “OZA” on the cap and “0.23 mg” on the body.

Zeposia 460 microgram capsules:

Light grey / orange opaque capsule, size 4, imprinted in black ink with “OZA” on the cap and “0.46 mg” on the body.

Zeposia 920 microgram capsules:

Orange opaque capsule, size 4, imprinted with “OZA” on the cap and “0.92 mg” on the body.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Zeposia is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis.

4.2. DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated under the supervision of a physician experienced in the management of multiple sclerosis (MS).

4.2.1. Dosage

The recommended dose of Zeposia for adults is 920 microgram once daily taken orally.

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

If a dose of Zeposia is missed, the next scheduled dose should be taken the following day.

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 920 microgram once daily taken orally starting on Day 8. Initiation of Zeposia without dose escalation may result in greater reductions in heart rate (see *Section 4.4)*.

Prior to Initiation of Therapy

- Obtain an electrocardiogram (ECG) to determine whether pre-existing cardiac conduction abnormalities are present (*see Section 4.4*).
- Obtain recent (i.e., within 6 months) liver function tests *(see Section 4.4).*
- Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC, including lymphocyte count) *(see Section 4.4).*
- Arrange an ophthalmological assessment before starting Zeposia treatment in patients with risk factors for macular oedema, such as diabetes mellitus, history of uveitis or history of retinal disease (*see Section 4.4*).

Current or Prior Medications

- If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with Zeposia (*see Section 4.4*).
- Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction (*see Section 4.5*).

Vaccinations

- 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.
- If live *attenuated* immunizations are required, administer at least 1 month prior to initiation of 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.

4.2.2. Method of administration

Table 1: Dose Escalation Regimen

Days 1-4	230 microgram once daily
Days 5-7	460 microgram once daily
Days 8 and thereafter	920 microgram once daily

Re-initiation of therapy following treatment interruption

If a dose of Zeposia is missed during the first 2 weeks of treatment, reinitiate treatment using the dose escalation regimen.

If a dose of Zeposia is missed after the first 2 weeks of treatment, continue with the treatment as planned.

If more than 7 consecutive days are missed between Day 15 and Day 28 of treatment, or more than 14 consecutive days after Day 28 of treatment, reinitiate treatment using the dose escalation regimen.

Special populations

Elderly

The safety and effectiveness of Zeposia in patients aged 55 years and over have not been established. There are limited data available on RMS patients > 55 years of age. Patients enrolled in the ongoing clinical trials continue to be dosed with 920 microgram Zeposia daily after they become 55 and older (see sections 5.1 and 5.2). No dose adjustment is needed in patients over 55 years of age.

Hepatic impairment

No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B).

The pharmacokinetics of Zeposia was not evaluated in subjects with severe hepatic impairment. Use in patients with severe hepatic impairment is not recommended (Child-Pugh class C).

Renal impairment

No dosage adjustment is necessary for patients with renal impairment.

Paediatric population

The safety and effectiveness of Zeposia in patients below the age of 18 years have not been established.

4.3. CONTRAINDICATIONS

- Hypersensitivity to ozanimod or any of the excipients (see Section 6.1).
- Treatment should not be initiated in patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure
- Treatment should not be initiated in patients who have a history or presence of second-degree atrioventricular (AV) block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker
- Treatment should not be initiated in patients with severe untreated sleep apnea.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1. Bradycardia - Reduction in heart rate

Initiation of Zeposia may result in transient reductions in heart rate (HR). In active-controlled MS clinical trials, after the initial dose of Zeposia 230 microgram, the greatest mean reduction from baseline in HR of 1.2 beats per minute (bpm) occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. HR below 40 bpm were not observed. Initiation of Zeposia without dose escalation may result in greater reductions in HR *(see Section 4.2).*

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

4.4.2. Elevated Hepatic Enzymes

Elevations of aminotransferases may occur in patients receiving Zeposia *(see Section 4.8)*.

Obtain liver function tests if not recently available (i.e., within 6 months), before initiation of Zeposia *(see Section 4.2.1).*

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 920 microgram and 1.3% of patients on interferon (IFN) beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients on Zeposia and 3.1% of patients on IFN beta-1a.

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 920 microgram and 0.8% of patients on IFN beta-1a.

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.

Resumption of therapy will be dependent on whether another cause of liver enzyme elevation is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction.

Patients with preexisting liver disease may be at increased risk of developing elevated hepatic enzymes when taking Zeposia.

4.4.3. Return of disease activity (rebound) after ozanimod 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 ozanimod treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon ozanimod discontinuation and appropriate treatment should be instituted as required.

4.4.4. Infections

Risk of Infections

Zeposia causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because

of reversible retention of lymphocytes in lymphoid tissues. Zeposia may therefore increase the susceptibility to infections.

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 Section 4.2.1)*.

Delay initiation of Zeposia in patients with an active infection until the infection is resolved.

After discontinuing Zeposia 920 microgram, 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.

Consider interruption of treatment with Zeposia if a patient develops a serious infection.

Because the elimination of Zeposia after discontinuation may take up to 3 months, continue monitoring for infections throughout this period.

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.

When switching to Zeposia from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects (*see Section 4.5.1*).

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

Progressive multifocal leukoencephalopathy (PML)

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 Zeposia should be suspended until PML has been excluded. If confirmed, treatment with Zeposia should be discontinued.

Herpes Viral Infection

In MS clinical studies, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with Zeposia 920 microgram 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. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against 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.

Vaccinations

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.

If live *attenuated* vaccine immunizations are required, administer at least 1 month prior to initiation of 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.

4.4.5. Macular Oedema

In the active-controlled MS clinical trials with Zeposia, macular oedema was observed in one (0.1%) patient with Zeposia 920 microgram and 3 (0.3%) patients with Zeposia 460 microgram and none with IFN beta-1a. Patients observed to have macular oedema had preexisting risk factors.

Patients with risk factors for macular oedema, such as a history of uveitis, diabetes mellitus or history of retinal disease, should have an ophthalmologic evaluation prior to treatment with Zeposia and have follow up evaluations while receiving therapy.

Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with Zeposia should be discontinued.

4.4.6. Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a syndrome characterized by sudden onset of severe headache, confusion, seizures and visual loss. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage.

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

If PRES is suspected, treatment with Zeposia should be discontinued.

4.4.7. Increased Blood Pressure

In MS clinical studies, hypertension was more frequently reported in patients treated with ozanimod 920 microgram (3.4%) than in patients treated with IFN beta-1a IM (2.0%), and in patients receiving concomitant ozanimod and SSRIs or SNRIs (*see Section 4.8*). Blood pressure should be regularly monitored during treatment with ozanimod.

4.4.8. Fetal Risk

There are no adequate and well-controlled studies in pregnant women. In animals, findings at similar exposure levels included embryo-fetal death, abnormal/delayed ossification, and abnormalities of the viscera and large blood vessels.

Before initiation of treatment, women of childbearing potential must be informed of this risk to the fetus, should have a negative pregnancy test and should use effective contraception during treatment and for 3 months after stopping Zeposia *(see Section 4.6.2)*.

4.4.9. Malignancies

Given the immunomodulatory/immunosuppressive properties of ozanimod a potential risk for increased malignancy cannot be ruled out.

Cutaneous neoplasms

An increased risk of cutaneous malignancies has been reported with S1P receptor modulators.

Half of the neoplasms reported with ozanimod in active controlled clinical trials consisted of skin malignancies, with basal cell carcinoma presenting as the most common skin neoplasm and reported with a similar incidence in the combined ozanimod (0.2%, 3 patients) and IFN beta-1a (0.1 %, 1 patient) group.

Since there is a potential risk of malignant skin growths, patients treated with Zeposia should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

4.4.10. Effects on Laboratory Tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

4.5.1. Effects of other drugs on ozanimod

Caution should be applied when switching patients from long-acting therapies with immune effects *(see Section 4.4.3)*

Inhibitors of Breast Cancer Resistance Protein (BCRP)

Inhibitor of BCRP (ciclosporin) had no effect on ozanimod exposure and doubled the exposure of the minor active metabolites RP101988 and RP101075 (the direct precursor of the major active metabolite CC112273). Co-administration of BCRP inhibitors may also increase exposure of CC112273 and CC1084037. Co-administration of inhibitors of BCRP (e.g., ciclosporin, eltrombopag) with Zeposia is not recommended.

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 460 microgram resulted in no clinically meaningful changes in exposure (AUC) of ozanimod and increased exposure (AUC) of active metabolites CC112273 and CC1084037 by approximately 47% and 69%, respectively. When co-administering Zeposia with CYP2C8 inhibitors, monitor patients as the risk of adverse reactions may be greater.

Strong CYP3A and P-gp Inhibitors

Co-administration of itraconazole (a strong inhibitor of CYP3A and P-gp) 200 mg once daily at steady state and a single dose of Zeposia 920 microgram resulted in no clinically meaningful changes in exposure of ozanimod, CC112273 and CC1084037.

Strong CYP3A/P-gp and Moderate CYP2C8 Inducers

Co-administration of rifampicin (a strong inducer of CYP3A and P-gp, and a moderate inducer of CYP2C8) 600 mg once daily at steady state and a single dose of Zeposia 920 microgram resulted in no clinically meaningful changes in exposure (AUC) of ozanimod and reduced exposure (AUC) for CC112273 and CC1084037 by approximately 60% and 55%, respectively. The effect of rifampicin on CC112273 and CC1084037 was due to CYP2C8 induction. The co-administration of CYP2C8 inducers (i.e., rifampicin) with Zeposia is not recommended.

Monoamine Oxidase (MAO) Inhibitors

Co-administration with MAO-B inhibitors may decrease exposure of CC112273 and consequently CC1084037. The potential for clinical interaction with MAO inhibitors has not been studied. Co-administration of MAO inhibitors (e.g., selegiline, phenelzine) with Zeposia is not recommended.

4.5.2. Effect of ozanimod on other drugs

Drugs That Slow Heart Rate or Atrioventricular Conduction (e.g., beta blockers or calcium channel blockers)

In healthy subjects, initiating ozanimod 230 microgram with steady-state propranolol long acting 80 mg once daily or diltiazem extended release 240 mg once daily did not result in any additional clinically meaningful changes in HR and PR interval compared to either propranolol or diltiazem alone.

Administration of Zeposia in subjects with both a beta blocker and a calcium channel blocker taken together has not been studied.

Adrenergic Agents

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.

Oral contraceptives

Co-administration of ozanimod 920 microgram once daily and a single dose of oral contraceptive containing ethinyl estradiol (EE) 35 microgram and norethindrone (NE) 1 mg resulted in no change in EE or NE exposure. Dosing duration of ozanimod was not long enough to attain steady state for the major active metabolites; however, CC112273 and CC1084037 have no in vitro effect on CYP enzymes and therefore are not expected to have any effect on EE and NE exposure.

MAO Activity

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. In a serotonergic mouse model study, CC112273 concentrations up to 84 nM (approximately 4-fold higher than the mean steady-state C_{max} of CC112273 [19.4 nM] in RMS patients receiving ozanimod 920 microgram QD for 12 weeks) did not induce signs of serotonin syndrome in normal mice or exacerbate mild serotonin syndrome in mice induced by 5-hydroxytryptophan. In a clinical study with Zeposia,

CC112273 and CC1084037 had no inhibition effect on human platelet MAO-B activity. In active-controlled MS clinical trials, the use of serotonergic agents including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) was not excluded and no patients with serotonin syndrome were identified.

CYP Enzymes

Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6, and 3A and no induction effect on CYPs 1A2, 2B6, and 3A.

Drug Transporters

Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on P-glycoprotein, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, and MATE2-K. CC112273 and CC1084037 inhibit BCRP with IC_{50} values of 25.2 nM and 22.8 nM, respectively. At clinically relevant concentrations of CC112273 and CC1084037, inhibition of BCRP is not expected.

4.6. FERTILITY, PREGNANCY AND LACTATION

4.6.1. Effects on fertility

No fertility data are available in humans. No effects on fertility were observed in animal studies. Ozanimod had no effect on fertility in rats up to 30 mg/kg/day (estimated systemic exposure more than 2000 times the anticipated clinical exposure) in a study in which both male and female animals were treated orally and mated. There was no apparent effect on sperm count/motility. Data from animals does not suggest that ozanimod would be associated with an increased risk of reduced fertility.

4.6.2. Use in pregnancy (Category D)

There are no adequate data on the developmental risk associated with the use of Zeposia in pregnant women. If the patient becomes pregnant or plans to become pregnant while taking Zeposia, she should be informed of the potential hazards and discontinuation of therapy should be considered.

Ozanimod and/or its metabolites crossed the placental barrier in pregnant rats and rabbits. When administered during organogenesis, ozanimod was teratogenic in the rat at oral doses of 5 mg/kg/day or higher (426 times the clinical exposure on an AUC basis) with a no effect dose of 1 mg/kg/day (63.7 times the clinical exposure). The most common findings were anasarca, malpositioned testes and delayed/incomplete ossification. Rabbits showed an increase in malformation of great blood vessels, incomplete ossification and malpositioned vertebrae at oral doses of 0.6 mg/kg/day or higher (8 times the clinical exposure on an AUC basis) with a no effect dose of 0.2 mg/kg/day (2.4 times the clinical exposure).

The vascular effects, as well as an increased incidence of post-implantation loss and resorptions seen in rats (5 mg/kg/day, 426 times the clinical exposure) and rabbits (2 mg/kg/day; 27.6 times the clinical exposure) are consistent with the pharmacological mechanism of ozanimod, since the sphingosine-1-phosphate receptor is involved in vascular formation during embryogenesis.

Women of childbearing potential should use effective contraception during Zeposia treatment and for 3 months after stopping Zeposia.

4.6.3. Use in lactation

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. Ozanimod and its metabolites are present in rat milk. Reduced immunocompetence was evident in juvenile rats following oral administration.

Due to the potential for serious adverse reactions to ozanimod/metabolites in nursing infants, women receiving ozanimod should not breastfeed.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

4.8.1. Tabulated Summary of Adverse Events

The Safety Population for the two active-controlled phase 3 MS clinical studies included 2659 subjects, of whom 882 subjects received at least 1 dose of ozanimod 920 microgram, 892 subjects received at least 1 dose of ozanimod 460 microgram, and 885 subjects received at least 1 dose of IFN beta-1a.

The system organ classes with the highest proportions of subjects reporting AEs were Infections and Infestations, Nervous System Disorders, and Investigations. Adverse events reported by ≥ 2% of subjects in any treatment group are provided in Table 2.

Table 2: Treatment-emergent Adverse Events Reported in ≥ 2% of Subjects in Any Treatment Group — (Safety Population)

Preferred Term	IFN beta-1a 30 microgram (N = 885) n (%)	Zeposia 460 microgram (N = 892) n (%)	Zeposia 920 microgram (N = 882) n (%)
Nasopharyngitis	84 (9.5)	103 (11.5)	98 (11.1)
Headache	78 (8.8)	82 (9.2)	78 (8.8)
Upper respiratory tract infection	61 (6.9)	67 (7.5)	52 (5.9)
Alanine aminotransferase increased	28 (3.2)	41 (4.6)	47 (5.3)
Influenza like illness	442 (49.9)	44 (4.9)	44 (5.0)
Orthostatic hypotension	28 (3.2)	32 (3.6)	38 (4.3)
Back pain	23 (2.6)	31 (3.5)	35 (4.0)
Gamma-glutamyltransferase	11 (1.2)	26 (2.9)	40 (4.5)
Urinary tract infection	27 (3.1)	30 (3.4)	36 (4.1)
Hypertension	18 (2.0)	31 (3.5)	30 (3.4)
Pharyngitis	20 (2.3)	30 (3.4)	28 (3.2)
Depression	25 (2.8)	22 (2.5)	23 (2.6)
Arthralgia	14 (1.6)	23 (2.6)	20 (2.3)
Insomnia	20 (2.3)	22 (2.5)	21 (2.4)
Bronchitis	17 (1.9)	18 (2.0)	23 (2.6)
Fatigue	16 (1.8)	21 (2.4)	20 (2.3)

Rhinitis	13 (1.5))	20 (2.2)	19 (2.2)
Abdominal pain upper	9 (1.0)	17 (1.9)	20 (2.3)

Preferred Term	**IFN beta-1a 30 microgram (N = 885) n (%)**	**Zeposia 460 microgram (N = 892) n (%)**	**Zeposia 920 microgram (N = 882) n (%)**
Respiratory tract infection viral	11 (1.2)	15 (1.7)	21 (2.4)
Pain in extremity	18 (2.0)	18 (2.0)	15 (1.7)
Pyrexia	56 (6.3)	17 (1.9)	16 (1.8)
Respiratory tract infection	21 (2.4)	13 (1.5)	18 (2.0)
Diarrhoea	12 (1.4)	18 (2.0)	12 (1.4)
Sinusitis	19 (2.1)	15 (1.7)	13 (1.5)
Anaemia	19 (2.1)	13 (1.5)	9 (1.0)

IFN = interferon.

Note: Preferred terms are listed in order of decreasing frequency in the ozanimod 920 microgram treatment group.

4.8.2. Tabulated summary of adverse drug reactions

The adverse drug reactions were determined based on data from the ozanimod clinical development programme. The frequencies of adverse drug reactions are those reported in the ozanimod arms of the
two active-controlled MS clinical studies. In these studies, 1774 patients received Zeposia with an overall exposure of 2641 person-years.

The most commonly reported adverse reaction in Phase 3 clinical studies were nasopharyngitis, alanine aminotransferase increased, and gamma-glutamyl transferase increased. The most common adverse reactions leading to discontinuation were related to liver enzyme elevations.

The adverse reactions observed in patients treated with ozanimod are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); Uncommon (≥ 1/1000 to < 1/100).

Table 3: Summary of Adverse Drug Reactions reported in the two MS studies

Frequency	**All ADRs**
Infections and infestations	
Very Common	Nasopharyngitis
Common	Pharyngitis, Respiratory tract infection viral, Urinary tract infection*
Uncommon	Herpes zoster
Blood and lymphatic system disorders	
Very Common	Lymphopenia

Immune system disorders	
Uncommon	Hypersensitivity (including rash and urticaria*)
Eye disorders	
Common	Macular oedema**

Frequency	**All ADRs**
Cardiac disorders	
Common	Bradycardia*
Vascular disorders	
Common	Hypertension*, Orthostatic hypotension
Investigations	
Common	Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Blood bilirubin increased, Pulmonary function test abnormal***

*At least one of these adverse reactions was reported as serious
** for patients with pre-existing factors (see section 4.4)
***including pulmonary function test decreased, spirometry abnormal, forced vital capacity decreased, carbon monoxide diffusing capacity decreased, forced expiratory volume decreased

4.8.3. Description of Selected Adverse Reactions

Bradycardia – reduction in heart rate

In active-controlled MS clinical trials, bradycardia was reported in 0.5% on Zeposia versus 0% on IFN beta-1a on the day of treatment initiation. After Day 1, the incidence of bradycardia was 0.8% on Zeposia versus 0.7% on IFN beta-1a.

In active-controlled MS clinical trials with dose escalation, second-or third-degree atrioventricular blocks were not reported with Zeposia.

Patients who experienced bradycardia were generally asymptomatic. In MS clinical studies, first-degree atrioventricular block was reported in 0.6% (5/882) of patients treated with Zeposia versus 0.2% (2/885) treated with IFN beta-1a IM. Of the cases reported with Zeposia, 0.2% were reported on Day 1 and 0.3% were reported after Day 1.

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 beta-1a, and no effect on diastolic pressure. The increase in systolic pressure was first detected after approximately 3 months of treatment initiation and remained stable throughout treatment. Hypertension-related events (hypertension, essential hypertension, and blood pressure increased) were reported as an adverse reaction in 4.5% of patients treated with Zeposia 920 microgram and in 2.3% of patients treated with IFN beta-1a IM.

Elevated Hepatic Enzymes

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 920 microgram and 1.3% of patients on interferon (IFN) beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients on Zeposia and 3.1%

of patients on IFN beta-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 920 microgram and 0.8% of patients on IFN beta-1a.

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 920 microgram, 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 MS clinical studies, the overall rate of infections (35%) with Zeposia 920 microgram was similar to IFN beta-1a IM. Zeposia increased the risk of upper respiratory tract infections and urinary tract infection. The overall rate of serious infections was similar between Zeposia (1%) and IFN beta-1a IM (0.8%) in MS clinical studies.

Herpes Zoster

In active-controlled MS trials, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with Zeposia 920 microgram and in 0.2% of patients on IFN beta-1a.

Hypersensitivity

Hypersensitivity, including rash and urticaria, has been reported with Zeposia in active-controlled MS clinical trials at a frequency of uncommon.

Respiratory system

Minor dose-dependent reductions in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were observed with Zeposia treatment.

At months 3 and 12 of treatment in MS clinical studies, median changes from baseline in FEV1 (FVC) in the Zeposia 920 microgram group were -0.07 L and -0.1 L (-0.05 L and -0.065 L), respectively, with smaller changes from baseline in the IFN beta-1a group (FEV1: - 0.01 L and -0.04 L, FVC: 0.00 L and -0.02 L).

4.8.4. Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems

4.9. OVERDOSE

In the event of overdose, patients should be managed by symptomatic and supportive care.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AA38

5.1.1. Mechanism of action

Ozanimod is a sphingosine 1-phosphate receptor modulator, which binds with a high affinity to sphingosine 1-phosphate receptor subtypes 1 and 5. Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts therapeutic effects in multiple sclerosis (MS) is unknown but may involve the reduction of lymphocyte migration into the central nervous system.

Ozanimod is 10-fold more selective for S1P1 relative to S1P5 and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$). Ozanimod is extensively metabolized in humans to form a number of circulating active metabolites. In vitro, ozanimod and its active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$. In humans, approximately 94% of circulating total active drug exposure is represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%).

5.1.2. Cardiac Electrophysiology

Ozanimod may cause a transient reduction in heart rate on initiation of dosing. A dose escalation schedule of Zeposia 230 microgram followed by doses of 460 microgram, and 920 microgram attenuates the magnitude of heart rate reductions.

In a randomized, positive- and placebo-controlled thorough QT study using a 14-day dose-escalation regimen of 230 microgram QD for 4 days, 460 microgram QD for 3 days, 920 microgram QD for 3 days, and 1.84 mg QD for 4 days in healthy subjects, no evidence of QTc prolongation was observed as demonstrated by the upper boundary of the 95% one-sided confidence interval (CI) that was below 10 ms. Concentration-QTc analysis for ozanimod and the major active metabolites, CC112273 and CC1084037, using data from another Phase 1 study showed the upper boundary of the 95% CI for model derived QTc (corrected for placebo and baseline) below 10 ms at maximum concentrations achieved with Zeposia doses $\geq$ 920 microgram once daily.

5.1.3. Reduction in Blood Lymphocyte Counts

In active-controlled MS clinical trials, mean lymphocyte counts decreased to approximately 45% 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 920 microgram, 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.

5.1.4. Clinical trials

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

The dose of Zeposia was 920 microgram and 460 microgram given orally once daily, with a starting dose of 230 microgram on Days 1-4, followed by an escalation to 460 microgram on Days 5-7, and followed by

the assigned dose on Day 8 and thereafter. The dose of IFN beta-1a, the active comparator, was 30 microgram 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 (Studies 1 and 2), 6 months (Study 1), 1 year (Studies 1 and 2), and 2 years (Study 2).

The primary outcome of both Study 1 and Study 2 was the annualized relapse rate (ARR) over 12 months for Study 1 and 24 months for Study 2. 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 Studies 1 and 2. An additional MRI outcome measure was the mean percentage change from baseline in normalized brain volume.

In Study 1, 1346 patients were randomized to receive Zeposia 920 microgram (n = 447), Zeposia 460 microgram (n= 451), or IFN beta-1a (n = 448); 94% of Zeposia-treated 920 microgram, 94% of Zeposia-treated 460 microgram, and 92% of IFN beta-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. 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 Study 2, 1313 patients were randomized to receive Zeposia 920 microgram (n = 433), Zeposia 460 microgram (n = 439), or IFN beta-1a (n = 441); 90% of Zeposia -treated 920 microgram, 85% of Zeposia-treated 460 microgram, and 85% of IFN beta-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 (median) EDSS score at baseline was 2.51 (2.5); 71% had not been treated with a disease-modifying therapy. At baseline, the mean number of relapses in the prior year was 1.3 and 43% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The median duration of treatment was 24 months.

The ARR was significantly lower in patients treated with ozanimod 920 microgram than in patients who received IFN beta-1a 30 microgram 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 beta-1a. Three month confirmed disability progression was low and similar between Zeposia and IFN beta-1a-treated patients over 2 years. The difference was not statistically significant.

A consistent reduction of the ARR compared to IFN beta-1a was observed in subgroups defined by sex, age, prior DMT therapy, and baseline disease activity.

Table 4: Key Clinical and MRI Endpoints in RMS Patients from Study 1 and Study 2

Endpoints	Study 1 (≥ 1 year)		Study 2 (2 year)	
	Zeposia 920 microgram (n=447) %	**IFN beta-1a 30 microgram (n=448) %**	**Zeposia 920 microgram (n=433) %**	**IFN beta-1a 30 microgram (n=441) %**
Clinical Endpoints				
Annualized Relapse Rate (Primary Endpoint)	0.181	0.350	0.172	0.276
Relative Reduction	48% (p<0.0001)		38% (p<0.0001)	
Proportion Relapse-free	78% (p=0.0002)[1]	66%	76% (p=0.0012)[1]	64%

Endpoints	Study 1 (≥ 1 year)		Study 2 (2 year)	
	Zeposia 920 microgram (n=447) %	**IFN beta-1a 30 microgram (n=448) %**	**Zeposia 920 microgram (n=433) %**	**IFN beta-1a 30 microgram (n=441) %**
Proportion of Patients with 3-Month Confirmed Disability Progression[2]	7.6% Zeposia vs. 7.8% IFN beta-1a			
Hazard Ratio	0.95			
	p=0.7651			
Proportion of Patients with 6-Month Confirmed Disability Progression[2]	5.8% Zeposia vs. 4.0% IFN beta-1a			
Hazard Ratio	1.413			
	p=0.1126			
MRI Endpoints				
Mean number of new or enlarging T2 hyperintense lesions per MRI[3]	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[4]	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 Studies 1 and 2: [3]Through the treatment period: [4]At the end of the treatment period for each study.

In Studies 1 and 2, treatment with Zeposia 920 microgram resulted in reductions in mean percent change from baseline in normalized brain volume compared to IFN beta-1a (-0.41% versus -0.61%, and -0.71% versus -0.94%, respectively, nominal p-value <0.0001 for both studies.

Long-term Data

Patients who completed the Phase 3 Studies 1 and 2 could enter an open label extension study (Study 3 - DAYBREAK). Of the 751 patients initially randomized to ozanimod 920 microgram and treated for up to

3 years, the (adjusted) ARR between year 2 and 3 of treatment was 0.124.

5.2. PHARMACOKINETIC PROPERTIES

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 460 microgram to 920 microgram (0.5 to 1 time the recommended dose). At a dose of 920 microgram orally once daily in RMS, 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.

5.2.1. Absorption

The T_{max} of ozanimod is approximately 6-8 hours. Administration of Zeposia 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). Ozanimod may be taken without regard to meals.

In a study of female rats, absolute oral bioavailability of ozanimod was 64% with an oral capsule formulation.

5.2.2. 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. Ozanimod and its metabolites do not bind extensively to whole blood components, such as red blood cells.

5.2.3. Metabolism

Ozanimod was extensively metabolized in humans with a number of metabolites identified in plasma, urine and feces. Multiple enzyme systems play an important role in the metabolism of ozanimod and no single enzyme system predominates in the overall metabolism of ozanimod. 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. Gut microbial flora plays an important role in vivo, via anaerobic reductive metabolism of the oxadiazole ring system in the formation of many inactive metabolites.

5.2.4. Excretion

Following a single oral 920 microgram 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, indicating that renal clearance is not an important excretion pathway for ozanimod, CC112273 and CC1084037.

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 920 microgram 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.

5.2.5. Renal impairment

In a dedicated renal impairment trial, following a single oral dose of 230 microgram 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). Based on this trial, renal impairment had no clinically important effects on pharmacokinetics of ozanimod or CC112273.

No dose adjustment is needed in patients with renal impairment.

5.2.6. Hepatic impairment

In a dedicated hepatic impairment trial, following a single oral dose of 230 microgram Zeposia, exposures (AUC_{last}) for ozanimod and CC112273 were approximately 11% lower and 31% lower, respectively, in subjects with mild hepatic impairment (Child-Pugh A; N=8) when compared to subjects with normal hepatic function (N=7). Exposures (AUC_{last}) for ozanimod and CC112273 were approximately 27% higher and 33% lower, respectively, in subjects with moderate hepatic impairment (Child-Pugh B; N=8) when compared to subjects with normal hepatic function (N=8). These differences were not considered clinically meaningful. The pharmacokinetics of ozanimod were not evaluated in subjects with severe hepatic impairment.

No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Use in patients with severe hepatic impairment is not recommended (Child-Pugh class C).

5.2.7. Pharmacokinetics in Children

No PK data are available on administration of Zeposia to pediatric or adolescent patients (< 18 years of age).

5.2.8. Pharmacokinetics in Elderly

No PK data are available on administration of Zeposia to patients aged 65 years and over.

5.2.9. Pharmacokinetics in 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.

5.2.10. Gender

While population PK of ozanimod are not affected by gender, CC112273 steady-state exposure (AUC) was lower in males than in females. The effect of gender on CC112273 systemic exposure was not deemed clinically meaningful.

5.2.11. Ethnicity

In a dedicated Japanese PK bridging study, following repeated dosing of 920 microgram, 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). These differences were not considered clinically meaningful.

5.3. PRECLINICAL SAFETY DATA

5.3.1. Genotoxicity

Ozanimod and multiple metabolites were evaluated for bacterial mutagenicity. These mutagenicity assays examined ozanimod, CC112273, CC1084037, RP101124, RP101988, RP101075, and RP101442, which were all negative for mutagenicity. In vitro aneugenicity/clastogenicity assessment included ozanimod (negative in the mouse lymphoma), CC112273 (negative in the human peripheral blood lymphocyte assay), and CC1084037 (positive in the TK6 assay). The positive in vitro TK6 result with CC1084037 was assessed using a two-organ in vivo study (negative bone marrow micronucleus assay and a negative hepatic comet assay at doses up to 1000 mg/kg/day for 3 days in mice). Ozanimod was also negative in the in vivo bone marrow micronucleus assay (at doses up to 800 mg/kg/day for 2 days in rats).

Overall, ozanimod and metabolites did not exhibit any in vitro or in vivo genotoxicity concerns.

5.3.2. Carcinogenicity

Ozanimod was evaluated for carcinogenicity in the 6-month Tg.rasH2 mouse bioassay and the two-year rat bioassay. In the 6-month Tg.rasH2 mouse study, a statistically significant increased incidence of hemangiosarcomas was seen at the mid and high dose (25 mg/kg/day and 80 mg/kg/day) across multiple organs. At the low dose (8 mg/kg/day), the hemangiosarcoma incidence was lower and remained within laboratory background levels.

Hemangiosarcomas in mice have been postulated to be a result of chronic stimulation of endothelial cells through the $S1P_1$ receptor (also known as the endothelial differentiation gene (EDG) 1 receptor). This receptor is abundant on vascular endothelial cells and is important in endothelial cell migration, differentiation, and survival. In mice, $S1P_1$ agonism results in sustained production of placental growth factor 2 (PlGF2) and subsequently, persistent vascular endothelial cell mitoses. In contrast, rat and human vascular endothelial cells do not release PlGF2 or only transiently release PlGF2 in response to S1P1 agonism, and subsequently, sustained stimulation and hemangiosarcoma formation are not observed in these species.

Based upon the evidence that hemangiosarcomas formation by S1P1 agonism is specific to mice and not relevant to humans, the Tg.rasH2 mouse exposure margin for human risk with the top dose of oral ozanimod at 80 mg/kg/day is 17364x. The metabolite exposure margin is 17.3x for CC112273 and is 15.5x for CC1084037. At the NOAEL dose in mice of 8 mg/kg/day, the exposure margins are 1795x for ozanimod, 1.4x for CC112273, and 1.40x for CC1084037.

In the two-year rat bioassay, no incidence of any tumor type was increased at any ozanimod dose (top dose of 2 mg/kg/day).

In rats, the exposure margin at the highest dose tested (2 mg/kg/day), which was the NOAEL, was 135x for ozanimod, 0.29x for CC112273, and 0.176x for CC1084037.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Capsule content:

Microcrystalline cellulose, silicon dioxide, croscarmellose sodium, and magnesium stearate

Capsule shell:

230 microgram capsule contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide and red iron oxide

460 microgram capsule contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide and red iron oxide

920 microgram capsule contains gelatin, titanium dioxide, yellow iron oxide and red iron oxide

Black ink:
TekPrint SW-9008 or TekPrint SW-9049

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package.

6.5. NATURE AND CONTENTS OF CONTAINER

Polyvinyl chloride (PVC) / polychlorotrifluoroethylene (PCTFE) / aluminium foil blisters.

Zeposia Initiation Pack

Pack size of 7 capsules (4 x 230 microgram, 3 x 460 microgram)

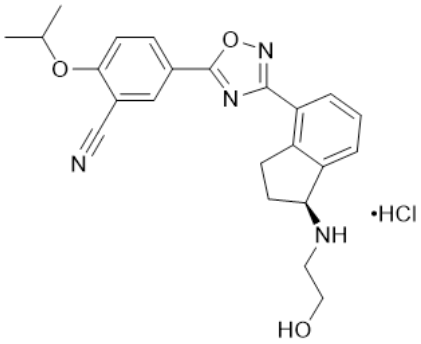
Zeposia 920 microgram capsules

Pack size of 28 capsules.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

None.

6.7. PHYSICOCHEMICAL PROPERTIES

Molecular formula	$C_{23}H_{24}N_4O_3$•HCl
Molecular weight	440.92
ATC code	L04AA38
Chemical name	5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1*H*-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile monohydrochloride
Chemical Abstract Service (CAS) registry number	1618636-37-5
Chemical structure	

7. MEDICINE SCHEDULE (POISONS STANDARD)

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8. SPONSOR

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9. DATE OF FIRST APPROVAL

17 July 2020

10. DATE OF REVISION

N/A

Summary table of changes

Section Changed	Summary of new information
N/A	First version