1. NAME OF THE MEDICINAL PRODUCT

Zeposia capsules 0.23 mg
Zeposia capsules 0.46 mg
Zeposia capsules 0.92 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zeposia capsules 0.23 mg

Each capsule contains ozanimod hydrochloride equivalent to 0.23 mg ozanimod.

Zeposia capsules 0.46 mg

Each capsule contains ozanimod hydrochloride equivalent to 0.46 mg ozanimod.

Zeposia capsules 0.92 mg

Each capsule contains ozanimod hydrochloride equivalent to 0.92 mg ozanimod.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

Zeposia capsules 0.23 mg

Light grey opaque capsule, 14.3 mm, imprinted in black ink with “OZA” on the cap and “0.23 mg” on the body.

Zeposia capsules 0.46 mg

Light grey opaque body and orange opaque cap capsule, 14.3 mm, imprinted in black ink with “OZA” on the cap and “0.46 mg” on the body.

Zeposia capsules 0.92 mg

Orange opaque capsule, 14.3 mm, imprinted in black ink with “OZA” on the cap and “0.92 mg” on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple sclerosis

Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features, to decrease the frequency of clinical exacerbations. (see section 5.1).

4.2 Posology and method of administration

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

Posology

The recommended dose is 0.92 mg ozanimod once daily.

The initial dose escalation regimen of ozanimod from Day 1 to Day 7 is required and shown below in Table 1. Following the 7-day dose escalation, the once daily dose is 0.92 mg, starting on Day 8.

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
The same dose escalation regimen described in Table 1 is recommended when treatment is interrupted for:

- 1 day or more during the first 14 days of treatment.
- more than 7 consecutive days between Day 15 and Day 28 of treatment.
- more than 14 consecutive days after Day 28 of treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

Special populations

Adults over 55 years old and elderly population
There are limited data available on RRMS patients > 55 years of. No dose adjustment is needed in patients over 55 years of age. Caution should be used in MS patients over 55, given the limited data available and potential for an increased risk of adverse reactions in this population, especially with long-term treatment (see section 5.1 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment.

Hepatic impairment
Patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day (see section 5.2).

Ozanimod was not evaluated in patients with severe hepatic impairment. Therefore, patients with severe hepatic impairment (Child-Pugh class C) must not be treated with ozanimod (see sections 4.3 and 5.2).

Paediatric population
The safety and efficacy of Zeposia in children and adolescents aged below 18 years have not yet been established. No data are available.

Method of administration

Oral use.
The capsules can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Immunodeficient state (see section 4.4).
- Patients who in the last 6 months experienced myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation or New York Heart Association (NYHA) Class III/IV heart failure.
- Patients with 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.
- Severe active infections, active chronic infections such as hepatitis and tuberculosis (see section 4.4).
- Active malignancies.
- Severe hepatic impairment (Child-Pugh class C).
- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).
- Patients who are taking a monoamine oxidase (MAO) inhibitor.

4.4 Special warnings and precautions for use

Bradyarrhythmia

Initiation of treatment with ozanimod
Prior to treatment initiation with ozanimod, an ECG in all patients should be obtained to determine whether any pre-existing cardiac abnormalities are present. In patients with certain pre-existing conditions, first-dose monitoring is recommended (see below).

Initiation of ozanimod may result in transient reductions in heart rate (HR) (see sections 4.8 and 5.1), and, therefore the initial dose escalation regimen to reach the maintenance dose (0.92 mg) on day 8 should be followed (see section 4.2).

After the initial dose of ozanimod 0.23 mg, the HR decrease started at Hour 4, with the greatest mean reduction at Hour 5, returning towards baseline at Hour 6. With continued dose escalation, there were no clinically relevant HR decreases. Heart rates below 40 beats per minute were not observed. If necessary, the decrease in HR induced by ozanimod can be reversed by parenteral doses of atropine or isoprenaline.

Caution should be applied when ozanimod is initiated in patients receiving treatment with a beta-blocker or a calcium-channel blocker (e.g. diltiazem and verapamil) because of the potential for additive effects on lowering HR. Beta-blockers and calcium-channel blockers treatment can be initiated in patients receiving stable doses of ozanimod.
The co-administration of ozanimod in patients on a beta-blocker in combination with a calcium channel blocker has not been studied (see section 4.5).

First dose monitoring in patients with certain pre-existing cardiac conditions
Due to the risk of transient decreases in HR with the initiation of ozanimod, first-dose, 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended in patients with resting HR <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (see section 4.3).

Patients should be monitored with hourly pulse and blood pressure measurement during this 6-hour period. An ECG prior to and at the end of this 6-hour period is recommended.
Additional monitoring is recommended in patients if at hour 6 post-dose:
- heart rate is less than 45 bpm
- heart rate is the lowest value post-dose, suggesting that the maximum decrease in HR may not have occurred yet
- there is evidence of a new onset second-degree or higher AV block at the 6-hour post-dose ECG
- QTc interval ≥500 msec

In these cases, appropriate management should be initiated and observation continued until the symptoms/findings have resolved. If medical treatment is required, monitoring should be continued overnight, and a 6-hour monitoring period should be repeated after the second dose of ozanimod.

Cardiologist advice should be obtained before initiation of ozanimod in the following patients to decide if ozanimod can safely be initiated and to determine the most appropriate monitoring strategy
- ischemic heart disease, heart failure, history of myocardial infarction, cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnoea, history of recurrent syncope or symptomatic bradycardia;
- pre-existing significant QT interval prolongation (QTcF > 450 msec in males, > 470 msec in females) or other risks for QT prolongation, and patients on medicinal products other than beta-blockers and calcium-channel blockers that may potentiate bradycardia;
- Patients on class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products, which have been associated with cases of torsades de pointes in patients with bradycardia have not been studied with ozanimod.

<u>Liver function</u>

Elevations of aminotransferases may occur in patients receiving ozanimod (see section 4.8).
Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with ozanimod. In the absence of clinical symptoms, liver transaminases and bilirubin levels should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted. If liver transaminases above 5 times the ULN are confirmed, treatment with ozanimod should be interrupted and only re-commenced once liver transaminase values have normalised.

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 ozanimod should be discontinued if significant liver injury is confirmed. Resumption of therapy will be dependent on whether another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction. Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ozanimod (see section 4.2).

Ozanimod has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and must not be used in these patients (see section 4.3).

Immunosuppressive effects

Ozanimod has an immunosuppressive effect that predisposes patients to a risk of infection, including opportunistic infections, and may increase the risk of developing malignancies, including those of the skin. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis (see section 4.3).

Infections

Ozanimod causes a mean reduction in peripheral blood lymphocyte count to approximately 45% of baseline values because of reversible retention of lymphocytes in the lymphoid tissues. Ozanimod may, therefore, increase the susceptibility to infections (see section 4.8).

A recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood cell count (CBC) should be obtained, including lymphocyte count, before initiation of ozanimod.

Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2 \times 10^9$/L, if confirmed, 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.

The initiation of ozanimod administration in patients with any active infection should be delayed until the infection is resolved.

Patients should be instructed to report promptly symptoms of infection to their physician. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. If a patient develops a serious infection, treatment interruption with ozanimod should be considered.

Because the elimination of ozanimod after discontinuation may take up to 3 months, monitoring for infections should be continued throughout this period.

Prior and concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies

In MS clinical studies, patients who received ozanimod were not to receive concomitant antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ozanimod with any of these therapies would be expected to increase the risk of immunosuppression and should be avoided.

When switching to ozanimod from immunosuppressive medicinal products, the half-life and mode of action must be considered to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation.

Ozanimod can generally be started immediately after discontinuation of interferon (IFN).

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. PML has been reported in patients treated with S1P receptor modulators, including ozanimod, and other therapies for MS. JCV infection resulting in PML 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 ozanimod should be discontinued.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations in patients taking ozanimod. The use of live attenuated vaccines should be avoided during and for 3 months after treatment with ozanimod.

If live attenuated vaccine immunizations are required, these should be administered at least 1 month prior to initiation of ozanimod. Varicella Zoster Virus (VZV) vaccination of patients without documented immunity to VZV is recommended prior to initiating treatment with ozanimod.

Cutaneous neoplasms

Half of the neoplasms reported with ozanimod in the MS controlled Phase 3 studies consisted of non-melanoma skin malignancies, with basal cell carcinoma presenting as the most common skin neoplasm and reported with similar incidence rates in the combined ozanimod (0.2%, 3 patients) and IFN ß-1a (0.1 %, 1 patient) groups.

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

Macular oedema

Macular oedema with or without visual symptoms was observed with ozanimod (see section 4.8) in patients with pre-existing risk factors or comorbid conditions.

Patients with a history of uveitis or diabetes mellitus or underlying/co existing retinal disease are at increased risk of macular oedema (see section 4.8). It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disease undergo an ophthalmological evaluation prior to treatment initiation with ozanimod 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 ozanimod should be discontinued. A decision on whether ozanimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.

Posterior reversible encephalopathy syndrome (PRES)

PRES is a syndrome characterised by sudden onset of severe headache, confusion, seizures and visual loss. Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral haemorrhage. In MS controlled clinical trials with ozanimod, one case of PRES was reported in a patient with Guillain-Barré syndrome. If PRES is suspected, treatment with ozanimod should be discontinued.

Blood pressure effects

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

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 ozanimod, 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 ozanimod.

Respiratory effects

Ozanimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease.

Concomitant medicinal products

Co-administration of ozanimod with monoamine oxidase (MAO) inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated. At least 14 days should elapse between discontinuation of ozanimod and initiation of treatment with MAO inhibitors.

The coadministration with strong CYP2C8 inducer (e.g. rifampicin) with ozanimod should be avoided (see section 4.5).

Women of childbearing potential

Due to risk to the foetus, ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment, and for 3 months after treatment discontinuation.

Return of MS 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.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of inhibitors of the breast cancer resistance protein (BCRP) on ozanimod

Coadministration of ozanimod with ciclosporin, a strong BCRP inhibitor, had no effect on the exposure of ozanimod and its major active metabolites (CC112273 and CC1084037).

Effect of inhibitors of CYP2C8 on ozanimod

The coadministration 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 the major active metabolites by approximately 47% to 69%. Concomitant use of ozanimod with strong CYP2C8 inhibitors (e.g. gemfibrozil, clopidogrel) is not recommended.

Effect of inducers of CYP2C8 on ozanimod

The coadministration 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 ozanimod 0.92 mg reduced exposure (AUC) of major active metabolites by approximately 60% via CYP2C8 induction which may result in reduced clinical response. The coadministration of CYP2C8 inducers (i.e. rifampicin) with ozanimod should be avoided (see section 4.4).

Effect of inhibitors of monoamine oxidase (MAO) on ozanimod

The potential for clinical interaction with MAO inhibitors has not been studied. However, the coadministration with MAO-B inhibitors may decrease exposure of the major active metabolites and may result in reduced clinical response. In addition, metabolites of ozanimod may inhibit MAO. The increased risk of nonselective MAO inhibition may lead to a hypertensive crisis. Co-administration of ozanimod with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated. At least 14 days should elapse between discontinuation of ozanimod and initiation of treatment with MAO inhibitors (see section 4.4).

Effects of ozanimod on medicinal products that slow heart rate or atrioventricular conduction (e.g., beta-blockers or calcium channel blockers)

In healthy subjects, a single dose of ozanimod 0.23 mg with steady state propranolol long acting 80 mg once daily or diltiazem 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. Caution should be applied when ozanimod is initiated in patients receiving treatment with a beta-blocker or a calcium-channel blocker (see section 4.4). Patients on other bradycardic medicinal products and on antiarrhythmic medicinal products (which have been associated with cases of torsades de pointes in patients with bradycardia) have not been studied with ozanimod.

Effect of ozanimod on adrenergic/serotonergic drugs

Because an active metabolite of ozanimod inhibits MAO-B in vitro, there is a potential for serious adverse reactions, including hypertensive crisis with coadministration of ozanimod with drugs or over-the-counter medications that can increase norepinephrine or serotonin [e.g., opioid drugs, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclics, tyramine].

Co-administration of ozanimod with drugs or over-the-counter medications that can increase norepinephrine or serotonin (e.g., opioid drugs, SSRIs, SNRIs, tricyclics, tyramine) is not recommended. Monitor patients for hypertension with concomitant use.

Vaccination

During and for up to 3 months after treatment with ozanimod, vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should, therefore, be avoided during and for up to 3 months after treatment with ozanimod (see section 4.4).

Anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies

Anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies should not be coadministered due to the risk of additive immune system effects (see sections 4.3 and 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females

Zeposia is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). 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 risk to the foetus. Women of childbearing potential must use effective contraception during ozanimod treatment and for 3 months after treatment discontinuation (see section 4.4).

When stopping ozanimod therapy for planning a pregnancy the possible return of disease activity should be considered (see section 4.4).

Pregnancy

There are no or limited amount of data from the use of ozanimod in pregnant women.
Studies in animals have shown reproductive toxicity including foetal loss and anomalies, notably malformations of blood vessels, generalised oedema (anasarca), and malpositioned testes and vertebrae (see section 5.3). Sphingosine 1-phosphate is known to be involved in vascular formation during embryogenesis (see section 5.3).

Consequently, Zeposia is contraindicated during pregnancy (see section 4.3). Zeposia should be stopped 3 months before planning a pregnancy (see section 4.4). If a woman becomes pregnant during treatment, Zeposia must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and ultrasonography examinations should be performed.

Breast-feeding

Ozanimod/metabolites are excreted in milk of treated animals during lactation (see section 5.3). Due to the potential for serious adverse reactions to ozanimod/metabolites in nursing infants, women receiving ozanimod should not breastfeed.

Fertility

No fertility data are available in humans. In animal studies, no adverse effects on fertility were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Zeposia has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are nasopharyngitis (11%), alanine aminotransferase (ALT) increased (5%), and gamma-glutamyl transferase (GGT) increased (5%).

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

Tabulated list of adverse reactions

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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Table 2: Summary of adverse reactions reported in MS

SOC	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Nasopharyngitis
	Common	Pharyngitis, respiratory tract infection viral, urinary tract infection*
	Uncommon	Herpes zoster
	Rare	Progressive multifocal leukoencephalopathy
Blood and lymphatic system disorders	Very common	Lymphopenia
Immune system disorders	Uncommon	Hypersensitivity (including rash and urticaria*)
Eye disorders	Uncommon	Macular oedema**
Cardiac disorders	Common	Bradycardia*
Vascular disorders	Common	Hypertension*†, orthostatic hypotension
Investigations	Common	Alanine aminotransferase increased, gamma-glutamyl transferase increased, blood bilirubin increased, pulmonary function test abnormal***

*At least one of these adverse reactions was reported as serious
† Includes hypertension, essential hypertension, and blood pressure increased (see section 4.4).
** 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

Description of selected adverse reactions

Elevated hepatic enzymes
In MS clinical studies, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ozanimod 0.92 mg and 1.3% of patients on IFN β-1a IM. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients on ozanimod and 3.1% of patients on IFN β-1a IM. The median time to elevation 3-fold the ULN was 6 months. The majority (79%) continued treatment with ozanimod with values returning to < 3-fold the ULN within approximately 2-4 weeks. Ozanimod was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes was 1.1% of MS patients on ozanimod 0.92 mg and 0.8% of patients on IFN beta-1a IM.

Bradyarrhythmia
After the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in sitting/ supine HR occurred at Hour 5 on day 1 (decrease of 1.2 bpm in MS clinical), returning towards baseline at Hour 6. With continued dose escalation, there were no clinically relevant HR decreases.

In MS clinical studies, bradycardia was reported in 0.5% of patients treated with ozanimod versus 0% of patients treated with IFN β-1a IM on the day of treatment initiation (Day 1). After Day 1, the incidence of bradycardia was 0.8% on ozanimod versus 0.7% on IFN β-1a IM. (see section 5.1). Patients who experienced bradycardia were generally asymptomatic. Heart rates below 40 beats per minute were not observed.

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

Increased blood pressure
In MS clinical studies, patients treated with ozanimod had an average increase of approximately 1-2 mm Hg in systolic pressure over IFN β-1a IM, and approximately 1 mm Hg in diastolic pressure over IFN β-1a IM. 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 ozanimod 0.92 mg and in 2.3% of patients treated with IFN β-1a IM.

Blood lymphocyte count reduction
In MS clinical studies, 3.3% of patients experienced lymphocyte counts less than 0.2×10^9/L with values generally resolving to greater than 0.2×10^9/L while remaining on treatment with ozanimod.

Infections
In MS clinical studies, the overall rate of infections (35%) with ozanimod 0.92 mg was similar to IFN β-1a IM. The overall rate of serious infections was similar between ozanimod (1%) and IFN β-1a IM (0.8%) in MS clinical studies.

Herpetic infections
In MS clinical studies, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ozanimod 0.92 mg and in 0.2% of patients on IFN β-1a IM.

Respiratory system
Minor dose-dependent reductions in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were observed with ozanimod treatment. At months 3 and 12 of treatment in MS clinical studies, median changes from baseline in FEV1 (FVC) in the ozanimod 0.92 mg 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 ß-1a group (FEV1: - 0.01 L and - 0.04 L, FVC: 0.00 L and -0.02 L).

4.9 Overdose

In patients with overdose of ozanimod, monitor for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of HR and blood pressure are required, and ECGs should be performed (see sections 4.4 and 5.1). The decrease in HR induced by ozanimod can be reversed by parenteral atropine or isoprenaline.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA38

Mechanism of action

Ozanimod is a potent sphingosine 1-phosphate (S1P) receptor modulator, which binds with high affinity to sphingosine 1-phosphate receptors 1 and 5. Ozanimod has minimal or no activity on $S1P_2$, $S1P_3$, and $S1P_4$. *In vitro*, ozanimod and its major active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$. The mechanism by which ozanimod exerts therapeutic effects in MS is unknown, but may involve the reduction of lymphocyte migration into the central nervous system (CNS) and intestine.

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

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites including two major metabolites (see section 5.2). In humans, approximately 94% of circulating total active substances exposure are represented by ozanimod (6%) and the two major metabolites CC112273 (73%), and CC1084037 (15%) (see section 5.2).

Pharmacodynamic effects

Reduction of peripheral blood lymphocytes
In active-controlled MS clinical studies, mean lymphocyte counts decreased to approximately 45% of baseline by 3 months (approximate mean blood lymphocyte count 0.8 x 10^9/L) and remained stable during treatment with ozanimod. After discontinuing ozanimod 0.92 mg, the median time to recovery of peripheral blood lymphocytes to the normal range was approximately 30 days, with approximately 80% to 90% of patients recovering to normal within 3 months (see sections 4.4 and 4.8).

Heart rate and rhythm
Ozanimod may cause a transient reduction in HR on initiation of dosing (see sections 4.4 and 4.8). This negative chronotropic effect is mechanistically related to the activation of G-protein-coupled inwardly rectifying potassium (GIRK) channels via $S1P_1$ receptor stimulation by ozanimod and its active metabolites leading to cellular hyperpolarisation and reduced excitability with a maximal effect on HR seen within 5 hours post dose. Due to its functional antagonism at $S1P_1$ receptors, a dose escalation schedule with ozanimod 0.23 mg followed by 0.46 mg, and 0.92 mg successively desensitises GIRK channels until the maintenance dose is reached. After the dose escalation period, with continued administration of ozanimod, HR returns to baseline.

Potential to prolong the QT interval
In a randomised, positive - and placebo-controlled thorough QT study using a 14-day dose-escalation regimen of 0.23 mg daily for 4 days, 0.46 mg daily for 3 days, 0.92 mg daily for 3 days, and 1.84 mg daily 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 the 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 ozanimod doses ≥0.92 mg once daily.

Clinical efficacy and safety

Multiple sclerosis

Ozanimod was evaluated in two randomised, double-blind, double-dummy, parallel-group, active controlled clinical trials of similar design and endpoints, in patients with relapsing MS. Study 1 – SUNBEAM, was a 1-year study with patients continuing assigned treatment beyond month 12 until the last enrolled patient completed the study. Study 2 -RADIANCE was a 2-year study.
The dose of ozanimod 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 with active disease as defined by having 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 (SUNBEAM), 1 year (Studies 1 and 2), and 2 years (RADIANCE).
The primary outcome of both SUNBEAM and RADIANCE was the annualised relapse rate (ARR) over the treatment period (minimum of 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 confirmed after 3 months and after 6 months. Confirmed disability progression was prospectively evaluated in a pooled analysis of Studies 1 and 2.
In SUNBEAM, 1346 patients were randomised to receive ozanimod 0.92 mg (n = 447), ozanimod 0.46 mg (n= 451), or IFN β-1a IM (n = 448); 94% of ozanimod treated 0.92 mg, 94% of ozanimod treated 0.46 mg, and 92% of IFN β-1a IM treated patients completed the study. In RADIANCE, 1313 patients were randomised to receive ozanimod 0.92 mg (n = 433), ozanimod 0.46 mg (n = 439), or IFN β-1a IM (n = 441); 90% of ozanimod treated 0.92 mg, 85% of ozanimod treated 0.46 mg, and 85% of IFN β-1a IM treated patients completed the study. Patients enrolled across the 2 studies had a mean age of 35.5 years (range 18-55), 67% were female, 98% had relapsing-remitting MS (RRMS), mean time since MS symptom onset was 6.7 years. The median EDSS score at baseline was 2.5; approximately one-third of the patients had been treated with a disease-modifying therapy (DMT), predominately interferon or glatiramer acetate. At baseline, the mean number of relapses in the prior year was 1.3 and 45% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The results for SUNBEAM and RADIANCE are shown in Table 3. The efficacy has been demonstrated for ozanimod 0.92 mg with a dose effect observed for study endpoints shown in Table 3. Demonstration of efficacy for 0.46 mg was less robust since this dose did not show a significant effect for the primary endpoint in RADIANCE when considering the preferred negative binomial model strategy.

Table 3: Key clinical and MRI endpoints in RMS patients from Study 1 - SUNBEAM and Study 2 - RADIANCE

Endpoints	SUNBEAM (≥ 1 year)*		RADIANCE (2 year)	
	Ozanimod 0.92 mg (n=447) %	**IFN β-1a IM 30 mcg (n=448) %**	**Ozanimod 0.92 mg (n=433) %**	**IFN β-1a IM 30 mcg (n=441) %**
Clinical endpoints				
Annualized relapse rate (Primary endpoint)	0.181	0.350	0.172	0.276
Relative reduction	48% (p<0.0001)		38% (p<0.0001)	
Proportion relapse-free**	78% (*p=0.0002*)[1]	66%	76% (*p=0.0012*)[1]	64%
Proportion with 3-month confirmed disability Progression (CDP)†[2] Hazard ratio (95% CI)	7.6% Ozanimod vs. 7.8% IFN β-1a IM 0.95 (0.679, 1.330)			
Proportion with 6-month CDP†[2#] Hazard ratio (95% CI)	5.8% Ozanimod vs. 4.0% IFN β-1a IM 1.413 (0.922, 2.165)			
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)	

* Mean duration was 13.6 months
** Nominal p-value for endpoints not included in the hierarchical testing and not adjusted for multiplicity
† Disability progression defined as 1-point increase in EDSS confirmed 3 months or 6 months later
\# In a post hoc analysis of 6-month CDP which included data from the open-label extension (Study 3), the HR (95% CI) was found to be 1.040 (0.730, 1.482).)
[1] Log rank test
[2] Prospectively planned pooled analysis of Studies 1 and 2
[3] Over 12 months for Study 1 and over 24 months for Study 2
[4] At 12 months for Study 1 and at 24 months for Study 2

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

The studies enrolled DMT naive and previously treated patients with active disease, as defined by clinical or imaging features. Post-hoc analyses of patient populations with differing baseline levels of disease activity, including active and highly active disease, showed that the efficacy of ozanimod on clinical and imaging endpoints was consistent with the overall population.

Long-term Data
Patients who completed the Phase 3 SUNBEAM and RADIANCE studies could enter an open label extension study (Study 3 - DAYBREAK). Of the 751 patients initially randomised to ozanimod 0.92 mg and treated for up to 3 years, the (adjusted) ARR was 0.124 after the 2nd year of treatment.

5.2 Pharmacokinetic properties

Ozanimod is extensively metabolised 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. The maximum plasma concentration (C_{max}) and area under the curve (AUC) for ozanimod, CC112273, and CC1084037 increased proportionally over the dose range of ozanimod 0.46 mg to 0.92 mg (0.5 to 1 times the recommended dose). Following multiple dosing, approximately 94% of circulating total active substances 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_{0-24h} 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_{0-24h} for CC1084037 are approximately 20% of that for CC112273. Factors affecting CC112273 are applicable for CC1084037 as they are interconverting metabolites.

Absorption

The T_{max} of ozanimod is approximately 6–8 hours. The T_{max} of CC112273 is approximately 10 hours. Administration of ozanimod with a high-fat, high-calorie meal had no effect on ozanimod exposure (C_{max} and AUC). Therefore, ozanimod may be taken without regard to meals.

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.

Biotransformation

Ozanimod is widely metabolised by multiple biotransformation pathways including aldehyde dehydrogenase and alcohol dehydrogenase (ALDH/ADH), cytochrome P450 (CYP) isoforms 3A4 and 1A1, and gut microflora and no single enzyme system predominates the overall metabolism. Following repeated dosing, the AUCs of the two major active metabolites CC112273 and CC1084037 exceed the AUC of ozanimod by 13-fold and 2.5-fold, respectively. *In vitro* studies indicated that monoamine oxidase B (MAO-B) is responsible for the formation of CC112273 (via an intermediate minor active metabolite RP101075) while CYP2C8 and oxido-reductases are involved in the metabolism of CC112273. CC1084037 is formed directly from CC112273 and undergoes reversible metabolism to CC112273. The interconversion between these 2 active metabolites is mediated by carbonyl reductases (CBR), aldo-keto reductase (AKR) 1C1/1C2, and/or 3β- and 11β- hydroxysteroid dehydrogenase (HSD).

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%) indicating the predominance of CC112273 over ozanimod. 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 faeces, 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.

Pharmacokinetics in specific groups of patients

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

Hepatic impairment
In single dose and multiple dose studies in subjects with chronic liver disease, there was no meaningful impact of mild or moderate chronic hepatic impairment (Child-Pugh class A or B) on the pharmacokinetics of ozanimod or the major metabolite CC112273 on Day 1, Day 5, or Day 8 of dosing. After dose escalation in the second trial, administration of 0.92 mg ozanimod resulted in increased CC112273 and CC1084037 mean unbound $AUC_{0\text{-}last}$ (measured up to 64 days post-dose) in subjects with mild or moderate chronic hepatic impairment of 99.64% to 129.74% relative to healthy control subjects. Patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day (see section 4.2).

The pharmacokinetics of ozanimod were not evaluated in patients with severe hepatic impairment. Use in patients with severe hepatic impairment is contraindicated (Child-Pugh class C) (see section 4.3).

Elderly
Population pharmacokinetic analysis showed that steady state exposure (AUC) of CC112273 in patients over 65 years of age were approximately 3 - 4% greater than patients 45 – 65 years of age and 27% greater than adult patients under 45 years of age. There is not a meaningful difference in the pharmacokinetics in elderly patients.

Paediatric population

No data are available on administration of ozanimod to paediatric or adolescent patients (< 18 years of age).

5.3 Preclinical safety data

In repeated dose toxicology studies in mice (up to 4 weeks), rats (up to 26 weeks) and monkeys (up to 39 weeks), ozanimod markedly affected the lymphoid system (lymphopenia, lymphoid atrophy and reduced antibody response) and increased lung weights and the incidence of mononuclear alveolar infiltrates, which is consistent with its primary activity at $S1P_1$ receptors (see section 5.1). At the no observed adverse effect levels in chronic toxicity studies, systemic exposures to the disproportionate main active and persistent human metabolites CC112273 and CC1084037 (see section 5.2), and even to the total human active substances (ozanimod combined with the mentioned metabolites), were lower than those expected in patients at the maximum human dose of 0.92 mg ozanimod.

Genotoxicity and carcinogenicity

Ozanimod and its main active human metabolites did not reveal a genotoxic potential *in vitro* and *in vivo*.
Ozanimod was evaluated for carcinogenicity in the 6-month Tg.rasH2 mouse bioassay and the two-year rat bioassay. In the two-year rat bioassay, no treatment-related tumours were present at any ozanimod dose. However, metabolite exposure at the highest dose tested, was 62% of the human exposure for CC112273 and 18% of the human exposure for CC1084037 at the maximum clinical dose of 0.92 mg ozanimod.
In the 6-month Tg.rasH2 mouse study, hemangiosarcomas increased in a statistically-significant and dose-related manner. At the low dose (8 mg/kg/day), the hemangiosarcoma incidence was increased statistically significant in males and in both males and females at the mid and high dose levels (25 mg/kg/day and 80 mg/kg/day) compared to concurrent controls. In contrast to rats and humans, mouse $S1P_1$ receptor agonism results in sustained production of placental growth factor 2 (PLGF2) and subsequently, persistent vascular endothelial cell mitoses, potentially leading to species specific hemangiosarcomas with $S1P_1$ agonists. Therefore, $S1P_1$ receptor agonism related hemangiosarcomas in mice may be species specific and not predictive of a risk in humans.
No other treatment-related tumours were present at any dose in the Tg.rasH2 mouse study. At the lowest dose tested, exposure in Tg.rasH2 mice to the disproportionate two main active human metabolites was for CC112273 2.95 fold and for CC1084037 1.4 fold above the human exposure at the maximum clinical dose of 0.92 mg ozanimod.

Reproductive toxicity

Ozanimod had no effect on male and female fertility up to approximately 150-fold the systemic exposure to total active substances (combined ozanimod and the metabolites CC112273 and CC1084037) at the maximum human dose of 0.92 mg ozanimod.
Embryofoetal development was adversely affected by maternal treatment with ozanimod, with low (rats) or no (rabbits) safety margins based on comparison of systemic exposures to total active substances, resulting in embryolethality and teratogenicity (generalised oedema/anasarca and malpositioned testes in rats, malpositioned caudal vertebrae and malformations of the great vessels in rabbits). The vascular findings in rats and rabbits are consistent with the expected $S1P_1$ pharmacology.
Pre- and post-natal development was not affected by ozanimod administration up to the 5.6-fold the systemic exposure to total active substances at the maximum human dose of 0.92 mg ozanimod.
Ozanimod and metabolites were present in rat milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Colloidal anhydrous silica
Croscarmellose sodium
Magnesium stearate

Capsule shell

Zeposia 0.23 mg and 0.46 mg
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Black iron oxide (E172)
Red iron oxide (E172).

Zeposia 0.92 mg
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172).

<u>Printing ink</u>

Shellac (E904)
Iron oxide black (E172)
Propylene glycol (E1520)
Concentrated ammonia solution(E527)
Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

0.23 mg and 0.46 mg (Treatment-initiation pack) - 2 years
0.92 mg - 3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

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

<u>Treatment initiation pack: Zeposia 0.23 mg and 0.46 mg</u>

Pack size of 7 capsules (4 x 0.23 mg, 3 x 0.46 mg).

<u>Maintenance pack: Zeposia 0.92 mg</u>

Pack size of 28 capsules.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb (S) Pte Ltd
80 Marine Parade Road,
#20-01/09 Parkway Parade,
Singapore 449269

8. DATE OF REVISION OF THE TEXT

09 May 2023