

Date: 17 September 2020

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Zeposia

International non-proprietary name: ozanimod as ozanimod hydrochloride

Pharmaceutical form: hard capsules

Dosage strength: 0.92 mg, 0.46 mg and 0.23 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Celgene GmbH

Marketing Authorisation No.: 67046

Decision and Decision date: approved on 11 August 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

About Swissmedic

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About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARR	Annualised relapse rate
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC _{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
AUC _{tau,ss}	Area under the plasma concentration-time curve over a dosing interval at steady state
AV	Atrioventricular
BCRP	Breast cancer resistance protein
Bpm	Beats per minute
CDP	Confirmed disability progression
CDP-3M	Confirmed disability progression after 3 months
CDP-6M	Confirmed disability progression after 6 months
CH	Switzerland
CIS	Clinically isolated syndrome
C _{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DMT	Disease-modifying therapy
ECG	Electrocardiogram
EDSS	Expanded disability status scale
ERA	Environmental Risk Assessment
ESRD	End-stage renal disease
FVC	Forced vital capacity
GdE	Gadolinium-enhancing
GLP	Good Laboratory Practice
hERG	Human ether-à-go-go-related gene
HR	Heart rate
ICH	International Council for Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IM	Intramuscular
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MAO	Monoamine oxidase
Max	Maximum
Min	Minimum
MO	Macular oedema
MPR	Metabolite/parent ratio
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
N/A	Not applicable
NEDA	No evidence of disease activity
NO(A)EL	No Observed (Adverse) Effect Level
OATP	Organic anion transport polypeptide
OCT	Optical coherence tomography
OLE	Open-label extension

PD	Pharmacodynamics
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/pharmacodynamics
PML	Progressive multifocal encephalopathy
PopPK	Population PK
PPMS	Primary progressive multiple sclerosis
PRES	Posterior reversible encephalopathy syndrome
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
RMP	Risk Management Plan
RMS	Relapsing multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
S1P	Sphingosine 1-phosphate
S1P1	Sphingosine 1-phosphate receptor type 1
S1P5	Sphingosine 1-phosphate receptor type 5
SPMS	Secondary progressive multiple sclerosis
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
ULN	Upper limit of normal
Vz/F	Apparent volume of distribution

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status

The applicant requested the status of a new active entity for the active substance ozanimod of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Zeposia is indicated for the treatment of adults with relapsing multiple sclerosis (RMS).

2.2.2 Approved Indication

Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

2.2.3 Requested Dosage

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

The initial dose escalation regimen of ozanimod from Day 1 to Day 7 is shown below in Table 1.

Following the 7-day dose escalation, the recommended maintenance dosage is 0.92 mg once daily taken orally starting on Day 8.

Initiation of ozanimod without dose escalation may result in greater reductions in heart rate.

Table 1: Dose Escalation Regimen

Day of Treatment	Dosage
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

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	08 May 2019
Formal control completed	10 May 2019
List of Questions (LoQ)	14 August 2019
Answers to LoQ	12 December 2019
Predecision	10 March 2020
Answers to Predecision	8 May 2020
Labelling corrections	16 July 2020
Answers to Labelling corrections:	22 July 2020
Final Decision	11 August 2020
Decision	approval

3 Medical Context

Multiple sclerosis (MS) is a chronic, predominantly immune-mediated inflammatory disease of the central nervous system (CNS), affecting approximately 2.5 million individuals worldwide. MS is characterised by autoreactive lymphocytes that attack and destroy the myelin sheath surrounding nerve cells, resulting in demyelination, axonal damage and disruption of the blood-brain barrier, causing neurological impairment and severe disability.

The prevalence is 100-150 per 100,000 inhabitants. Around 8,000-10,000 people with MS live in Switzerland (CH). The annual incidence is circa 3.5–5 per 100,000 inhabitants (CH: 4.0–5.5 / 100,000) and is increasing according to data from Scandinavian registries.

Clinically, MS starts in approximately 85% of patients as relapsing remitting MS (RRMS), with variable disease activity interspersed with periods of stability. The onset of RRMS typically occurs between the ages of 20 and 40 and predominantly affects women (2 to 3 times more frequently than men). Approximately 70% of patients with RRMS develop, within the first 10 to 15 years after diagnosis, a secondary progressive MS (SPMS), which is characterised by worsening of disability in the absence or independent of relapses.

Relapsing forms of MS (RMS) include patients with RRMS, patients with clinically isolated syndrome (CIS – refers to the first clinical event and evidence of dissemination of lesions in time and space on the magnetic resonance imaging (MRI) scan) and those with SPMS with superimposed relapses. There are no clear criteria that mark the transition from RRMS to SPMS.

Additionally, around 15% of patients demonstrate progressive neurological deterioration without superimposed relapses at the beginning of the disease. This form is called primary progressive MS (PPMS), begins typically in the 4th or 5th decade of life and affects men equally as women.

The current therapeutic approach of treating RMS involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies (DMTs). The goal of a DMT is to modify the natural course of disease by reducing the rate of relapses and MRI disease activity, and delay disability progression. There are a number of DMTs available for the treatment of MS with different mechanisms of action and differentiated efficacy and safety profiles, but there is still no cure available for MS.

Sphingosine 1-phosphate (S1P) receptor modulation has been shown to be a highly effective treatment for MS (Brinkman, 2010). Antagonism of S1P receptor type 1 (S1P1) inhibits the egress of lymphocytes from lymph nodes, thereby decreasing circulating lymphocytes (Scott, 2016; Tran, 2017), and preclinical evidence suggests that S1P1 and sphingosine 1-phosphate 5 receptor (S1P5) modulation also may have direct CNS effects resulting in reduction of inflammatory cytokines, demyelination, and axonal loss, and preservation of GABAergic transmission. (Gentile, 2016; Groves, 2013; Slowik, 2015).

Ozanimod is a sphingosine 1-phosphate (S1P) receptor agonist, which binds with high affinity and selectively to S1P subtypes 1 (S1P1) and 5 (S1P5). It is 10-fold more selective for S1P1 relative to S1P5 and has little activity on the other S1P receptors (S1P2, S1P3, and S1P4). Ozanimod causes internalisation of S1P1 and retention of lymphocytes in the lymphoid tissues, as evidenced by a dose-dependent reduction in peripheral lymphocyte count.

4 Quality Aspects

4.1 Drug Substance

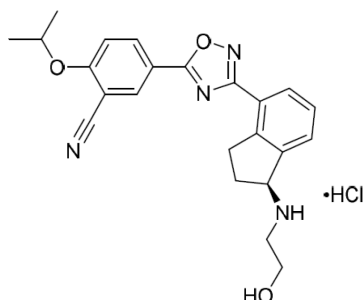
INN: Ozanimod hydrochloride

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

Molecular formula: $C_{23}H_{24}N_4O_3 \cdot HCl$

Molecular mass: 440.92 g/mol

Molecular structure:



Ozanimod hydrochloride is a white to off-white solid. Ozanimod HCl is considered to be poorly hygroscopic. Ozanimod HCl is highly soluble across the pH range between 1.2 and 7.5. The confirmation of (S) configuration was assigned by X-ray crystal structure determination. The drug substance is manufactured by a multiple step chemical synthesis with final isolation by crystallisation.

The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, chiral purity, assay, impurities, and particle size.

Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

The drug product is supplied as hard gelatin capsules for oral administration with 0.25 mg, 0.5 mg, and 1.0 mg ozanimod HCl dosage strengths. 0.23 mg ozanimod is equivalent to 0.25 mg ozanimod HCl. 0.46 mg ozanimod is equivalent to 0.5 mg ozanimod HCl. 0.92 mg ozanimod is equivalent to 1.0 mg ozanimod HCl.

The composition of the drug product is adequately described, qualitatively and quantitatively. Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including a risk assessment for the attributes of the drug substance, excipients and the manufacturing process for potential impact on the critical quality attributes (CQAs) of the intended commercial drug product.

The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

Adequate validation data pertaining to the commercial manufacturing process are available.

The drug product specification covers relevant physicochemical characteristics; identification, assay, purity, and dissolution tests are included as well. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.

The drug product capsules are packaged into a polyvinylchloride/polychlorotrifluoroethylene (PVC/PCTFE) blister.

Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical Aspects

Zeposia (ozanimod HCl salt) is a sphingosine 1-phosphate (S1P) receptor agonist with selectivity for the receptor subtypes S1P₁ and S1P₅. As it is highly metabolised, a comprehensive preclinical programme was conducted for ozanimod and the most relevant metabolites, consistent with the recommendations of ICH guideline M3 (R2). The pivotal toxicology studies were performed in accordance with GLP regulations.

Pharmacology

Ozanimod had activity on human S1P₁ and S1P₅ in the low nanomolar or subnanomolar range with up to 100-fold higher potency on S1P₁. Activity on S1P₂₋₄ was several thousand-fold lower. All eight human metabolites except RP101124, a major human metabolite, had *in vitro* and/or *in vivo* activity on S1P receptors. Potency of ozanimod and the other two major metabolites, CC112273 and CC1084037, on S1P₁ was similar across species (mouse, rat, monkey, human) while activity on mouse and rat S1P₅ was 100- to 1000-fold lower compared to human and monkey S1P₅. Overall, functional *in vitro* activity was similar to other marketed S1P receptor agonists. Ozanimod improved clinical scores in the murine experimental autoimmune encephalomyelitis model and protected against demyelination, but did not improve remyelination.

The off-target activity of ozanimod and/or metabolites on receptors or ion channels with neurological activity, particularly serotonin transporter and monoamine oxidase B, are considered of no concern based on margins of at least 100-fold and/or absence of symptoms of serotonin-like syndrome in mechanistic *in vivo* follow-up studies and in clinical trials.

While the hERG assay did not indicate any clinically relevant cardiovascular risk, decreased diastolic blood pressure (20%), increased PR interval (10%), and decreased heart rate (29%), which probably caused the observed slight prolongation of the RR, QT and QTc intervals, was noted in telemetered male cynomolgus monkeys (but no arrhythmia). At the NOAEL, exposure (C_{max}) was 11-fold the clinical C_{max} at 1 mg ozanimod salt, the maximum recommended human dose (MRHD). Bradycardia and hypertension were noted in clinical trials and are also known side effects of other S1P receptor agonists. In rats, increases in the respiratory rate, decreases in the tidal volume and increased lung weights were noted at clinically relevant exposures. However, pulmonary function was not affected in clinical trials. Effects on the central nervous system were assessed in repeated-dose toxicology studies and did not indicate any concern at clinically relevant exposures.

Pharmacokinetics

Ozanimod is a highly permeable compound. Oral bioavailability was 47 to 70% in rats. Exposure of ozanimod and its metabolites was independent of sex and dosing duration and increased dose-proportionally or less than dose-proportionally in mice, rats, monkeys, and rabbits. There was no accumulation after repeated dosing. Ozanimod and its metabolites were eliminated with a t_{1/2} < 12 hours. Plasma protein binding of ozanimod was 83 to 98.7% in animals and comparable to that in humans (98.3%).

¹⁴C-ozanimod-derived radioactivity distributed widely into tissues, blood cells, and pigmented skin, and was detectable for more than 500 hours in the eye and central nervous system (CNS)/meninges in rats. Levels were 10- to 20-fold (brain) and 100- to 350-fold (lung) the blood levels in mice and rats. Ozanimod crossed the placenta of rats and rabbits and was detectable in the milk of rabbits above plasma levels. It is assumed that the same applies to the major active metabolites CC112273 and CC1084037.

Across all species, ozanimod is highly metabolised via different metabolic pathways. Primary transformation involves oxidation, CYP450-mediated dealkylation, and gut microbial-mediated oxadiazole ring scission. Several additional enzymes are involved in the subsequent biotransformation.

CC112273 and CC1084037 were identified only late in drug development and additional PK bridging studies were conducted to compare exposures in animals to human exposures. In animals,

CC112273 and CC1084037 had a low oral bioavailability (< 10% in rats and mice), a $t_{1/2}$ of 4 to 12 hours and a stable exposure after repeated dosing for 14 days whereas, in humans, $t_{1/2}$ was 11 days, exposure accumulated 16-fold after repeated dosing and reached steady state after 45 days. Direct dosing of the two metabolites did not increase exposures over levels that were achieved through dosing of ozanimod.

Ozanimod was excreted mainly via faeces and bile, in rats and monkeys, mostly as metabolites. In humans, metabolites are excreted via urine and faeces. Multiple ozanimod drug-drug interactions were identified and are commented in the information for healthcare professionals.

Toxicology

Toxicology of ozanimod was assessed in subchronic and chronic studies in rats and monkeys and, in a 28-day study, in mice. The selected nonclinical species are considered acceptable as pharmacological activity was shown in all species, metabolic profiles were qualitatively comparable to humans, and exposures at the highest applied doses covered the clinical exposures of ozanimod and the major human metabolites. The clinical (oral) route was used throughout the animal studies.

Toxicities were mainly related to S1P receptor agonism and are similar to those of other drugs of this class. The main target organs across all species were the lymphoid system (lymphopenia, decreased spleen and thymus weights along with pathology (decreased cellularity and/or loss of differentiation)) and lung (increased weight, alveolar macrophages histiocytosis and/or oedema). Rats and monkeys also had findings in the medullary lymph nodes, kidneys and adrenal glands. Additional target organs in monkeys were the bone marrow, intestine, and liver. In rats, hypertrophy in the mammary glands, and in mice, decreased heart weight was noted. Overall, the findings were reversible or tended to recover. The changes in the lung determined the NOAEL in all three species with exposure multiples < 1 for total active drug including metabolites. Additional target organs were identified in the carcinogenicity studies (epididymis, testicles, and stomach in mice and brain in rats), while S1P-related changes (lung, lymphoid tissues) and kidney toxicities were no longer present in rats and were present in mice to a lesser extent. Direct repeated dosing of CC112273 in mice and rats was well tolerated, which is consistent with its low bioavailability and fast elimination. Thus, animals cannot inform adequately about the safety risk for humans. However, as human exposure at the MRHD was covered at the highest applied doses in animals, the observed toxicities were mainly related to S1P receptor agonism, and no unexpected findings were noted, the major metabolites are considered sufficiently characterised in animals.

Ozanimod and the major metabolites were not mutagenic or clastogenic in a standard testing battery. In a 6-month carcinogenicity study in transgenic mice, mortalities occurred from the lowest dose level of 8 mg/kg/day onwards mainly due to dose-dependent increased incidences of haemangiosarcoma. Therefore, a NOEL could not be established. There are data from literature suggesting that haemangiosarcoma may be mouse-specific due to SP1-related induction of growth factors. However, these data are not yet confirmed and human relevance cannot be excluded. The exposure of total active drug at the lowest dose exceeded the human exposure at MRHD 50-fold, but was within clinical exposure for CC112273 and CC1084037. In rat, ozanimod up to 2 mg/kg/day was not carcinogenic, but exposure was only 3.9-fold the clinical exposure for total active drug and < 0.5-fold for the major active metabolites.

Ozanimod did not affect the fertility of rats but was teratogenic (abnormalities of great blood vessels and generalised oedema) and embryotoxic in rats and rabbits at clinically relevant exposures. The detrimental vascular changes are attributed to S1P₁ agonism. A pre- and postnatal development study in rats did not reveal adverse findings at exposure multiples of 90 for ozanimod, but were below 1 for the major metabolites.

Studies in juvenile rats did not reveal any specific concern for the paediatric population. Immunotoxicity studies, also conducted in juvenile animals, showed slightly stronger inhibitory effects on the T-cell dependent antibody response in adult rats. The information for professionals recommends an off-treatment period of 3 months before vaccinations and contains appropriate information related to increased risks for infections and immunosuppression.

The drug abuse and phototoxic potential of ozanimod and the metabolites were sufficiently characterised and are of no concern. There are no concerns with regard to impurities and excipients. No environmental risk is expected from the use of ozanimod.

Non-clinical Conclusions:

The provided non-clinical documentation is considered sufficient to conduct a risk assessment. The major active metabolites CC112273 and CC1084037 could not be appropriately assessed in animal studies due to their pharmacokinetics. Toxicities were mainly related to the S1P₁ agonism and are similar to toxicities of other S1P₁ agonists. Therefore, Zeposia can be approved for the requested indication from a preclinical point of view, and appropriate information should be provided in the information for healthcare professionals with regard to limited toxicological data of the metabolites. The risk management plan reflects the nonclinical data appropriately.

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Pharmacokinetics

Ozanimod was extensively metabolised. Most metabolites showed pharmacological activity similar to that of the parent compound.

The main metabolite CC112273 was identified relatively late in the development programme. Therefore, some of the clinical pharmacology studies did not reflect the clinical situation.

Overview of ozanimod metabolites:

CC112273 (RP112273)

CC1084037 (RP100798)

RP101988

RP112289

RP101075

RP101442

RP101124 => inactive metabolite.

ADME

Absorption

A low-fat meal had no effect on the pharmacokinetics of ozanimod. A high-fat meal resulted in a prolongation of ozanimod t_{max} from 8 h to 12 h, but had no impact on ozanimod C_{max} or AUC. Therefore, ozanimod can be taken independently of food.

Dose Proportionality

After administration of single or multiple doses between 0.3 mg to 2 mg, there was a dose-proportional increase in ozanimod exposure. The exposure to CC112273 also showed a dose-proportional increase after administration of single doses between 0.5 mg and 1 mg, or multiple doses between 0.5 mg and 2 mg of ozanimod. Based on the close correlation between the plasma concentrations of CC112273 and CC1084037, similar results are expected for CC1084037.

Multiple Dosing

Ozanimod reached its steady state within 5 to 7 days after once daily administration. There was an approximately 2-fold accumulation.

CC112273 reached its steady state after approximately 44 days following once daily administration with a 16.2-fold accumulation. Based on the close correlation between the plasma concentrations of CC112273 and CC1084037, similar results were expected for CC1084037.

Distribution

The plasma protein binding of ozanimod and its metabolites was high (ozanimod: 98.2%, CC112273: 99.1%). The ozanimod V_z/F was 7144 L.

Metabolism

Hepatic CYPs were involved in the *in vitro* metabolism of ozanimod. However, considering the many other enzyme systems involved, their role was likely to be minor (formation of RP101075 by CYP3A4, oxidation of CC112273 by CYP2C8). The main metabolite CC112273 was not directly formed from ozanimod, but via the intermediate RP101075. The conversion of RP101075 to CC112273 was catalysed by MAO-B. The second main metabolite, CC1084037, and CC112273, were interconvertible, with CC112273 as the dominant species. No CYPs were involved in this

interconversion, but carbonyl reductases, aldo-keto reductases and hydroxysteroid dehydrogenases were involved. The interconversion to CC112273 was the only elimination pathway of CC1984037. CC112273 was eliminated either by reduction to CC1084037 or oxidation to RP101509 by CYP2C8.

A summary of the metabolite/parent ratio (MPR) and the contribution of the metabolites to the total active AUC is presented below:

Analyte	AUC0-24 MPR	% Total AUC0- 24	% Active AUC0-24
OZA		5.44	6.06
CC112273	12.9	65.6	73.1
CC1084037	2.57	13.1	14.7
RP101988	0.916	4.84	5.39
RP101442	0.0176	0.0973	0.108
RP112289	0.111	0.589	0.661
RP101124 (inactive metabolite)	2.06	10.3	

In summary, CC112273 was the major carrier of pharmacological activity/clinical efficacy.

Elimination

The half-life of ozanimod was about 20 h. The half-life of CC112273 and CC1084037 was about 230 h.

The mass balance study with administration of a ¹⁴C-labelled dose was conducted prior to the identification of CC112273 and CC1084037. The collection interval for blood and excreta was too short, resulting in a low total recovery of 63.1%. Therefore, the results should be regarded with caution. About 26% and 37.1% of the total radioactivity were excreted in urine and faeces, respectively. Neither ozanimod nor CC112273 and CC1084037 were detected in urine or faeces.

Special Populations

Mild or moderate **hepatic impairment** had only a minimal effect on the exposure of ozanimod and its main metabolite:

Analyte	C _{max}	AUC _{last}	AUC _{inf}
Ozanimod			
Mild hepatic impairment	1.148 (0.898, 1.468)	0.886 (0.676, 1.163)	1.016 (0.758, 1.363)
Moderate hepatic impairment	1.308 (0.936, 1.828)	1.272 (0.933, 1.733)	1.257 (0.925, 1.708)
CC112273			
Mild hepatic impairment	0.775 (0.652, 0.921)	0.689 (0.369, 1.286)	
Moderate hepatic impairment	0.592 (0.462, 0.759)	0.673 (0.317, 1.429)	
RP101988			
Mild hepatic impairment	1.094 (0.710, 1.687)	1.139 (0.436, 2.975)	
Moderate hepatic impairment	1.088 (0.717, 1.651)	1.880 (0.979, 3.609)	

No pharmacokinetic data were available for subjects with severe hepatic impairment. The PK data support the proposed dosing recommendations (no dose adjustments in patients with mild or

moderate hepatic impairment, and ozanimod is contraindicated in patients with severe hepatic impairment).

The effect of severe **renal impairment** (ESRD without dialysis) on the exposure of ozanimod and its main metabolite was also small:

Analyte	C _{max}	AUC _{last}	AUC _{inf}
Ozanimod	0.922 (0.682, 1.247)	1.270 (0.951, 1.696)	1.377 (0.863, 2.197)
CC112273	0.781 (0.666, 0.917)	0.766 (0.606, 0.969)	
RP101988	1.125 (0.850, 1.488)	1.673 (1.018, 2.750)	
RP101075	0.806 (0.615, 1.057)		

The PK data support the proposed dosing recommendations for patients with renal impairment (no dose adjustments required).

The results of a population PK analysis indicated that the CC112273 AUC_{tau,ss} was 35% lower in men compared to women, 52% lower in smokers compared to non-smokers and 40% higher in healthy subjects compared to RMS patients. Since the oldest RMS patient in the pop PK dataset was 55 years old, no dosing recommendations can be given for elderly patients.

Interactions

The unbound C_{max} of ozanimod and CC112273 after therapeutic dosing were 10.9 pM and 427 pM, respectively.

In vitro Data – Interactions with CYPs

Ozanimod and its metabolites did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4. There was no induction of CYP1A2 or 2B6, but an *in vivo* induction of CYP3A4 by ozanimod and some of its metabolites (but not CC112273 and CC1084037) could not be excluded. A clinical interaction study with oral contraceptives was therefore conducted (see below).

In vitro Data – Interactions with Transporters

The *in vitro* studies conducted for ozanimod and its metabolites covered all transporters listed in the relevant regulatory guidelines. The main results are summarised below.

Ozanimod possibly was a substrate for P-gp. It inhibited P-gp (IC₅₀ 8.8 µM) and BCRP (IC₅₀ 3.5 µM)

CC112273 and CC1084037 inhibited BCRP (IC₅₀ 25.2 nM and 22.8 nM, respectively). The risk of an *in vivo* inhibition appeared to be low.

RP101988 was a substrate of P-gp and BCRP. It did not inhibit any transporters.

RP101075 was not a substrate or an inhibitor of transporters.

RP101124 was a substrate for BCRP and possibly for OATP1B1, but did not inhibit any transporters.

Other In vitro Data

CC112273, CC1084037 and RP101075 inhibited MAO-B with an IC₅₀ of 5.72 nM, 58 nM and 56.13 nM, respectively. The three metabolites did not inhibit MAO-A. The inhibition of MAO-B was further investigated in a clinical interaction study with pseudoephedrine (see below).

RP101124 and RP112402 did not inhibit UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15 or 2B17

Clinical Data – Impact of other Drugs on Ozanimod and its Metabolites

The effects of gemfibrozil, itraconazole and rifampin on the exposure of ozanimod and its metabolites are summarised below:

Index Modulator and Dose	Enzyme Effect	Ratio of Geometric LSM (90% CI) ^a		
		Ozanimod AUC _{0-∞}	CC112273 AUC _{0-12h}	CC1084037 AUC _{0-12h}
Gemfibrozil 600 mg BID	CYP2C8 inhibition	n = 19 vs. 20 0.972 (0.850, 1.111)	n = 19 vs. 20 1.470 (1.108, 1.950)	n = 19 vs. 20 1.687 (1.255, 2.270)
Itraconazole 200 mg QD	CYP3A inhibition	n = 19 1.125 (0.970, 1.305)	n = 19 0.945 (0.811, 1.102)	n = 19 0.883 (0.755, 1.032)
Rifampin 600 mg QD	CYP2C8/3A induction	n = 19 0.758 (0.641, 0.897)	n = 19 0.402 (0.319, 0.506)	n = 19 0.446 (0.346, 0.577)

Itraconazole had no effect on the exposure of ozanimod and its main metabolites, while gemfibrozil caused an increase and rifampicin a decrease in the exposure. The data support the proposed dosing recommendations (monitoring for AEs in case of co-administration of CYP2C8 inhibitors, co-administration of inducers not recommended).

Cyclosporine, a strong inhibitor of several transporters, including BCRP and P-gp, had no effect on the exposure of ozanimod, but it caused an about 2-fold increase in the exposure of RP101988 and RP101075. The CC112273 plasma concentrations were not measured in the respective interaction study, but as RP101075 is the precursor of CC112273, the exposure of the main metabolite is likely to be affected as well. The proposed dosing recommendation (concomitant administration of BCRP inhibitors not recommended) is therefore acceptable from a pharmacokinetic point of view.

Clinical Data – Impact of Ozanimod on other Drugs

Ozanimod had no effect on the exposure of ethinylestradiol and norethindrone. This interaction study was also conducted prior to the identification of CC112273. The treatment duration and the washout period between the treatments was therefore too short. However, CC112273 and CC1084037 did not induce CYP3A4 *in vitro*.

Ozanimod had no effect on pseudoephedrine exposure.

Pharmacodynamics

Secondary Pharmacology (Safety)

Ozanimod did not cause a QTc prolongation at therapeutic and suprathreshold (C_{max} 1.66-fold ↑) exposure. The corresponding tQT study was conducted prior to the identification of CC112273, i.e. the treatment duration of 14 days was too short. However, exposure-response analyses indicated a low risk of QTc prolongations at therapeutic exposure of CC112273.

Pharmacodynamic Interactions

There were no data regarding pharmacodynamic interactions with beta blockers and calcium channel blockers and ozanimod at therapeutic exposures. The available clinical interaction study was conducted prior to the identification of CC112273 (=> treatment duration and washout period too short). Furthermore, only a single dose of 0.25 mg ozanimod was administered.

The co-administration of ozanimod and pseudoephedrine in a study appropriately accounting for CC112273 PK resulted in a heart rate increase of 3 beats per minute compared to pseudoephedrine alone.

The co-administration of ozanimod and tyramine had no effect on blood pressure compared to the administration of tyramine alone. The primary endpoint of the study, the tyramine sensitivity factor (TSF), was not evaluable due to a pronounced placebo effect.

6.2 Dose Finding and Dose Recommendation

Two dose levels for ozanimod once daily (0.5 mg ozanimod hydrochloride equivalent to 0.46 mg ozanimod and 1 mg ozanimod hydrochloride equivalent to 0.92 mg ozanimod) were selected for the pivotal Phase 3 studies based on the results of the dose-ranging Phase 2 study, RPC01-201A (0.46 mg, 0.92 mg and placebo).

The available clinical efficacy data and PD data for other S1P receptor modulators evaluated in MS (fingolimod and siponimod) indicated that an approximately 70% reduction in the absolute lymphocyte count (ALC) would be associated with maximal efficacy for S1P1 modulators in MS (Kappos, 2006; Selmaj, 2013). Based on the Phase 1 data (RPCS 001), ozanimod 0.92 mg was predicted to produce an approximately 70% decrease in ALC at steady state and was therefore selected as the high dose for Phase 2 evaluation. A dose higher than 0.92 mg once daily (QD) was not selected as results from the Phase 1 study (RPCS 001) showed a plateau effect on ALC reduction at 0.92 mg.

An ozanimod dose of 0.46 mg was predicted to produce a 50% reduction in ALC at steady state and therefore was selected as the low dose for Phase 2 evaluation.

In the placebo-controlled period of Study RPC01-201A, both doses showed similar efficacy for the primary endpoint of the total number of gadolinium-enhancing (GdE) brain magnetic resonance imaging (MRI) lesions from Weeks 12 to 24. However, the ozanimod 0.92 mg dose was numerically better than the 0.46 mg dose for new or enlarging hyperintense T2-weighted brain MRI lesions from Week 12 to Week 24 and for the adjusted annualised relapse rate (ARR) at Week 24, with no meaningful differences in safety noted.

Both doses of ozanimod (0.92 mg and 0.46 mg) were carried forward in the controlled Phase 3 studies (Study RPC01-301 and Study RPC01-201B) to further establish efficacy on the primary endpoint, annualised relapse rate (ARR), as well as the safety profiles of the two doses.

The overall magnitude of effect and consistency of response was greater with ozanimod 0.92 mg at Month 12 (Study RPC01-301) and Month 24 (Study RPC01-201B), and in the pooled analyses, indicating better early disease control. In subgroup analyses of the ARR, new or enhancing hyperintense T2-weighted brain MRI lesions, and GdE T1 brain MRI lesions, consistently greater responses were observed with ozanimod 0.92 mg compared to ozanimod 0.46 mg for each subgroup analysed.

The ozanimod 0.92 mg dose was selected for use in the uncontrolled Phase 3 open-label extension study (RPC01-3001) based on the ARR data from the placebo-controlled period of Study RPC01-201A and an acceptable safety profile similar to that of ozanimod 0.46 mg.

Data from the Phase 1 study RPCS 001 provided evidence that the magnitude of the negative chronotropic and adverse conduction effects of S1P modulation was exposure-dependent and could be mitigated by gradually increasing exposure. Based on Phase 1 data, a 7-day dose escalation regimen was implemented in the Phase 2 study and supported the ability of a dose escalation regimen to mitigate the chronotropic and dromotropic effects of ozanimod. Thus, in order to mitigate potential cardiac effects, an initial 7-day dose escalation regimen was used for all subjects in the pivotal studies.

Dose Recommendation

The recommended dose is 0.92 mg ozanimod once daily.

An initial dose escalation regimen of ozanimod is required:

Days 1-4: 0.23 mg once daily

Days 5-7: 0.46 mg once daily

The maintenance dose is 0.92 mg once daily, starting on Day 8.

Despite the dose titration, ozanimod induces temporary bradycardia due to the S1P1 agonism at the start of treatment, which is why cardiac monitoring over 6 hours is recommended at least in patients with certain cardiac pre-existing conditions (resting heart rate <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure).

6.3 Efficacy

The clinical programme of ozanimod in RMS patients includes:

- a Phase 1, multiple-dose PK/PD study (RPC01-1001)
- a Phase 2, randomised, double-blind, placebo-controlled study with a blinded extension period (RPC01-201A)
- two double-blind, active-controlled pivotal Phase 3 studies with the same enrolment criteria, active comparators and endpoints, but that differed in duration (RPC01-201B (RADIANCE) [24 months] and RPC01-301 (SUNBEAM) [12+ months])
- one long-term open-label extension (OLE) study (RPC01-3001, DAYBREAK)

The pivotal Phase 3 studies of ozanimod in RMS (Studies RPC01-301 (SUNBEAM) and RPC01-201B (RADIANCE)) used a similar study design.

Both studies consisted of a 30-day screening period, a randomised, double-blind, double-dummy, active-controlled, parallel-group treatment period of at least 12 months (of the last enrolled patient) (SUNBEAM) or 24 months (RADIANCE) with a 7-day dose-escalation period beforehand and a 28-day safety follow-up period.

As active comparator interferon (IFN) β -1a was chosen in comparison with two dose levels of ozanimod (0.46 mg and 0.92 mg).

The two pivotal 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 GdE lesion in the prior year and with an Expanded Disability Status Scale (EDSS) score from 0 to 5.0.

All statistical tests for comparing the two ozanimod dose groups to IFN β -1a were two-sided with overall type I controlled at the 0.05 level of significance using a pre-specified hierarchical procedure. The primary outcome was the ARR over the treatment period (minimum of 12 months for SUNBEAM and 24 months for RADIANCE).

Key secondary endpoints in ranked order included the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 and 24 months, the number of GdE T1 brain MRI lesions at 12 and 24 months, and the time to onset of disability progression, defined as at least a 1-point increase from baseline EDSS, confirmed prospectively after 3 months and after 6 months (pooled analysis).

In SUNBEAM, 1,346 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, 1,313 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 patients treated with ozanimod 0.92 mg, 85% treated with ozanimod 0.46 mg, and 85% treated with IFN β -1a IM completed the study.

Patients enrolled across the two studies had a mean age of 35.5 years (range 18-55). The majority of the subjects had RRMS (98.2%), were female (67%), white (99%) and were enrolled in the Eastern

European region (90%). 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 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).

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

Endpoints	SUNBEAM (≥ 1 year) ^a		RADIANCE (2 year)	
	Ozanimod 0.92 mg (n=447) %	IFN β-1a IM 30 µg (n=448) %	Ozanimod 0.92 mg (n=433) %	IFN β-1a IM 30 µg (n=441) %
Clinical Endpoints				
Annualised Relapse Rate (Primary Endpoint) Relative Reduction	0.181	0.350	0.172	0.276
	48 % (p < 0.0001)		38 % (p < 0.0001)	
Proportion Relapse-free Kaplan-Meier ^b	78 % p = 0.0002 ^c	66 %	76 % (p = 0.0012) ^c	64 %
Proportion with 3-month Confirmed Disability Progression (CDP) ^{d, e} Hazard Ratio (95% CI)	7.6 % Ozanimod vs. 7.8 % IFN β-1a IM 0.95 (0.679 – 1.330) p = 0.7651			
Proportion with 6-month CDP ^{d, e} Hazard Ratio (95% CI)	5.8% Ozanimod vs. 4.0% IFN β-1a IM 1.413 (0.922 – 2.165) p=0.1126			
MRI Endpoints				
Mean number of new or enlarging T2 hyperintense lesions per MRI ^f Relative Reduction	1.465	2.836	1.835	3.183
	48 % (p < 0.0001)		42 % (p < 0.0001)	
Mean number of T1 Gd-enhancing lesions ^g Relative Reduction	0.160	0.433	0.176	0.373
	63 % (p < 0.0001)		53 % (p = 0.0006)	

^a Mean duration was 13.6 months

^b Nominal p-value for endpoints not included in the hierarchical testing and not adjusted for multiplicity

^c Log-Rank Test

^d Disability progression defined as 1-point increase in EDSS confirmed 3 months or 6 months later.

^e Prospectively planned pooled analysis of Studies 1 and 2

^f Over 12 months for Study 1 and at 24 months for Study 2

^g At 12 months for Study 1 and at 24 months for Study 2

Efficacy has been demonstrated for ozanimod 0.92 mg, with a dose effect observed for study endpoints as shown in the table above. 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.

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.

Independently of the DMT-status, efficacy for ozanimod on CDP (-3M and -6M) was not demonstrated. This is in line with the original analysis of the key secondary endpoint “confirmed disability progression” at 3 months (p=0.7651) and 6 months (p=0.1126).

In general, an effective treatment intended to modify the natural course of relapsing (remitting) multiple sclerosis has to show an effect on both relapses and progression. Since an active comparator was chosen in the clinical studies, an effect that has not shown statistical significance can be accepted as long as it is described in the label accordingly.

Besides the assessment of ARR and disability progression, the assessment of NEDA (no evidence of disease activity) is of interest in evaluating new drugs for multiple sclerosis.

The applicant conducted the requested pooled analysis of NEDA-4 (no relapses, no EDSS progression, no new or enlarging T2 lesions, no new GdE lesions, and annualised brain volume loss $\leq 0.4\%$). A treatment effect in favour of ozanimod 0.92 mg versus IFN β -1a was observed for NEDA-4 at Months 12 and 24 in these post hoc analyses.

20.7% (non-responder imputation, 24.5% observed cases) and 22.7% (observed cases) in the ozanimod 0.92 mg treatment group versus 16.7% (20.4% observed cases) and 14.8% treated with IFN β -1a fulfilled the NEDA 4 criteria in the pooled analyses of both pivotal studies after 12 and 24 months, respectively.

Patients who completed the Phase 3 SUNBEAM and RADIANCE studies could enter an open-label extension study (Study 3 - DAYBREAK).

As of the data cutoff date of 30 June 2018, a total of 2,494 subjects had been enrolled and treated. The majority of the subjects were ongoing (2,323 [93.1%] subjects), and 172 (6.9%) subjects had discontinued the study. The most frequent reason for discontinuation was voluntary withdrawal in 91 [3.6%] of subjects.

760 subjects were dosed with ozanimod 0.92 mg for up to 5 years, including up to 24 months in the controlled Phase 3 studies and up to 30 months in the Phase 3 OLE (Study RPC01-3001). There were 398 subjects (52%) with at least 3 years, and 44 subjects (6%) with at least 4 years of ozanimod 0.92 mg treatment.

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 second year of treatment.

The applicant was requested to provide an updated report of the ongoing open-label long-term follow up study DAYBREAK. The US NDA 4-month safety update (4MSU) and efficacy data from DAYBREAK were submitted with a new data cutoff date of 31 Jan 2019. Compared to the original submission there were 7 months of additional follow-up data.

The updated data suggested persistent efficacy without new safety signals.

There has been no evidence of a rebound effect after termination of ozanimod treatment so far.

6.4 Safety

A total of 3,441 subjects were exposed to ozanimod in the clinical studies (2,787 subjects with RMS, 654 subjects with ulcerative colitis or Crohn's disease), including 3,276 subjects treated with ozanimod 0.92 mg and 1,098 subjects treated with ozanimod 0.46 mg.

Approximately 92% of patients in both pivotal studies (SUNBEAM, RADIANCE) were exposed to ozanimod or IFN β -1a for at least 12 months, and approximately 34% of subjects were exposed to ozanimod or IFN β -1a for at least 24 months.

Total cumulative exposures to ozanimod 0.92 mg and 0.46 mg were 1,323.3 and 1,318.0 patient-years, respectively.

The adverse reactions presented in the information for healthcare professionals are based on safety information from 882 patients treated with ozanimod 0.92 mg and 885 treated with IFN beta-1a. The most common adverse reactions were nasopharyngitis (11%), increased levels of alanine aminotransferase (5%) and increased levels of gamma-glutamyltransferase (5%).

The incidences of severe adverse events (AEs) were low and similar across the ozanimod 0.92 mg, ozanimod 0.46 mg, and IFN β -1a treatment groups (2.5%, 3.3%, and 3.3%, respectively). The incidence of moderate AEs was lower in the ozanimod treatment groups compared with the IFN β -1a treatment group, largely due to the higher incidence of moderate influenza-like illness in the IFN β -1a group.

There were six subject deaths over the entire ozanimod clinical development programme as of 30 Jun 2018. All subjects had exposure to study drug with ozanimod. Even though all cases were considered to be unrelated to study drug by the investigator/sponsor, one case of posterior reversible encephalopathy syndrome (PRES) during treatment with ozanimod 0.92mg resulted in chronic kidney failure after discontinuation of the study drug, which might be considered to be a consequence of the treatment with ozanimod. A secondary connection due to autonomic dysfunction and/or therapy with immunoglobulins with a previously occurring Guillain-Barré syndrome (GBS) (Basavaraj et al., 2014) under treatment with ozanimod cannot be excluded in this case.

A warning in the product information concerning PRES was implemented.

Based on the known biology of S1P modulators, special attention was paid to the assessment of cardiac effects, hepatic effects, infections, consequences of lymphopenia, macular oedema, malignancies, and pulmonary effects. Depression and suicidality were also identified for detailed analysis because of their association with the underlying disease state.

Cardiac effects

In the phase 3 studies of approximately 1,774 subjects treated with ozanimod, initiation of the dose escalation regimen resulted in modest and not clinically meaningful reductions in heart rate (HR) on Day 1 (mean HR reduction from baseline of 1.2 bpm with a nadir at Hour 5, with return towards baseline by Hour 6). There were no reports of HR < 40 bpm. There were no occurrences of second- or third-degree AV block. It should be noted that patients with clinically significant cardiovascular history were excluded from these studies, as were patients taking medications that reduce HR or affect cardiac conduction.

With the help of the selected dose escalation regimen, the cardiac safety profile is improved to a certain extent. However, the risk of bradyarrhythmia is still maintained in all patients, not only in patients with certain pre-existing cardiac conditions. The need for additional monitoring, at least during treatment initiation, was questioned and according contraindications and warnings implemented in the labelling. Before initiation of treatment with ozanimod, an ECG should be performed in all patients to determine whether any pre-existing cardiac conditions are present. A 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended after administration of the first dose in the case of patients with a resting HR <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure.

During chronic treatment in the phase 3 studies, subjects treated with ozanimod 0.92 mg for up to 24 months showed an increase in supine systolic blood pressure (SBP) versus IFN β -1a of 1.6 mm Hg and a 0.9 mm Hg increase versus IFN β -1a in supine diastolic blood pressure (DBP).

Hypertension as an AE was reported in a greater proportion of subjects in the ozanimod treatment groups compared with IFN β -1a (3.4%, 3.5%, and 2.0% in the ozanimod 0.92 mg, ozanimod 0.46 mg, and IFN β -1a treatment groups, respectively).

The incidence of AEs in the cardiac disorders and vascular disorders system organ classes (SOCs) did not increase with longer term exposure with ozanimod 0.92 mg.

Hepatic effects

Consistent with what has been observed with other S1P receptor modulators, hepatic enzyme elevations, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT), were seen with ozanimod treatment.

Pre-existing liver disease or male gender may be risk factors for the development of elevated hepatic enzymes when taking ozanimod. Therefore, ozanimod should be used with caution in these patients and is contraindicated in patients with severe pre-existing liver damage (Child-Pugh Class C).

In the pivotal trials, elevations of ALT to 5-fold the upper limit of normal (ULN) or above has occurred in 1.6% of patients treated with 0.92 mg of ozanimod and 1.3% of patients treated with IFN beta-1a. Elevations of 3-fold the ULN or above has occurred in 5.5% of patients on ozanimod and 3.1% of patients on IFN beta-1a. The median time to elevation of 3-fold the ULN was 6 months. The majority (79%) continued the treatment with ozanimod, with the values returning to < 3-fold the ULN within approximately 2 to 4 weeks.

In clinical trials, ozanimod has been discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes has been 1.1% of patients on 0.92 mg of Zeposia and 0.8% of patients on IFN beta-1a.

No case of Hy's law was documented.

Small increases in mean total bilirubin, primarily unconjugated bilirubin, occurred with ozanimod relative to IFN β -1a. Subjects with underlying total bilirubin elevation, including those with Gilbert's syndrome, may be at increased risk of developing elevated bilirubin when taking ozanimod.

Elevations that occurred in hepatic tests occurred were generally asymptomatic and resolved with continued treatment and were not observed to lead to severe drug-induced liver injury.

Infections

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

In the phase 3 RMS studies, the incidence of infections was similar between the ozanimod (0.92 mg and 0.46 mg) and IFN β -1a treatment groups (35.1%, 33.9%, 34.5%, respectively). Adverse events of infections leading to discontinuation of study drug were low (0.1% in all 3 treatment groups).

Ozanimod treatment in the OLE for up to 68 months demonstrated that the rate of overall infections, serious infections, and opportunistic infections did not increase over time.

The most frequently reported infections with ozanimod that occurred at $\geq 1\%$ higher incidence than with IFN β -1a were non-serious infections of the upper respiratory tract (nasopharyngitis, pharyngitis, viral respiratory tract infection) and urinary tract infection. The incidence of serious infections was low and similar across treatment groups.

There were no disseminated or serious opportunistic infections reported with ozanimod treatment.

The majority of serious infections were typical bacterial infections and resolved without clinical sequelae following standard medical management. Herpes zoster, an opportunistic infection of special interest, was infrequent in ozanimod groups but tended to increase in frequency with time.

No serious infections were reported in subjects with an ALC < 0.2×10^9 .

No case of progressive multifocal leukoencephalopathy (PML) has been reported so far.

Macular oedema (MO)

In the ozanimod RMS programme, optical coherence tomography (OCT) was used as a standard screening tool to identify subjects for further ophthalmologic examination. No trend in macular thickness changes were noted over time with repeat OCTs with mild increases balanced across groups.

A total of 7/2,787 subjects (0.3%) in the RMS clinical programme with ozanimod treatment had confirmed MO. Two confirmed cases were identified in the IBD programme. Overall, there were 9/3,441 (0.3%) confirmed cases of MO reported in the entire ozanimod programme. All cases of confirmed MO were identified with OCT findings consistent with MO, and all cases were associated with pre-existing risk factors or comorbid conditions that are known to cause MO. Eight of the 9 subjects recovered following discontinuation of study drug; the remaining case (secondary to ocular trauma) was reported to be stable as of the last available follow-up. No confirmed cases were seen in the IFN β -1a treatment group.

Malignancies

Malignancies were examined due to the potential effects of ozanimod as an immunomodulatory agent. In the pivotal trials, the incidence of AEs in the SOC of Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps) was similar across treatment groups (21 [2.4%] subjects, ozanimod 0.92 mg; 19 [2.1%] subjects, ozanimod 0.46 mg; 24 [2.7%] subjects, IFN β -1a). Subjects with a history of malignancies (other than treated basal cell carcinoma) were excluded from the phase 3 RMS studies.

Of the 10 total malignancies in the ozanimod groups (including 2 that were retrospectively determined to be pre-existing), 5 were cutaneous and 5 were non-cutaneous.

The most frequently reported cutaneous malignancy with ozanimod was basal cell carcinoma (n = 3) and the most frequently reported non-cutaneous malignancies, consistent with the mostly female RMS population, were breast cancers (n = 3). There were 2 malignancies in the IFN β -1a treatment group, a basal cell carcinoma and chronic lymphocytic leukaemia.

Pulmonary Effects

Pulmonary function is known to be affected by other S1P receptor modulators, and patients with MS may be at increased risk of respiratory problems.

Pulmonary safety for ozanimod was examined in the clinical development programme using spirometry, diffusing capacity (DLCO) and AEs related to pulmonary function designated as adverse events of special interest (AESIs) in Phase 2 and Phase 3 RMS studies.

Small decreases in these spirometry assessments were observed in the ozanimod 0.92 mg treatment group relative to the 0.46 mg or IFN β -1a treatment groups with up to 24 months of treatment. These changes were not clinically meaningful and were primarily driven by changes during the first 3 months. These early small changes for the 0.92 mg ozanimod dose were not progressive through 12 months.

Of 8 subjects with concurrent decreases in forced vital capacity (FVC) and DLCO (5 of these came from one investigator site), the baseline % predicted FVC was greater than 100 in 7 out of 8 with the 2 highest likely representing erroneous and/or unphysiological values.

Collectively, the declines in FVC in these subjects may represent regression to the mean or learning effect rather than a clinically significant reduction in lung function.

Absolute Lymphocyte Count (ALC)

Decreases in ALC are an expected treatment effect of ozanimod and were observed as early as 1 month after the start of therapy. For subjects in the ozanimod 0.92 mg and ozanimod 0.46 mg groups, sustained reduction was seen throughout the treatment period.

The decrease in ALC was dose-dependent. The number of subjects with an ALC $< 0.2 \times 10^9/L$ was higher in the 0.92 mg ozanimod group (n = 29, 3.3%) than in the ozanimod 0.46 mg group (n = 4,

0.4%) and the IFN β -1a (n = 0). The majority of these subjects (22/29 [75.9%] in the ozanimod 0.92 mg group and 3/4 [75%] in the ozanimod 0.46 mg group) recovered to levels $\geq 0.2 \times 10^9/L$ while on treatment.

Lymphocyte counts collected from approximately 200 subjects following discontinuation of study drug allowed for a post hoc assessment of off-treatment recovery of ALC).

Based on the Kaplan-Meier estimate, the median time to recovery of ALC to the normal range ($\geq 1 \times 10^9/L$) was 30 days after treatment discontinuation in the ozanimod 0.92 mg treatment group and 28 days after treatment discontinuation in the ozanimod 0.46 mg treatment group. In the ozanimod 0.92 mg treatment group, approximately 80% of subjects recovered to the normal range 2 months after treatment discontinuation and approximately 90% recovered to the normal range 3 months after treatment discontinuation. In the ozanimod 0.46 mg treatment group, approximately 80% of subjects recovered to the normal range approximately 35 days after treatment discontinuation and approximately 90% of subjects recovered to the normal range 2 months after treatment discontinuation.

Cholesterol/lipoprotein

Modest, dose-dependent, non-progressive increases from baseline in total cholesterol and low-density lipoprotein (LDL) levels were observed at Month 6 with ozanimod 0.92 mg and 0.46 mg relative to IFN β -1a. These changes were accompanied by corresponding increases in high-density lipoprotein (HDL) and no meaningful changes in triglyceride levels.

Depression and suicidal ideation or behaviour

Across the ozanimod programme, the incidence of depression and suicidal ideation or behaviour was infrequent, balanced across the treatment groups, and consistent with the background rates of these events for the MS patient population.

Pregnancy/Lactation

Non-clinical toxicology data suggest that ozanimod may - like other S1P receptor modulators - harm the unborn baby. As long as no sufficient clinical data with ozanimod are available, and as long as the results with S1P receptor modulators are inconclusive, pregnancy is a contraindication for the treatment of ozanimod. A follow-up on pregnancy outcomes in the development programme for ozanimod in the post-marketing setting as well as in the clinical trial programme (ongoing open-label extension study) is mandatory to gather sufficient data on this topic.

Available pharmacokinetic data in animals have shown excretion of ozanimod/metabolites in milk. Physicochemical data suggest the excretion of ozanimod and/or its metabolites in human milk. A risk to newborns/infants cannot be excluded.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Ozanimod is a selective S1P receptor modulator that binds to S1P₁ >> S1P₅ with high affinity. It only has a minor effect on the other S1P receptors (S1P₂₋₄).

The application of ozanimod is based on two double-blind, double-dummy, active-controlled pivotal parallel-group studies (SUNBEAM, RADIANCE).

The proposed indication was initially RMS. Since the majority of the study population (98.2%) had RRMS the indication was revised accordingly.

Treatment with ozanimod 0.92 mg showed statistically significant and clinically meaningful differences relative to the active comparator IFN β -1a in all relapse-based and MRI measures of MS disease activity in both pivotal studies.

The secondary endpoints CDP-3M and CDP-6M were not statistically significant for both doses of ozanimod. This might be explained by the relatively short duration of the controlled study phase (12 months, 24 months) and the choice of an active comparator.

A numerical dose-dependent effect was observed favouring the 0.92 mg dose over the 0.46 mg dose in both studies.

Ozanimod demonstrated an acceptable safety profile and was generally well tolerated with approximately 90% completion rates in the pivotal studies.

Potential risks [e.g. bradycardia, liver injury, infections (with/without prolonged lymphopenia), macular oedema, PRES, PML, long-term risk of malignancy, effects of withdrawal/rebound] are addressed in the information for healthcare professionals.

With the help of the selected dose escalation regimen the cardiac safety profile is improved to a certain extent. Despite that, there is still a remaining risk of bradyarrhythmia. An ECG is to be performed in all patients in order to establish the presence of pre-existing cardiac abnormalities. In patients with certain pre-existing conditions, first-dose monitoring is recommended. Based on post-marketing data, the possibility that recommendations on first-dose monitoring will have to be adjusted later on cannot be ruled out.

Non-clinical toxicology data suggest that ozanimod may harm the unborn baby. As long as clinical experience is insufficient to reach a final recommendation, pregnancy and lactation are contraindications for the treatment of ozanimod. A follow-up on pregnancy outcomes in the development programme for ozanimod in the post-marketing setting as well as in the clinical trial programme (ongoing open-label extension study) is mandatory to gather sufficient data on this topic.

In conclusion, the benefit / risk assessment of ozanimod in the indication "Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis." is considered to be positive.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Zeposia was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Zeposia[®]

Composition

Active substances

Ozanimod (as hydrochloride)

Excipients

Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, gelatin, titanium dioxide, iron oxide, printing ink (shellac, propylene glycol, potassium hydroxide, iron oxide).

One hard capsule contains 0.187 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Hard capsules containing 0.23 mg of ozanimod (equivalent to 0.25 mg of ozanimod hydrochloride)

Hard capsules containing 0.46 mg of ozanimod (equivalent to 0.5 mg of ozanimod hydrochloride)

Hard capsules containing 0.92 mg of ozanimod (equivalent to 1.0 mg of ozanimod hydrochloride)

Indications/Uses

Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

Dosage/Administration

The recommended dose of Zeposia is 0.92 mg orally once a day.

Initiation of treatment

The initial dose escalation regimen of Zeposia shown in Table 1 is required from Day 1 to Day 7. Following the 7-day dose escalation, the maintenance dosage is 0.92 mg orally once a day starting on Day 8. Initiation of Zeposia without dose escalation may result in greater reductions in heart rate (see section "Warnings and precautions").

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

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

Table 1: Dose escalation regimen

Days 1 - 4	0.23 mg once a day
Days 5 - 7	0.46 mg once a day
Days 8 and after this	0.92 mg once a day

Reinitiation of therapy following treatment interruption

The same dose escalation regimen as 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 interruption of the treatment is of a shorter duration than described above, continue the treatment with the next dose as planned.

Prior to initiation of therapy

Liver function test

The results of a recent (i.e. performed within the last 6 months) liver function test (transaminase and bilirubin levels) are to be obtained (see section "Warnings and precautions").

Blood count

The results of a recent (i.e. performed within the last 6 months or after discontinuation of the previous MS treatment) complete blood count, including the lymphocyte count) are to be obtained (see section "Warnings and precautions").

Cardiac examination

In order to check whether any pre-existing cardiac conduction abnormalities are present, an electrocardiogram (ECG) should be performed (see section "Warnings and precautions").

Ophthalmological examination

In patients with a history of diabetes mellitus, uveitis or a retinal disease, an ophthalmological examination should be performed (see section "Warnings and precautions").

(2.7.4 Summary of Clinical Safety, Section 2.1.5.4.3.2)

Current or previous medication

You can find recommendations about patients switching to Zeposia from other disease-modifying treatments and other immunosuppressive or immunomodulating treatments in "Warnings and precautions: Prior treatment with immunosuppressants or immunomodulating treatments".

Vaccinations

Before initiating treatment with Zeposia, all necessary vaccinations are to be completed in accordance with current vaccination guidelines.

No clinical data are available with regard to the efficacy and safety of vaccinations in patients who are taking Zeposia. Avoid the use of live attenuated vaccines during and for 3 months after treatment with Zeposia.

If live attenuated immunisations are required, the vaccination must be administered at least 1 month before the initiation of Zeposia.

Varicella zoster virus (VZV) vaccination of patients without documented immunity to VZV is recommended at least 1 month prior to initiating treatment with Zeposia.

Patients with impaired hepatic function

The pharmacokinetics of ozanimod have not been evaluated in subjects with severe hepatic impairment. Use in patients with severe hepatic impairment (Child-Pugh Class C) is contraindicated (see section “Contraindications”).

There have been no clinically meaningful differences in systemic exposure to ozanimod or its major active metabolite CC112273 in subjects with mild or moderate hepatic impairment (Child-Pugh Classes A and B) compared with their matched healthy subjects. No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B).

Patients with impaired renal function

No adjustment of the dose is necessary for patients with renal impairment.

There have been no clinically meaningful differences in systemic exposure to ozanimod or its active metabolites in subjects with end-stage renal disease compared with healthy subjects.

Elderly patients

Limited data are available for RRMS patients >55 years of age.

Children and adolescents

The safety and efficacy of Zeposia in paediatric and adolescent patients (<18 years) have not yet been studied.

Contraindications

- Hypersensitivity to ozanimod or any of the excipients.
- Treatment should not be initiated in patients who have experienced myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation or Class III/IV heart failure during the last 6 months.
- Treatment should not be initiated in patients who have a known history or the current presence of second-degree atrioventricular (AV) block Type II or third-degree AV block or sick sinus syndrome, unless the patient has a functioning pacemaker.
- Treatment should not be initiated in patients with severe untreated sleep apnoea.
- Immunodeficient state (see section “Warnings and precautions”).
- Patients with an increased risk of opportunistic infections, including patients who are currently receiving immunosuppressive treatment or who are immunocompromised (see section “Warnings and precautions”).
- Severe active infections or active chronic infections (hepatitis, tuberculosis) (see section “Warnings and precautions”).
- Active malignancy.
- Severe hepatic impairment (corresponding to Child-Pugh Class C).
- Active macular oedema.
- Pregnancy.

Warnings and precautions

Reduction in Heart Rate

Initiation of treatment with Zeposia

Prior to the initiation of treatment with Zeposia, an ECG is to be performed in all patients in order to establish the presence of any pre-existing cardiac abnormalities. In patients with certain pre-existing conditions, first-dose monitoring is recommended (see below).

The initiation of Zeposia may result in transient reductions in the heart rate (HR) (see section “Undesirable effects”) and, therefore, the initial dose escalation regimen to reach the maintenance dose (0.92 mg) on Day 8 should be followed (see section “Dosage/Administration”). In active-controlled MS clinical trials, the greatest mean reduction in HR compared with baseline after the initial dose of 0.23 mg of Zeposia was 1.2 beats per minute (bpm); this reduction started in Hour 4, with the greatest reduction occurring in Hour 5 of Day 1, and there was a return to near baseline at Hour 6.

Heart rates (HR) below 40 bpm have not been observed. Initiation of Zeposia without dose escalation may result in greater reductions in the heart rate.

First-dose monitoring in patients with certain pre-existing cardiac conditions

Due to the risk of transient decreases in the HR with the initiation of Zeposia, 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended after administration of the first dose in the case of patients with a resting HR <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (see section “Contraindications”).

Patients should be monitored by means of hourly pulse and blood pressure measurements during this 6-hour period. An ECG is recommended prior to and at the end of this 6-hour period.

Additional monitoring after this 6-hour period is recommended in patients with:

- a heart rate below 45 bpm;
- a heart rate at lowest value post dose, suggesting that the maximum decrease in HR may not yet have occurred;
- evidence of a new onset second-degree or higher AV block on 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 Zeposia.

Cardiologist advice should be obtained prior to the initiation of Zeposia in the following patients in order to decide whether the use of Zeposia can be safely initiated and in order to determine the most appropriate monitoring strategy:

- a history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnoea, or a history of recurrent syncope or symptomatic bradycardia;
- pre-existing significant QT interval prolongation (QTcF >450 ms in men and >470 ms in women) or other risks of QT prolongation and treatment with other medicinal products which may potentiate bradycardia;
- treatment with Class Ia antiarrhythmics (e.g. quinidine disopyramide) or Class III antiarrhythmics (e.g. amiodarone sotalol) which have been associated with cases of torsades de pointes in patients with bradycardia has not been studied in the case of Zeposia.

Elevated hepatic enzymes

Elevations of aminotransferases may occur in patients who are receiving Zeposia (see section “Undesirable Effects”).

Prior to the initiation of Zeposia, liver function tests (transaminase and bilirubin levels) are to be performed, if no recent results (i.e. from the last 6 months) are available.

If there are no clinical symptoms, the liver transaminase and bilirubin levels should be monitored at Months 1, 3, 6, 9 and 12 during treatment and periodically after this.

If the liver parameters are increased to above 5 fold the Upper Limit of Normal (ULN), the tests should be carried out more frequently. If an increase to above 5 fold the ULN is confirmed, treatment with Zeposia should be interrupted and should only be resumed in the case of normalised liver parameters.

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

Patients with pre-existing liver disease may be at an increased risk of developing elevated hepatic enzymes when taking Zeposia. Therefore, Zeposia should be used with caution in these patients.

Zeposia has not been studied in patients with severe pre-existing liver damage (Child-Pugh Class C) and it should not be used in these patients (see "Contraindications").

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

In clinical trials, Zeposia has been discontinued for a confirmed elevation which has been greater than 5 fold the ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes has been 1.1% of patients on 0.92 mg of Zeposia and 0.8% of patients on IFN beta-1a. No cases of severe drug-induced liver injury have been reported with Zeposia in active-controlled MS clinical trials.

Immunosuppressive effects

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

Infections

Risk of infections

Zeposia causes a mean reduction in the peripheral blood lymphocyte count to 45% of baseline values because of the reversible retention of lymphocytes in lymphoid tissues. Zeposia may, therefore, increase the susceptibility to infections.

A recent (i.e. obtained within the last 6 months or after the discontinuation of previous MS therapy) complete blood count, including the lymphocyte count, is to be obtained prior to the initiation of Zeposia.

Periodic assessments of the CBC are also recommended during treatment. Absolute lymphocyte counts $<0.2 \times 10^9/L$, if confirmed, should lead to interruption of Zeposia treatment until the level reaches $>0.5 \times 10^9/L$, when the reinitiation of Zeposia can be considered.

The initiation of Zeposia in patients with an active infection is to be delayed until the infection has been resolved.

In active-controlled MS clinical trials, the overall rate of infections with Zeposia (35%) has been similar to that with IFN beta-1a. Zeposia has increased the risk of viral infections of the upper respiratory tract, urinary tract infections and herpes zoster (see "Undesirable effects"). The overall rate of serious infections has been similar in the case of Zeposia (1%) and IFN beta-1a (0.8%) in active-controlled MS clinical trials.

After discontinuing 0.92 mg of Zeposia 0.92 mg, the median time taken for peripheral blood lymphocytes to return to the normal range has been 30 days, with approximately 90% of patients recovering within 3 months (see section "Properties/Effects").

If a patient develops a serious infection, interruption of the Zeposia treatment is to be considered. Because it can take up to 3 months for Zeposia to be eliminated after discontinuation, monitoring for infections is to be continued during this period.

Patients receiving Zeposia should be instructed to report symptoms of infection to their physicians. Effective diagnostic and therapeutic measures should be applied to patients who experience symptoms of infections during treatment.

If progressive multifocal leukoencephalopathy (PML) or a serious opportunistic infection is suspected, the treatment with Zeposia should be suspended until these conditions can be excluded.

Cases of herpes virus infection have been reported in the Zeposia development programme (see "Undesirable effects"). Patients without a varicella anamnesis (chickenpox) confirmed by a physician and without complete vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV prior to the initiation of Zeposia. (see subsection "Vaccinations").

Prior and concomitant treatment with antineoplastic, immunosuppressive or immune-modulating treatments

In clinical studies, patients who have received Zeposia have not been allowed to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating

therapies used for treatment of MS. The concomitant use of Zeposia with any of these treatments would be expected to increase the risk of immunosuppression.

When switching to Zeposia from immunosuppressive medications, the duration of their effects and their mode of action are to be considered in order to avoid unintended additive immunosuppressive effects (see section “Properties/Effects, Clinical efficacy”).

The use of immunosuppressive agents which deplete lymphocytes as well as the use of lymphocyte trafficking inhibitors has been excluded at all times prior to the entry of a patient to a clinical trial and so no clinical data are available.

Zeposia can generally be started immediately after the discontinuation of interferons or glatiramer acetate.

Progressive multifocal leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) which typically occurs in patients who are immunocompromised and which may lead to death or severe disability.

JCV infection resulting in PML has been observed in patients who have been treated with MS treatments and it has been associated with some risk factors (e.g. polytherapy with immunosuppressants or 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 which lead to confusion and personality changes. Physicians should be alert to the possibility of clinical symptoms or MRI findings which may be suggestive of PML. MRI findings may appear before clinical symptoms. If PML is suspected, treatment with Zeposia should be suspended until PML has been excluded.

If PML is confirmed, the treatment with Zeposia should be discontinued.

Vaccinations

No clinical data are available about the efficacy and safety of vaccinations in patients taking Zeposia. Avoid the use of live attenuated vaccines during and for 3 months after treatment with Zeposia, as they may be less effective and may increase the risk of infection.

If live attenuated vaccine immunisations are required, the vaccination must be administered at least 1 month prior to the initiation of Zeposia.

Varicella zoster virus (VZV) vaccination of patients who have no documented immunity to VZV is recommended at least 1 month prior to the initiation of treatment with Zeposia.

Cutaneous malignant diseases

Half of the neoplasias reported in controlled phase 3 studies with ozanimod have consisted of non-melanoma skin neoplasias. The most common basal cell carcinomas have occurred with similar incidence rates in the combined ozanimod (0.2%, 3 patients) and IFN β -1a groups (0.1%, 1 patient).[new reference]

As there is a potential risk of malignant skin lesions, patients who are treated with ozanimod should avoid unprotected exposure to solar radiation. These patients should not receive concurrent phototherapy with UV-B radiation or PUVA photochemotherapy.

Macular oedema

Macular oedema has been observed with Zeposia (see “Undesirable effects”) in patients with pre-existing risk factors or co-morbid conditions.

Patients with a history of uveitis or diabetes mellitus or underlying/co-existing retinal disease are at an increased risk of macular oedema (see “Undesirable Effects”). It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disease undergo ophthalmological evaluation prior to the initiation of treatment with Zeposia and that they have follow up evaluations while receiving treatment.

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

A decision on whether Zeposia should be reinitiated after resolution of the condition needs to take account of the potential benefits and risks to the individual patient.

Posterior reversible encephalopathy syndrome (PRES)

PRES is a syndrome which is characterised by the sudden onset of severe headache, confusion, seizures and visual impairment/loss. Symptoms of PRES are usually reversible, but they may evolve into ischaemic stroke or cerebral haemorrhage.

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

Delayed diagnosis and treatment can lead to chronic consequential damage. If PRES is suspected, the treatment with Zeposia must be discontinued.

Blood pressure effects

In MS clinical studies, hypertension has been 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 “Interactions” and “In vitro studies”). The blood pressure should be regularly monitored during treatment with ozanimod.

Discontinuation of treatment with Zeposia

Severe disease exacerbation, including a return of disease activity (rebound), has in rare cases been reported after the discontinuation of another S1P receptor modulator. The possibility of severe disease exacerbation after stopping Zeposia treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or the return of a high level of disease activity upon Zeposia discontinuation and appropriate treatment should be instituted as required. [new reference 2]

Co-medications

The joint administration of ozanimod with BCRP inhibitors, MAO inhibitors and CYP2C8 inducers (e.g. rifampicin) is not recommended (see "Interactions").

Other warnings

This medicine contains less than 1 mmol of sodium (23 mg) per capsule; i.e. it is almost "free of sodium".

Interactions

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites, including the two major active metabolites, CC112273 and CC1084037, and several minor active metabolites such as RP101988 and RP101075. Multiple enzyme systems play an important role in the metabolism of ozanimod and no single enzyme system determines the overall metabolism of ozanimod.

Effect of ozanimod on other medicinal products

Effects of ozanimod on oral contraceptives

The co-administration of 0.92 mg of ozanimod once a day and a single dose of oral contraceptive containing 35 µg of ethinyl estradiol (EE) and 1 mg of norethindrone (NE) has not resulted in a change in the exposure to EE or NE. The dosing duration of ozanimod was not long enough for the active main metabolites to reach steady state. However, CC112273 and CC1084037 do not have an effect on CYP enzymes *in vitro* and so they are not expected to have any effect on the exposure to EE and NE.

Effects of ozanimod on medicinal products which slow the heart rate or atrioventricular conduction (e.g. beta blockers and calcium channel blockers)

In healthy subjects, the initiation of treatment with an initial single dose of 0.23 mg of ozanimod and 80 mg of long-acting propranolol once a day at steady state or 240 mg of diltiazem once a day has

not resulted in any additional clinically meaningful changes in heart rate or PR interval compared with either propranolol or diltiazem alone. No data about possible interactions beyond the initiation dose of ozanimod are available.

The administration of ozanimod in patients receiving both a beta blocker as well as a calcium channel blocker has not been studied.

Effects of ozanimod on adrenergic agents

A placebo-controlled crossover study was conducted to assess the potential of Zeposia to enhance pressor responses to pseudoephedrine in healthy subjects. The co-administration of Zeposia with pseudoephedrine did not potentiate the pseudoephedrine-induced blood pressure response. Zeposia increased the pseudoephedrine-induced heart rate response by approximately 3 beats per minute.

Effect of other medicinal products on ozanimod

Inhibitors of the breast cancer resistance protein (BCRP)

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

Effect of strong inhibitors of CYP2C8

The co-administration of gemfibrozil (a strong inhibitor of CYP2C8) in a dose of 600 mg twice a day at steady state and a single dose of 0.46 mg of ozanimod has not resulted in clinically meaningful changes in ozanimod exposure (AUC), but it has increased the exposure (AUC) to the active metabolites CC112273 and CC1084037 by approximately 47% and 69% respectively. When co-administering ozanimod with strong CYP2C8 inhibitors, it is necessary to monitor patients, as there may be a greater risk of adverse reactions.

Effect of strong CYP3A and P-gp inhibitors

The co-administration of itraconazole (a potent inhibitor of CYP3A and P-gp) in a dose of 200 mg once a day at steady state and a single dose of 0.92 mg of ozanimod has not resulted in any clinically meaningful changes in ozanimod, CC112273 or CC1084037 exposure, suggesting that CYP3A makes only a minor contribution to the overall availability of ozanimod.

Effect of strong CYP3A/P-gp and moderate CYP2C8 inducers

The co-administration of rifampicin (a strong inducer of CYP3A and P-gp and a moderate inducer of CYP2C8) in a dose of 600 mg once a day at steady state and a single dose of 0.92 mg of ozanimod

has not resulted in any clinically meaningful changes in ozanimod exposure (AUC) and has reduced CC112273 and CC1084037 exposure (AUC) by approximately 60% as a result of CYP2C8 induction, which may result in a reduced clinical response. The co-administration of CYP2C8 inducers (e.g. rifampin) with ozanimod is not recommended.

Monoamine oxidase (MAO) inhibitors

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

In vitro studies

Effect of ozanimod and metabolites on CYP enzymes

Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on the CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6 and 3A and they do not have an induction effect on the CYPs 1A2, 2B6 and 3A.

Effect of ozanimod and metabolites on drug transporters

Ozanimod and its metabolites have no inhibitory effect on the drug transporters P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K or BCRP at clinically relevant concentrations. Therefore, ozanimod administration is not expected to have any effect on the pharmacokinetics of other medicinal products which are substrates of these transporters.

Effect of drug transporter modulators on ozanimod and major active metabolites

In vitro data show that ozanimod may be a substrate of P-gp, but the potent P-gp inhibitor itraconazole has no clinically meaningful effect on ozanimod exposure. *In vitro*, CC112273 is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, MATE1 or MATE2-K. CC1084037 is not a substrate of P-gp, BCRP, OATP1B1 or OATP1B3. The minor active metabolite RP101988 is a substrate of P-gp and BCRP.

Effect of ozanimod on MAO activity

CC112273 and CC1084037 inhibited MAO-B with IC₅₀ values of 5.72 nM and 58 nM respectively, showing more than 1'000-fold selectivity over monoaminoxidase (MAO-A) (IC₅₀>1'000 nM). In a serotonergic mouse model study, CC112273 concentrations of up to 84 nM (approximately 4 fold higher than the mean steady-state C_{max} of CC112273 [19.4 nM] in patients with relapsing MS (RMS) treated with 0.92 mg of ozanimod QD for 12 weeks did not induce signs of serotonin syndrome in normal mice or exacerbate mild serotonin syndrome in mice induced by 5-hydroxytryptophan. In a

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

Pregnancy, lactation

Women of childbearing potential/Contraception in females

Zeposia is contraindicated in women of childbearing potential who do not use effective contraception. Therefore, a negative pregnancy test result must be available and counselling about the risk to the foetus should be provided prior to the initiation of treatment in women of childbearing potential.

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

When stopping Zeposia treatment to plan a pregnancy, the possibility of a return of disease activity should be considered (see "Warnings and precautions").

Pregnancy

There are no adequate data on the developmental risk associated with the use of Zeposia in pregnant women. Studies in animals have shown foetotoxicity and teratogenicity (see "Preclinical data").

Zeposia is contraindicated during pregnancy (see "Contraindications") and is not recommended in women of childbearing potential who are not using effective contraception.

Zeposia should be stopped 3 months before planning a pregnancy. 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.

Lactation

Available pharmacokinetic data in animals have shown excretion of ozanimod/metabolites in milk (see section "Preclinical data"). Physicochemical data suggest the excretion of ozanimod and/or its metabolites in human milk. A risk to newborns/infants cannot be excluded.

A decision should be made whether to discontinue nursing or to discontinue the drug.

Fertility

No fertility data are available in humans. In animal studies, no adverse effects on fertility have been observed (see section "Preclinical data").

Effects on ability to drive and use machines

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

Undesirable effects

The adverse drug reactions were determined on the basis of data from the Zeposia clinical development programme. The frequencies of adverse drug reactions correspond to those reported in the Zeposia arms of the two active-controlled MS clinical studies. In these studies, 1774 patients received 0.92 mg of Zeposia with an overall exposure of 2'641 person years. The adverse reactions presented are based on safety information from 882 patients treated with 0.92 mg of Zeposia and 885 treated with IFN beta-1a.

The most common adverse reactions were nasopharyngitis (11%), increased levels of alanine aminotransferase (5%) and increased levels of gamma-glutamyltransferase (5%).

[\(2.5 Clinical Overview, section 5.10\)](#)

[\(Integrated Summary of Safety, Tables 25.1, 14.2, 39.1, 24.2.1\)](#)

[\(Integrated Summary of Safety, Table 55.2, 64.1, 114.1, 112.2\)](#)

The adverse reactions observed in patients treated with Zeposia are listed below by organ system and frequency for all adverse reactions in descending order of severity within each frequency group. The frequencies of the adverse reactions are defined as: very common ($\geq 1/10$); common ($< 1/10$, $\geq 1/100$); uncommon ($< 1/100$, $\geq 1/1000$); rare ($< 1/1000$, $\geq 1/10'000$); very rare ($< 1/10'000$).

Infections and Infestations

Very common: Nasopharyngitis (11%).

Common: Pharyngitis, respiratory tract infection viral, urinary tract infection.

Uncommon: Herpes zoster.

Blood and lymphatic system disorders

Common: Lymphopenia.

Immune system disorders

Uncommon: Hypersensitivity (including rash and urticaria).

Eye disorders

Uncommon: Macular oedema.*

* for patients with pre-existing factors

Cardiac disorders

Common: Bradycardia.

Vascular Disorders

Common: Hypertension, orthostatic hypotension.

Hepatobiliary disorders

Common: Alanine aminotransferase increased, gamma-glutamyltransferase increased.

Description of selected undesirable effects

Elevated liver enzymes

In clinical MS studies, ALT increased to ≥ 5 fold the ULN in 1.6% of patients treated with 0.92 mg Zeposia and in 1.3% of patients treated with IFN β -1a IM. Increases of to 3 fold occurred in 5.5% of patients treated with Zeposia and in 3.1% of patients treated with IFN β -1a IM. The median time to 3 fold the ULN was 6 months. The majority (79%) continued the treatment with Zeposia, with the values decreasing to <3 fold the ULN within about 2-4 weeks. In clinical MS studies, Zeposia was discontinued at a confirmed increase of to 5 fold the ULN. Overall, the discontinuation rate due to elevated liver enzymes was 1.1% of patients on 0.92 mg of Zeposia and 0.8% of patients on IFN beta-1a IM.

Bradycardia

In MS clinical trials, after the initial dose of Zeposia 0.23 mg, the greatest mean reduction in the HR in a sitting/lying position of 1.2 bpm from baseline after the initial dose of 0.23 mg of Zeposia occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. With continued dose escalation, there were no clinically relevant decreases in the heart rate.

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

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 has been reported in 0.6% (5/882) of patients treated with Zeposia versus 0.2% (2/885) patients treated with IFN β -1a IM. Of the cases reported with ozainomd, 0.2% were reported on Day 1 and 0.3% were reported after Day 1.

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

Increased blood pressure

In active-controlled MS clinical trials, patients treated with Zeposia had average increases in systolic blood pressure of approximately 1 to 2 mm Hg compared with IFN beta-1a, while no effect on diastolic pressure was observed. The increase in systolic pressure was first detected approximately 3 months after treatment initiation and remained stable throughout the treatment. Adverse effects associated with hypertension (hypertension, essential hypertension and high blood pressure) were reported in 4.5% of patients treated with 0.92 mg of Zeposia 0.92 mg and 2.3% of patients 3 treated with IFN beta-1a

Blood lymphocyte count reduction

In active-controlled MS clinical trials, 3.3% of patients had lymphocyte counts less than $0.2 \times 10^9/L$, with values generally resolving to greater than $0.2 \times 10^9/L$ with continued treatment with Zeposia. After discontinuing the 0.92 mg of Zeposia, the median time taken for the peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients recovering within 3 months.

Infections

In clinical MS studies, the total infection rate (35%) of 0.92 mg of Zeposia was similar to that with IFN β -1a. Zeposia increased the risk of upper respiratory tract infections and urinary tract infections. The overall rate of serious infections was similar between Zeposia (1%) and IFN β -1a IM (0.8%) in clinical MS studies.

Herpes zoster

In active-controlled MS trials, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with 0.92 mg of Zeposia and in 0.2% of patients on IFN beta-1a.

Respiratory system

Slight dose-dependent reductions in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) have been observed with Zeposia treatment. In Months 3 and 12 of treatment in the clinical MS studies, the median changes in FEV1 (FVC) from baseline in the 1 mg of Zeposia group were -0.07 l and -0.1 l (-0.05 l and -0.065 l) with minor changes from baseline in the IFN β -1a group (FEV1: -0.01 l and -0.04 l; and FVC: 0.00 l and -0.02 l).

Hypersensitivity

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIVIS (Electronic Vigilance System) portal. You can find information about this at www.swissmedic.ch.

Overdose

Patients should be managed by symptomatic and supportive care in the event of an overdose. In particular, patients should be examined for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of the heart rate and blood pressure are necessary and an ECG should be performed. Where necessary, a decrease in the heart rate can be treated by the parenteral administration of atropine or isoprenaline.

Properties/Effects

ATC code

L04AA38

Mechanism of action

Ozanimod is a sphingosine 1-phosphate receptor modulator, which selectively binds with high affinity to sphingosine 1-phosphate receptor subtypes 1 and 5 (S1P₁ and S1P₅). Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts its therapeutic effects in multiple sclerosis (MS) is not known, but it may involve the reduction of lymphocyte migration into the central nervous system.

Ozanimod is 10 fold more selective for S1P₁ than for S1P₅ and it has little activity on other S1P receptors (S1P₂, S1P₃ and S1P₄). Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites. *In vitro*, ozanimod and its active metabolites have demonstrated similar activity and selectivity for S1P₁ and S1P₅. In humans, approximately 94% of the total exposure to the circulating active substance is accounted for by ozanimod (6%), CC112273 (73%) and CC1084037 (15%).

Pharmacodynamics

Reduction in peripheral blood lymphocytes

The main pharmacodynamic effect of S1P receptor modulators is an exposure-dependent reduction in the absolute lymphocyte count, which is believed to be an important mechanism in the achievement of the clinical benefit.

In active-controlled MS clinical trials, mean lymphocyte counts decreased to approximately 45% of baseline at 3 months (approximate mean blood lymphocyte counts $0.8 \times 10^9/L$) and remained stable during treatment with Zeposia.

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

Heart rate and rhythm

Zeposia may cause a transient reduction in the heart rate on the initiation of dosing. A dose escalation schedule starting with 0.23 mg of Zeposia followed by doses of 0.46 mg and 0.92 mg attenuates the magnitude of heart rate reductions. The maximum effect on the heart rate occurs within 5 hours post dose. After the dose escalation period, the heart rate returns to baseline with the continued administration of Zeposia.

At treatment initiation, cardiac monitoring is required for the first six hours in patients with pre-existing cardiovascular conditions (see "Warning and precautions").

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 QD for 4 days, 0.46 mg QD for 3 days, 0.92 mg QD for 3 days, and 1.84 mg QD for 4 days in healthy subjects, no evidence of QTc prolongation was observed as demonstrated by the upper boundary of the 95% one-sided confidence interval (CI), which was below 10 ms. The 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 the model-derived QTc (corrected for placebo and baseline) to be below 10 ms at maximum concentrations achieved with Zeposia doses >0.92 mg once a day.

Clinical efficacy

Zeposia was evaluated in two randomised, double-blind, double-dummy, parallel-group, active-controlled clinical trials of similar design and endpoints in patients with predominantly (98.2%) relapse-remitting MS (RRMS) treated for at least 1 year (Study 1 (SUNBEAM) - Treatment continued for all patients until the last enrolled patient completed 1 year) and 2 years (Study 2 (RADIANCE)).

The doses of Zeposia were 0.92 mg and 0.46 mg given orally once a day, 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 after this. The dose of the active comparator, IFN beta-1a, was 30 mcg given intramuscularly (IM) once a week. Both studies included patients who had experienced at least one relapse in the previous year or one relapse in the previous two years with evidence of at least one

gadolinium-enhancing (GdE) lesion in the previous year and who had an Expanded Disability Status Scale (EDSS) score of 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), after 6 months (Study 1), after 1 year (Studies 1 and 2) and after 2 years (Study 2).

Patients who were MS treatment naïve or who had received previous MS therapies were eligible for inclusion in the clinical studies. Not eligible for inclusion in the studies were patients who received one of the following MS therapies: lymphocyte trafficking inhibitors (fingolimod, natalizumab), immunosuppressive agents which deplete lymphocytes (e.g. alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone), total body irradiation and bone marrow transplantation.

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

In Study 1, 1'346 patients were randomised to receive 0.92 mg of Zeposia (n = 447), 0.46 mg of Zeposia (n= 451) or IFN beta-1a (n = 448); 94% of patients treated with 0.92 mg of Zeposia, 94% of patients treated with 0.46 mg of Zeposia and 92% of patients treated with IFN beta-1a-completed the study. The mean age was 35.6 years; 66% of patients were female; and the mean time since MS symptom onset was 7 years. The mean EDSS score at baseline was 2.62; 70% had not previously been treated with a disease-modifying therapy. At baseline, the mean number of relapses in the previous year had been 1.3 and 47% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The median duration of treatment was 13.6 months.

In Study 2, 1'313 patients were randomised to receive 0.92 mg of Zeposia (n = 433), 0.46 mg of Zeposia (n = 439) or IFN beta-1a (n = 441); 90% of patients treated with 0.92 mg of Zeposia, 85% of patients treated with 0.46 mg of Zeposia and 85% of patients treated with IFN beta-1a-treated patients completed the study. The mean age was 35.5 years; 67% of patients were female; the mean time since MS symptom onset was 6.5 years and the mean EDSS score at baseline was 2.51; and approximately one-third (29%) of the patients had previously been treated with a disease-modifying therapy, predominately interferon or glatiramer acetate. At baseline, the mean number of relapses in

the previous year was 1.3 and 43% of the patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The median duration of treatment was 24 months.

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

Three month- and six month-confirmed disability progression were low and similar between Zeposia and IFN beta-1a-treated patients over 2 years. The difference was not statistically significant.

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

The results for Study 1 and Study 2 are shown in Table 2.

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

Endpoints	Study 1 (SUNBEAM) (≥ 1 year)		Study 2 (RADIANCE) (2 year)	
	Zeposia 0.92 mg (n=447) %	IFN β-1a IM 30 mcg (n=448) %	Zeposia 0.92 mg (n=433) %	IFN β-1a IM 30 mcg (n=441) %
Clinical endpoints				
Annualised relapse rate (primary endpoint)	0.181 ^a	0.350 ^a	0.172	0.276
Relative reduction	48% (p<0.0001)		38% (p<0.0001)	
Proportion relapse-free Kaplan-Meier estimate ^b	78% 0.781 (p=0.0002) ^c	66% 0.663	76% 0.756 (p=0.0012) ^c	64% 0.642
Proportion of patients with 3-Month confirmed disability progression (CDP) ^d	7.6% Zeposia vs. 7.8% IFN β-1a IM			
Hazard ratio (95% CI)	0.95 (0.679, 1.330) p=0.7651			
Proportion of patients with 6-Month confirmed disability progression (CDP) ^d	5.8% Zeposia vs. 4.0% IFN β-1a IM			
Hazard ratio (95% CI)	1.413 (0.922-2.165) p=0.1126			
MRI endpoints				
Mean number of new or enlarging T2 hyperintense lesions per MRI ^e	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 ^f	0.160	0.433	0.176	0.373
Relative reduction	63% (p<0.0001)		53% (p=0.0006)	

^a Through the treatment period (mean duration 13.6 months).

^b Over treatment period for Study 1 and over 24 months for Study 2.

^c Based on log rank test.

^d Disability progression defined as 1-point increase in Expanded Disability Status Scale (EDSS) confirmed 3 months or 6 months later.

^e Over 12 months for Study 1 and over 24 months for Study 2.

^f At the end of the treatment duration for each study i.e. at 12 months for Study 1 and at 24 months for Study 2.

In Studies 1 and 2, treatment with Zeposia 0.92 mg resulted in reductions in mean percentage change (loss) from baseline in normalised brain volume compared with IFN beta-1a IM (-0.41% versus -0.61% and -0.71% versus -0.94% respectively, nominal p-value <0.0001 for both studies).

Patients who completed the 12- and 24-month main studies were able to enter an open label extension [OLE] study (Study 3 - DAYBREAK) and receive 0.92 mg of Zeposia. Of 760 patients initially randomised to 0.92 mg of Zeposia who entered Study 3, there was a mean cumulative exposure of approximately 3 years. In these patients, the ARR was 0.148 over the cumulative treatment period.

Pharmacokinetics

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 S1P₁ and S1P₅ to the parent drug. The maximum plasma concentration (C_{max}) and area under the curve (AUC) for ozanimod, CC112273 and CC1084037 increased proportionally over the dose range of Zeposia of 0.46 mg to 0.92 mg (0.5 to 1 fold the recommended dose).

Following multiple dosing, approximately 94% of the circulating total active drug exposure is accounted for by ozanimod (6%), CC112273 (73%) and CC1084037 (15%).

At an oral dose of 0.92 mg orally once a day in RRMS patients, the geometric mean [coefficient of variation (CV%)] C_{max} and AUC_{0-24h} at steady state were 231.6 pg/mL (37.2%) and 4'223 pg*h/mL (37.7%) respectively, for ozanimod and 6'378 pg/mL (48.4%) and 132'861 pg*h/mL (45.6%) respectively for CC112273. The C_{max} and AUC_{0-24h} for CC1084037 are approximately 20% of those for CC112273.

Factors affecting CC112273 are also applicable for CC1084037, as they are interconverting metabolites.

Absorption

Following oral administration, the median time to maximum plasma concentration (T_{max}) of ozanimod was approximately 6 to 8 hours. Food intake (high- and low-fat meals) did not alter ozanimod exposure. Food is not expected to have an effect on the metabolism or elimination of metabolites since food only affects the absorption of the parent drug. Thus, ozanimod can be administered with or without food.

Distribution

The mean (CV%) apparent volume of distribution of ozanimod (V_z/F) was 5'590 L (27%), indicating extensive tissue distribution. Binding of ozanimod, CC112273 and CC1084037 to human plasma proteins is high at approximately 98.2%, 99.8%, and 99.3%, respectively.

Metabolism

Ozanimod was extensively metabolized in humans with a number of metabolites identified in plasma, urine and feces. Multiple enzyme systems play an important role in the metabolism of ozanimod and

no single enzyme system predominates in the overall metabolism of ozanimod. The oxidative pathway to formation of carboxylate metabolite RP101988 is mediated by ALDH/ADH while formation of RP101075 by dealkylation is predominantly carried out by CYP3A4. RP101075 is N-acetylated by NAT-2 to form RP101442 or deaminated by MAO-B to form the major metabolite CC112273. CC112273 is either reduced to form CC1084037 or undergoes CYP2C8 mediated oxidation to form RP101509. CC1084037 is oxidized rapidly to form CC112273 by AKR 1C1/1C2, and/or 3 β - and 11 β -HSD and undergoes reversible metabolisation to CC112273. The oxido-reduction interconversion between CC112273 and CC1084037 favours the formation of CC112273 and there are no direct metabolites of CC1084037 other than its metabolisation to CC112273 and its subsequent elimination via that pathway. *In vivo*, gut microbial flora plays an important role in the formation of many inactive metabolites via anaerobic reductive metabolism of the oxadiazole ring system.

Elimination

The mean (CV%) 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 an estimated accumulation ratio following repeated oral administration of 0.92 mg once a day 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 a mean (CV%) time to steady state of approximately 45 days (45%) and an accumulation ratio of approximately 16 (101%). Plasma levels of CC112273 and its direct, interconverting metabolite CC1084037 declined in parallel in the terminal phase, yielding a similar $t_{1/2}$ for both metabolites. Steady state attainment and accumulation ratios 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 and it was primarily composed of inactive metabolites. The concentrations of ozanimod, CC112273 and CC1084037 in the urine were negligible, indicating that renal clearance is not an important excretion pathway for ozanimod, CC112273 or CC1084037.

Kinetics in specific patient groups

Hepatic impairment

In a dedicated hepatic impairment trial, the exposures (AUC_{last}) for ozanimod and CC112273 were approximately 11% lower and 31% lower respectively in subjects with mild hepatic impairment (Child-Pugh A; N=8) when compared with subjects with normal hepatic function (N=7) following a single oral dose of 0.23 mg of ozanimod. Exposures (AUC_{last}) for ozanimod and CC112273 were approximately

27% higher and 33% lower respectively in subjects with moderate hepatic impairment (Child-Pugh B; N=8) when compared with subjects with normal hepatic function (N=8). These differences were not considered clinically meaningful. The pharmacokinetics of ozanimod were not evaluated in patients with severe hepatic impairment.

Renal impairment

In a dedicated renal impairment trial, 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 subjects with normal renal function (N=8). following a single oral dose of 0.23 mg ozanimod Based on this trial, renal impairment had no clinically important effects on pharmacokinetics of ozanimod or CC112273.

Elderly patients

No pharmacokinetic data and insufficient clinical data are available regarding the administration of Zeposia to patients aged 55 years and over.

Children and adolescents

No data are available regarding the administration of Zeposia to paediatric or adolescent patients (<18 years of age).

Gender

While the population pharmacokinetics of ozanimod are not affected by gender, CC112273 steady-state exposure (AUC) was 35% lower in males than in females. The effect of gender on CC112273 exposure was not considered to be clinically meaningful.

Smoking

Population pharmacokinetic results showed that CC112273 steady-state exposure (AUC) was 50% lower in smokers than in non-smokers. The clinical effects of smoking on ozanimod treatment for patients with RRMS is not known.

Preclinical data

In general toxicology studies conducted in rats (26 weeks) and monkeys (39 weeks), ozanimod produced lymphopenia which was similar to the decreases in lymphocytes observed in humans. In these studies, ozanimod increased lung weights and increased the incidence of mononuclear alveolar

infiltrates. Ozanimod administration to rats also had an inhibitory effect on T-cell-dependent IgG and IgM antibody responses.

At the no observed adverse effect levels (NOAELs) 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 drug (ozanimod combined with the mentioned metabolites), were lower than those expected in patients at the maximum human dose of 0.92 mg ozanimod.

Mutagenicity

Overall, ozanimod and main metabolites do not exhibit any *in vitro* or *in vivo* genotoxicity concerns.

Carcinogenicity

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 tumors were present at any ozanimod dose (up to 19 fold above the recommended human equivalent dose (RHED)). However, exposures of metabolites at the highest dose tested were 62% (CC112273) and 18% (CC1084037) of human exposures at the maximum clinical dose of 0.92 mg ozanimod.

In the 6-month Tg.rasH2 mouse study, a dose-related statistically significant increase in haemangiosarcomas was observed from the lowest dose. Haemangiosarcomas in mice treated with S1P₁ agonists are thought to be species specific and not predictive of a risk in humans. At the lowest dose, the total ozanimod exposure was 1'680-fold, that of CC112273 was 2.95 fold and that of CC1084037 was 1.4 fold human exposure at a clinical dose of 0.92 mg of ozanimod.

No other treatment-related tumors were present at any dose in the Tg.rasH2 mouse study.

Reproductive toxicity

Fertility was examined in male and female rats dosed for two weeks prior to and during mating. No effects on fertility were present at the highest dose tested. Exposure multiples (AUC₀₋₂₄) were 2'550 fold for ozanimod, 14.7 fold for CC112273 and 3.08 fold for CC1084037.

In reproductive toxicity studies, foetal toxicity was observed in rats and rabbits during embryogenesis. The manifestations of oetal toxicity included embryo-foetal death, abnormal and delayed ossification, visceral abnormalities and malformations of the major blood vessels. The cumulative exposure multiples (AUC₀₋₂₄) of the active substances were below 4 (for the NOAEL in the rat) and below 1 (for the rabbit).

Pre- and post-natal development were not affected by ozanimod administration in rats up to the highest dose tested (2 mg/kg/day). The rat NOAEL exposure margins (AUC_{0-24}) were 90.2 fold for ozanimod and they were below 1 for both metabolites (CC112273 and CC1084037).

Ozanimod and its metabolites were detected in rat milk.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 25°C. Keep out of the reach of children.

Authorisation number

67046 (Swissmedic)

Packs

Zeposia 0.23 mg/0.46 mg: 7 hard capsules (4 x 0.23 mg, 3 x 0.46 mg) initiation pack (B)

Zeposia 0.92 mg: 28 hard capsules (B)

Marketing authorisation holder

Celgene GmbH, Zürich

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