Summary Report of Benefit-Risk Assessment

ZEPOSIA CAPSULES 0.92MG
ZEPOSIA CAPSULES TREATMENT INITIATION PACK

NEW DRUG APPLICATION

Active Ingredient(s)	Ozanimod Hydrochloride
Product Registrant	Bristol-Myers Squibb (Singapore) Pte Ltd
Product Registration Number	SIN16785P, SIN16786P
Application Route	Abridged evaluation
Date of Approval	17 May 2023

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A INTRODUCTION

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.

The active substance, ozanimod, is a sphingosine-1-phosphate (S1P) receptor agonist, which binds with high affinity and selectively to S1P1 and S1P5. 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 (CNS).

Zeposia is available as capsules containing 0.23mg, 0.46mg and 0.92mg of ozanimod, as 0.25mg, 0.5mg and 1mg of ozanimod hydrochloride, respectively. Other ingredients in the capsule content are microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate. Ingredients in the capsule shell include gelatin, titanium dioxide (E171), yellow iron oxide (E172), black iron oxide (E172), red iron oxide (E172), shellac (E904), propylene glycol (E1520), concentrated ammonia solution (E527), and potassium hydroxide (E525).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, ozanimod, is manufactured at Patheon API Manufacturing Inc., South Carolina, USA and Carbogen Amcis AG, Hunzenschwil, Switzerland. The drug products, Zeposia capsules 0.92 mg and the treatment initiation pack (which contains the 0.23 mg and 0.46 mg capsules), are manufactured at Celgene International Sàrl, Boudry, Switzerland.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at 25°C with a re-test period of 36 months. The packaging is double polyethylene bags within a high-density polyethylene drum, and each bag is zip-tied.

Drug product:
The capsules are manufactured using a dry blending approach which is considered to be a standard manufacturing process.
The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC for the 0.92mg capsules, and 24 months when stored at or below 30ºC for the initiation pack of 0.23mg and 0.46mg capsules. The container closure system consists of PVC/PCTFE blister with aluminum push through foil containing seven 0.92mg capsules or for the initiation pack, four 0.23mg and three 0.46mg capsules.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy dataset of ozanimod for the treatment of RRMS comprised data from two pivotal Phase III studies of similar design, RPC-01-301 (SUNBEAM) and RPC01-201B (RADIANCE) conducted in 2,666 subjects with relapsing MS (RMS), as well as three supportive studies, RPC01-1001, RPC01-201A and RPC01-3001 (DAYBREAK). The ozanimod doses investigated in the pivotal studies were based on the results from studies RPC01-1001 and RPC01-201A.

Study RPC01-1001
Study RPC01-1001 was a Phase I, multicentre, randomised, 12-Week, open-label study in 24 patients with RMS that investigated oral ozanimod hydrochloride 0.5mg and 1mg doses, with 7-day dose escalation. The study demonstrated reductions of absolute lymphocyte count (ALC) reached a nadir by Day 56 for both dose groups, with the mean reductions from baseline of approximately 50% and 70% for the 0.5 mg and 1 mg dose groups, respectively. Additionally, a mean ALC reduction of 50% to 70% which was expected to demonstrate a therapeutic effect was reached earlier (as early as Day 28) with the 1mg dose than with the 0.5mg dose.

Study RPC01-201A
Study RPC01-201A was a Phase II, multi-centre, randomised, 24-week, double-blind, placebo-controlled, and parallel group study in 258 patients with RMS that investigated oral ozanimod hydrochloride 0.5mg and 1mg doses. The primary efficacy endpoint of mean cumulative total number of Gadolinium-enhanced (GdE) lesions from Week 12 to Week 24 in the intent-to-treat population was statistically significantly reduced by 86% in the ozanimod hydrochloride 0.5 and 1 mg treatment groups, as compared to placebo ($p<0.0001$ with both treatment groups).

A key secondary endpoint of the number of new or enlarging T2 lesions from Week 12 to Week 24 was statistically significantly reduced by 84% and 91% in the ozanimod hydrochloride 0.5 and 1 mg treatment groups, respectively, as compared to placebo ($p<0.0001$), with no meaningful differences in safety observed. Therefore, both doses of ozanimod hydrochloride (1 mg and 0.5 mg) were tested in the Phase 3 studies to further establish the efficacy as well as safety profiles of the 2 doses.

Studies SUNBEAM and RADIANCE (Pivotal)
Studies SUNBEAM and RADIANCE were Phase III, randomised, double-blinded, double-dummy studies comparing ozanimod with interferon (IFN) β-1a in adult patients aged 18 to 55 years with RMS, who had an expanded disability status scale (EDSS) score between 0 and 5, and had experienced at least one documented relapse during the previous year or at least one documented relapse within the last 2 years with evidence of at least one GdE T1 brain magnetic resonance imaging (MRI) lesion during the previous year. The study population included 2,611 (98.2%) patients with RRMS and 42 (1.6%) patients with Progressive-Relapsing MS.

In SUNBEAM, the treatment period lasted until the last enrolled subject was treated for 12 months, and in RADIANCE, the treatment period was 24 months. Patients in both studies were randomised in a 1:1:1 ratio to receive oral ozanimod hydrochloride 0.5mg daily after 4-day titration, ozanimod hydrochloride 1mg after 1 week titration or intramuscular IFN β-1a 30µg (Avonex®) once weekly. Interferon β -1a is an accepted disease-modifying therapy (DMT) for the treatment of RMS. The use of IFN β-1a as an active comparator was considered acceptable. Patients who completed the treatment period were eligible to enter an open-label extension (OLE) Study RPC01-3001 (DAYBREAK).

The primary efficacy endpoint was the annualised relapse rate (ARR) during the treatment period. A relapse was defined as the occurrence of new or worsening neurological symptoms attributable to MS that persisted for longer than 24 hours, was not attributable to confounding clinical factors and was immediately preceded by a relatively stable or improving neurological state for at least 30 days. A relapse was confirmed by the treating investigator when it was accompanied by objective neurologic worsening, as measured by a change in EDSS (≥0.5 point on the EDSS, or 2 points on one of the appropriate Functional System [FS] scores, or 1 point on 2 or more of the appropriate FS scores), as assessed by the same independent EDSS evaluator blinded to treatment and previous EDSS assessments. Key secondary efficacy endpoints were the number of new/enlarging hyperintense T2-weighted brain MRI lesions, the number of GdE brain MRI lesions, and time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 point or more, confirmed after 3 months or 6 months, i.e., confirmed disability progression (CDP)-3M and CDP-6M. A pre-specified pooled analysis from RADIANCE and SUNBEAM were performed for CDP-3M and CDP-6M.

To control for Type 1 error, the primary efficacy endpoint testing was followed by the three key secondary endpoints tested in a sequential, closed hierarchical testing procedure that ranked the 1 mg ozanimod hydrochloride dose above the 0.5 mg ozanimod hydrochloride dose. The order of the key secondary endpoints was as follows: (1) the number of new or enlarging hyperintense T2-weighted brain MRI lesions; (2) the number of GdE brain MRI lesions and (3) CDP-3M and CDP-6M.

A total of 1,346 in SUNBEAM and 1,313 subjects in RADIANCE were randomised and included in the modified Intention to Treat (mITT) population (SUNBEAM: 448 subjects in the IFN β -1a arm, 451 subjects in ozanimod 0.5mg arm and 447 subjects in the ozanimod 1mg arm; RADIANCE: 441 subjects in the IFN β -1a arm, 439 subjects in ozanimod 0.5mg arm and 433 subjects in the ozanimod 1mg arm). The demographic characteristics of subjects were generally well-balanced across treatment groups within each study as well as across the two studies. The median age was 35.0 years (range 18 to 55 years), majority of subjects were female (67%), White (99%), and enrolled in the Eastern Europe region (90%). The study population included 2,611 (98.2%) patients with RRMS and 42 (1.6%) patients with Progressive-Relapsing MS and the baseline mean EDSS score was 2.6 (range: 0 to 5.5). The mean time since onset of MS symptoms was 6.7 years. The mean number of relapses in the

last 12 months prior to screening was 1.3. Active disease was evidenced by the presence of GdE lesions at baseline in 45% of subjects. The mean number of GdE lesions on baseline MRI scan was 1.7 (range 0 to 53).

A total of 23% of subjects met the definition of a highly active MS at baseline as defined as (1) at least 2 relapses in the prior 12 months and at least 1 baseline GdE lesion, and/or (2) having received at least 1 year of DMT in the prior 2 years, having the most recent relapse in the previous 12 months while on that DMT, and having at least 9 baseline hyperintense T2-weighted brain MRI lesions or at least 1 baseline GdE brain MRI lesion. Approximately 70% of the population was DMT-naïve despite a mean disease duration of more than 6 years and presence of significant level of inflammatory activity.

The primary analysis of ARR using Poisson regression model demonstrated a statistically significant percent reduction for subjects in the ozanimod hydrochloride 1mg arm compared to IFN β -1a (SUNBEAM 48.2%; p<0.0001; RADIANCE 37.7%, p<0.0001). The ARR results in the ozanimod hydrochloride 1mg arm were consistent in various sensitivity analyses involving confirmed or unconfirmed relapses and using negative binomial regression model. In the pooled subgroup analysis, treatment effect in favour of ozanimod hydrochloride 1mg versus IFN β-1a was observed for patients regardless of the presence of highly active relapsing MS, number of relapses in the prior 1 and 2 years, presence of GdE lesions, number of T2 lesions, EDSS score at baseline, or prior DMT use status at baseline. A smaller reduction in ARR was observed for the ozanimod hydrochloride 0.5 mg dose (SUNBEAM 31.2%; p=0.0013; RADIANCE 20.9%, p=0.0167) and this dose was not proposed in the posology.

A statistically significant reduction was also observed for subjects in the ozanimod hydrochloride 1mg arm compared to IFN β -1a in the key secondary endpoints of new or enlarging T2 MRI lesions (SUNBEAM 48.3%; p<0.0001; RADIANCE 42.4%, p<0.0001) and GdE MRI Lesions (SUNBEAM 63.0%; p<0.0001; RADIANCE 52.9%, p=0.0006).

Summary of Key Efficacy Results (Studies SUNBEAM and RADIANCE)

	SUNBEAM			**RADIANCE**		
	IFN β-1a 30 µg (N = 448)	**Ozanimod HCl 0.5 mg** (N = 451)	**Ozanimod HCl 1 mg** (N = 447)	**IFN β-1a 30 µg** (N = 441)	**Ozanimod HCl 0.5 mg** (N = 439)	**Ozanimod HCl 1 mg** (N = 433)
Primary efficacy endpoint						
Annual Relapse Rate [a]						
Total no of relapses	184	125	97	236	186	143
Adjusted ARR (95% CI) [b]	0.350 (0.279, 0.440)	0.241 (0.188, 0.308)	0.181 (0.140, 0.236)	0.276 (0.234, 0.324)	0.218 (0.183, 0.259)	0.172 (0.142, 0.208)
Percent Reduction (Zeposia/INF β-1a)	--	31.24	48.21	--	20.95	37.66
P-value[c]	--	**0.0013**	**<0.0001**	--	**0.0167**	**<0.0001**
Relapse-free rate						
KM estimate	0.663	0.772	0.781	0.642	0.715	0.756
p-value[d]	--	*0.0022*	*0.0002*	--	0.0702	*0.0012*

	SUNBEAM			RADIANCE		
	IFN β-1a 30 µg (N = 448)	**Ozanimod HCl 0.5 mg** (N = 451)	**Ozanimod HCl 1 mg** (N = 447)	**IFN β-1a 30 µg** (N = 441)	**Ozanimod HCl 0.5 mg** (N = 439)	**Ozanimod HCl 1 mg** (N = 433)
Secondary efficacy endpoints						
New or enlarging T2 MRI lesions[e]						
N	382	397	388	336	329	327
Adjusted mean (95% CI) per scan [f]	2.836 (2.331, 3.451)	2.139 (1.777, 2.575)	1.465 (1.203, 1.784)	3.183 (2.640, 3.838)	2.092 (1.741, 2.514)	1.835 (1.523, 2.211)
Percent reduction vs INF β-1a (95% CI) [f]	-	24.58 (9.02, 37.48)	48.33 (37.47, 57.30)	-	34.28 (18.68, 46.90)	42.35 (28.58, 53.47)
p-value [f]	-	**0.0032**	**<0.0001**	-	**0.0001**	**<0.0001**
GdE MRI Lesions[g]						
N	382	397	388	336	329	327
Adjusted mean (95% CI) per scan [f]	0.433 (0.295, 0.635)	0.287 (0.197, 0.418)	0.160 (0.106, 0.242)	0.373 (0.256, 0.543)	0.197 (0.131, 0.296)	0.176 (0.116, 0.266)
Percent reduction vs IFN β-1a (95% CI) [f]	-	33.76 (6.78, 52.93)	62.97 (46.41, 74.42)	-	47.24 (19.52, 65.42)	52.94 (27.53, 69.45)
p-value [f]	-	**0.0182**	**<0.0001**	-	**0.0030**	**0.0006**
Other Secondary MRI Endpoints						
% Change in whole brain volume [h]						
N	406	420	397	397	398	390
Mean (SD)	-0.61 (0.686)	-0.49 (0.610)	-0.41 (0.640)	-0.94 (0.944)	-0.71 (0.746)	-0.71 (0.878)
Difference in means vs INF β-1a (95% CI)[i]	-	0.12 (0.03, 0.20)	0.19 (0.10, 0.28)	-	0.22 (0.11, 0.35)	0.24 (0.12, 0.36)
p-value [i]	-	*0.0092*	*<0.001*	-	*0.0002*	*<0.0001*

Key disability-related secondary endpoints (combined data of Study SUNBEAM and RADIANCE)

	IFN β-1a 30 µg	Ozanimod HCl 0.5 mg	Ozanimod HCl 1 mg
CDP-3M			
Number (%) of subjects	69 (7.8)	58 (6.5)	67 (7.6)
Hazard ratio vs INF β-1a [j] (95% CI)		0.822 (0.579, 1.165)	0.950 (0.679, 1.330)
p-value		0.2698	0.7651
CDP-6M			
Number (%) of subjects	36 (4.0)	43 (4.8)	51 (5.8)
Hazard ratio vs INF β-1a [j] (95% CI)		1.189 (0.763, 1.851)	1.413 (0.922, 2.165)
p-value		0.4447	0.1126

[a] The endpoint was assessed during the treatment period for Study SUNBEAM and through the end of Month 24 for Study RADIANCE. The primary analysis included confirmed relapses only.
[b] Based on the Poisson regression model, adjusted for region (Eastern Europe vs Rest of the World), age at baseline, and the baseline number of GdE lesions, and included the natural log transformation of time on study as an offset term.
[c] The comparison of each ozanimod group vs IFN β-1a group was performed at the 2-sided, 0.025 significance level according to the hierarchical statistical testing procedure.
[d] P-value for the comparison between the ozanimod and IFN β-1a treatment groups was based on the log rank test.
[e] Number of new or enlarging hyperintense T2-weight brain MRI lesions were assessed over 12 months in Study RPC01-301 and over 24 months in Study RPC01-201B.
[f] Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs Rest of the World), age at baseline, and baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 12 or 24 months is used as an offset term.
[g] Number of GdE brain MRI lesions were assessed at Month 12 in Study RPC01-301 and at Month 24 in Study RPC01-201B.

[h] Brain volume changes based on last observation carried forward (LOCF) analysis.
[i] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study is based on the ANCOVA model adjusted for region and EDSS category per interactive voice randomization system.
[j] Based on the Cox proportional hazard model with factors for treatment group and adjusted for region (Eastern Europe vs Rest of World), age at baseline, and baseline EDSS score.
Notes: P-values in bold are considered statistically significant. P-values in italics are considered nominally significant.
CI = confidence interval

The efficacy of ozanimod hydrochloride 1mg with respect to delaying the progression of physical disability compared to IFN β -1a was not demonstrated. In the pooled analysis of SUNBEAM and RADIANCE, the Hazard Ratio (HR) of CDP-3M and CDP-6M of ozanimod hydrochloride 1mg versus IFN- β-1a was 0.950 (95% confidence interval (CI) 0.679, 1.330; p=0.7651) and 1.413 (95% CI 0.922, 2.165; p=0.1126), respectively. Similar results were observed in the prespecified sensitivity analysis considering tentative progression at last EDSS assessment in the pivotal studies as CDP: CDP-3M HR of ozanimod hydrochloride 1mg vs IFN β -1a was 0.766 (95% CI 0.570, 1.029; p=0.0768) and CDP-6M HR was 0.837 (95% CI 0.614, 1.140; p=0.2585); as well as the post-hoc sensitivity analysis including CDP confirmed in the open label extension (OLE) study DAYBREAK: CDP-3M HR was 0.848 (95% CI 0.615, 1.170; p=0.3153) and CDP-6M HR was 1.040 (95% CI 0.730, 1.482; p=0.8275).

Study DAYBREAK (OLE)
Study DAYBREAK is an ongoing, multi-site, OLE study to evaluate the long-term safety and efficacy of ozanimod in subjects with RMS who completed one of the following studies: RPC01-1001, RPC01-201A Extension, RADIANCE, or SUNBEAM. All subjects were assigned to ozanimod hydrochloride 1 mg daily. Only the interim study report was submitted at the time of application. The final study results of DAYBREAK, which will provide more data on the long-term effect of ozanimod on disability progression, was requested as a post registration condition.

As of the data cut-off date of 30 June 2018, 2,495 subjects (84.6% of all subjects randomised in the parent studies) were enrolled into the OLE study: 2,323 (93.1%) subjects were ongoing, and 172 (6.9%) subjects discontinued the study early. Duration of treatment with ozanimod 1 mg was up to 30 months. There were 398 subjects (52%) with at least 3 years, and 44 subjects (6%) with at least 4 years of ozanimod 1 mg treatment throughout the parent and OLE studies combined.

Open-label treatment with ozanimod hydrochloride 1 mg resulted in a sustained low unadjusted ARR in subjects who were already treated with ozanimod hydrochloride 1 mg during the parent studies (0.174 in parent studies and 0.164 in OLE) and led to decreased relapse rates in subjects who switched from ozanimod hydrochloride 0.5 mg to 1 mg (from 0.213 in parent studies to 0.161 in OLE) or from INF β-1a treatment to ozanimod hydrochloride 1 mg (0.285 to 0.160). A similar pattern was observed for the ARR adjusted for region, age, and baseline number of GdE lesions, which was 0.153 in the parent studies and 0.133 in OLE in the 1mg/1mg ozanimod hydrochloride group. The results suggested maintenance of the efficacy of ozanimod hydrochloride 1mg in terms of relapse rates beyond the study duration of the parental studies.

Reduction in the number of new/enlarging hyperintense T2-weighted brain MRI lesions and GdE T1 brain MRI lesions followed a similar pattern to that of the reduction in ARR over time. The proportion of subjects with CDP-3M or CDP-6M continued to be low during OLE Study. The overall proportion of subjects with CDP-3M and CDP-6M during the OLE mITT population were 7.0% and 5.1%, respectively.

Overall, the submitted efficacy data supported the requested indication of ozanimod 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. The final study results of the Study DAYBREAK, which will provide more data on the long-term effect of ozanimod on disability progression, was requested as a post registration condition.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of ozanimod was based primarily on safety data derived from the pivotal Phase III SUNBEAM and RADIANCE studies, comprising a total of 2,659 patients who had received at least one dose of study treatment: 892 subjects in the ozanimod hydrochloride 0.5mg arm, 882 subjects in the ozanimod hydrochloride 1mg arm and 885 subjects in the IFN β-1a arm. The median duration of exposure (approximately 18 months) and proportions of patients with exposure of more than 12 and 24 months (approximately 92% and 34%, respectively) were similar in the treatment arms. The total duration of exposure was 1,323 patient-years in the ozanimod hydrochloride 1mg arm, 1,318 patient-years in the ozanimod hydrochloride 0.5mg arm and 1,305 patient-years in the IFN β-1a arm.

Overview of safety profile (Studies SUNBEAM and RADIANCE)

AE	IFN β -1a 30mcg (N=885) N (%)	Ozanimod hydrochloride 0.5mg (N=892) N (%)	Ozanimod hydrochloride 1mg (N=882) N (%)
Any AE	701 (79.2)	585 (65.6)	592 (67.1)
Treatment-related AE	43 (4.9)	20 (2.2)	26 (2.9)
Serious AE (SAE)	39 (4.4)	47 (5.3)	41 (4.6)
Treatment-related SAE	0	1 (0.1)	2 (0.2)
Discontinuations due to AE	34 (3.8)	21 (2.4)	26 (2.9)
Deaths	0	1 (0.1)	1 (0.1)
Deaths on Study	0	1 (0.1)	0

Approximately two-thirds of subjects in the ozanimod arms experienced an adverse event (AE). The commonly reported treatment-emergent AEs (frequency ≥5%) in the ozanimod hydrochloride 1mg vs ozanimod hydrochloride 0.5mg vs IFN β-1a arms, respectively, were nasopharyngitis (11.1% vs 11.5% vs 9.5%), headache (8.8% vs 9.2% vs 8.8%), upper respiratory tract infection (5.9% vs 7.5% vs 6.9%), alanine aminotransferase (ALT) increased (5.3% vs 4.6% vs 3.2%), influenza-like illness (5.0% vs 4.9% vs 49.9%) and pyrexia (1.8% vs 1.9% vs 6.3%). The safety profiles of the two tested doses of ozanimod were similar and no dose-response relationship was observed. The overall incidences of AEs, treatment-related AEs and rates of discontinuation due to AE in the pivotal clinical studies were lower in the ozanimod arms compared to the IFN β-1a arm, and the safety profiles were different as expected based on the different mechanisms of action.

The most frequently reported treatment-emergent AEs with ozanimod were predominantly mild or moderate in severity across all 3 treatments. The incidences of severe treatment-emergent adverse events (TEAEs) were low and similar across the ozanimod hydrochloride 1 mg, ozanimod hydrochloride 0.5 mg, and IFN β-1a treatment groups (2.5%, 3.3%, and 3.3%, respectively). Severe AEs reported for >1 ozanimod-treated subject were ALT increased (1 subject [0.1%] on ozanimod hydrochloride 1 mg and 2 subjects [0.2%] on ozanimod hydrochloride 0.5 mg), gamma-glutamyl transferase increased (2 subjects [0.2%] on ozanimod

hydrochloride 0.5 mg), and upper abdominal pain (1 subject [0.1%] on ozanimod hydrochloride 1 mg and 1 subject [0.1%] on ozanimod hydrochloride 0.5 mg). Severe AEs reported in >1 subject in the IFN β-1a group were influenza-like illness (8 subjects, 0.9%) and MS relapse (2 subjects, 0.2%).

The incidences of SAEs were very low and similar across treatment groups (4.6%, 5.3% and 4.4% in the ozanimod hydrochloride 1 mg, ozanimod hydrochloride 0.5 mg, and IFN β-1a treatment groups, respectively), with most SAE terms reported in single subjects.

The incidences of discontinuations from study drug due to AEs were low with slightly more subjects discontinued from IFN β-1a (3.8%) as compared to ozanimod (2.9% in ozanimod 1 mg arm, 2.4% in ozanimod 0.5 mg arm). This was attributed to events of influenza-like illness (1.4% of subjects on IFN β-1a vs none in the ozanimod groups).

The AESIs reported with ozanimod and known to be associated with S1P receptor modulators included hypertension, bradyarrhythmia and atrioventricular (AV) conduction delays, lymphopenia and opportunistic infections, malignancies, macular oedema, abnormal pulmonary function tests (PFT) and hepatotoxicity. While higher incidences of bradycardia were seen in the ozanimod hydrochloride 1mg and 0.5mg arms compared to IFN β-1a arm (7.6% and 6.8% vs 4.0%), second- or third-degree AV block were not reported. TEAEs reported on Day 1 of dose escalation (bradycardias in 0.5% of subjects on ozanimod vs. 0 on IFN β-1a) subsided thereafter without medical intervention, which supports the proposed treatment initiation of ozanimod without post-dose observation in patients with normal cardiac status. Appropriate risk mitigation measures in patients with pre-existing cardiac conditions or potential interacting medications have been included in the Package Insert.

Opportunistic infections included herpes zoster/ varicella zoster virus infections were reported. These were more frequently reported in subjects on ozanimod vs. IFN β-1a (0.6%, 0.3%, and 0.2% in subjects on ozanimod hydrochloride 1 mg, 0.5mg and IFN β-1a). Nonetheless, no differences were observed between treatment groups in the overall incidence of infections (33.9% to 35.1%). No disseminated or serious opportunistic infections were reported.

There were more malignancies reported with ozanimod (n=5, 0.6% with both doses) than with IFN β-1a (n=2, 0.2%). The numbers were small and these malignancies such as basal cell carcinoma and breast cancer did not demonstrate any specific pattern and were also not typical of those observed in an immunosuppressed population such as lymphoma.

The incidence of AEs of special interest (AESI) leading to discontinuation of ozanimod was low and included ≤3 subjects per treatment group with hepatic enzyme elevations, single cases of macular oedema (≤ 3 subjects per group) and bradycardia (2 subjects on ozanimod hydrochloride 0.5mg). Only one on-study death was reported in the 2 pivotal Phase III studies. The death occurred in the ozanimod hydrochloride 0.5mg arm due to drowning and was considered unrelated to study treatment by the investigators.

The types of AEs reported with ozanimod were generally consistent with the known safety profile of S1P receptor modulators used for the treatment of MS. Ozanimod was associated with generally lower cardiac effects . The AESIs have been adequately described in the warnings and precautions sections of the package insert and risk management plan (RMP) materials. Long-term safety data from the ongoing OLE study DAYBREAK would be required as post registration condition. Overall, the safety profile of ozanimod in RRMS was assessed to be manageable and no major concerns were raised.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Approximately 50% of patients with RRMS will, within the first 20 years after diagnosis, develop secondary progressive MS (SPMS), characterized by worsening disability independent of the presence or absence of relapses. Currently, patients with RRMS are managed with disease-modifying therapies with the objective of shortening the duration and severity of symptoms of acute relapses, and/or delaying accumulation of disability. Despite the availability of treatment options for RRMS, there remains a need for a highly effective oral agent with a favourable benefit, safety and tolerability profile.

Ozanimod hydrochloride 1mg demonstrated treatment benefits in terms of statistically significant reductions in ARR compared to IFN β-1a by 48.2% in study SUNBEAM and 37.7% in study RADIANCE. The treatment benefits were further supported by MRI-related key secondary endpoints including statistically significant reductions in the number of new or enlarging T2 MRI lesions by 48.3% in SUNBEAM and 42.4% in RADIANCE compared to IFN β-1a, as well as the number of GdE MRI lesions by 63.0% in SUNBEAM and 52.9% in RADIANCE compared to IFN β-1a.

Nonetheless, the efficacy of ozanimod hydrochloride 1mg with respect to CDP-3M and CDP-6M has not been shown when compared with IFN β -1a. In the pooled analysis of SUNBEAM and RADIANCE: CDP-3M HR 0.950 (95% CI 0.679, 1.330; p=0.7651) and CDP-6M HR 1.413 (95% CI 0.922, 2.165; p=0.1126). To reflect the efficacy benefit demonstrated in ARR but not in CDP endpoints, the indication has been revised to specify ‘to decrease the frequency of clinical exacerbations’.

The safety profile of ozanimod was similar to that of other S1P receptor modulators and was observed to have milder cardiac effects. In patients without significant cardiac disease, there were no cases of cardiac events that were persistent, required treatment, or were symptomatic. Hence, the proposed dose escalation over 7 days without post-dose observation was considered acceptable. The types and frequencies of AESIs with ozanimod were consistent with other S1P receptor modulators, which include hypertension, lymphopenia and opportunistic infections, malignancies, macular oedema, abnormal PFTs and hepatotoxicity. Warnings on the potential risks of hypertensive crisis with co-administration with monoamine oxidase inhibitors or dietary tyramine has been included in the Package Insert.

The overall benefit-risk profile of ozanimod was considered favourable for the treatment of adult patients with RRMS with active disease evidenced by relapses or imaging features, to decrease the frequency of clinical exacerbations. Longer-term data from the ongoing OLE DAYBREAK will be required to further characterise the efficacy and safety profile.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of ozanimod for the treatment of adult patients with RRMS with active disease evidenced by relapses or imaging features, to decrease the frequency of clinical exacerbations was deemed favourable and approval of the product registration was granted on 17 May 2023. The approval of this application is subject to the submission of the final study report of the open-label extension study DAYBREAK to confirm the long-term efficacy of ozanimod.

APPROVED PACKAGE INSERT AT REGISTRATION

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 x 10^9/L with values generally resolving to greater than 0.2 x 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 $AUC_{0\text{-}24h}$ 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.

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).

Printing ink

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.

Treatment initiation pack: Zeposia 0.23 mg and 0.46 mg

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

Maintenance pack: Zeposia 0.92 mg

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
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Singapore 449269

8. DATE OF REVISION OF THE TEXT

09 May 2023