Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ozanimod hydrochloride

Proprietary Product Name: Zeposia

Sponsor: Celgene Pty Ltd

November 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
%CV	Coefficient of variation
ACM	Advisory Committee on Medicines
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific Annex
AUC	Area under the plasma concentration-time curve
BBB	Blood brain barrier
CC112273	Major ozanimod metabolite
CC1084037	Major ozanimod metabolite
C_{max}	Maximum (peak) plasma drug concentration
CNS	Central nervous system
CYP	CYP P450 enzyme family
DDI	Drug-drug interaction
DLP	Data lock point
EU	European Union
FEV_1	Forced expiratory volume in 1 second
GLP	Good Laboratory Practice
HCP	Healthcare professional
ICH	International Conference on Harmonisation
IFN β1a	Interferon beta-1-a (also known as interferon beta-1-alpha)
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Affairs

Abbreviation	Meaning
mmHg	Millimetres of mercury (blood pressure measurement)
MS	Multiple sclerosis
PASS	Post-authorisation safety study
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PopPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
QTc	Cardiac TQ interval corrected for heart rate
QTi	Cardiac QT interval
RMS	Relapsing multiple sclerosis (including both relapsing remitting; and secondary progressive multiple sclerosis)
RRMS	Relapsing remitting multiple sclerosis
RMP	Risk management plan
S1P	Sphingosine-1-phosphate
S1P1	Sphingosine-1-phosphate receptor 1 subtype
S1P5	Sphingosine-1-phosphate receptor 5 subtype
SAE	Serious adverse event
SOC	System Organ Class
SPMS	Secondary progressive multiple sclerosis
$T_{1/2}$	Half life
T_{max}	Time to reach maximum (peak) plasma concentration following drug administration

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Zeposia
Active ingredient:	Ozanimod hydrochloride
Decision:	Approved
Date of decision:	16 July 2020
Date of entry onto ARTG:	17 July 2020
ARTG numbers:	318800; 318801
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Celgene Pty Ltd Level 15 / 60 City Road Southbank, VIC, 3006
Dose form:	Capsule
Strengths:	230 µg; 460 µg composite pack; and 920 µg capsules
Containers:	Blister pack, blister wallet composite pack
Pack sizes:	Blister pack of 28 x 920 µg capsules Blister wallet composite pack of 7 capsules (4 x 230 µg capsules and 3 x 460 µg capsules)
Approved therapeutic use:	*Zeposia is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis.*
Route of administration:	Oral

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Dosage:	The recommended dose of Zeposia for adults is 920 µg once daily taken orally, following an initial 7 day dose escalation regimen. Treatment should be initiated under the supervision of a physician experienced in the management of multiple sclerosis (MS). Zeposia capsules should be swallowed whole and can be administered with or without food. If a dose of Zeposia is missed, the next scheduled dose should be taken the following day. The initial dose escalation regimen of Zeposia from Day 1 to Day 7 and thereafter is as follows: • Days 1 to 4: 230 µg capsule, once daily • Days 5 to 7: 460 µg capsule, once daily • Days 8 and thereafter: 920 µg capsule, once daily. Initiation of Zeposia without dose escalation may result in greater reductions in heart rate (see Section 4.4 of the Product Information (PI)). For further information regarding dosage, refer to the Product Information.
Pregnancy category:	Category D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Celgene Pty Ltd (the sponsor) to register Zeposia (ozanimod hydrochloride) 230 µg; 460 µg and 920 µg oral capsules for the following proposed indication:

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

Ozanimod hydrochloride;[2] is an orally bioavailable sphingosine 1-phosphate (S1P) receptor agonist, which binds with high affinity and selectivity to S1P receptor subtype 1 (S1P1) and S1P receptor subtype 5 (S1P5).[3]

[2] Ozanimod hydrochloride has also been known by the drug development code RPC1063.

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system (CNS) characterised by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier (BBB). Autoreactive lymphocytes attack and destroy the myelin sheath surrounding nerve cells, resulting in demyelination and axonal damage, leading to irreversible deficits in physical function and cognition, and an impaired quality of life) with an increased socio-economic burden on patients and families.

Incidence and prevalence of MS varies between regions and countries. Prevalence of MS is increasing and is estimated to affect 2.3 million persons worldwide. In Europe, highest prevalence of MS occurs in countries with high latitude; for example, in Denmark (232 persons per 100,000 population) and the United Kingdom (UK; at 164 per 100,000), and the lowest prevalence of MS is reported in Portugal (56.2 per 100,000). This compares with an estimated prevalence in Australia of 125 per 100,000 (estimated 23,700 persons or 0.1% of the Australian population have MS). Prevalence of MS is highest in Tasmania and almost double that of Queensland and Western Australia. Onset of MS typically occurs between 20 to 40 years of age and predominantly affects females (2 to 3 fold higher frequency than males).

Relapsing-remitting multiple sclerosis (RRMS) is the most common form of MS, representing approximately 85% of patients at diagnosis. The course of RRMS is unpredictable, with variable periods of disease activity interspersed with periods of stability. Approximately 50% patients with RRMS will, within the first 10 years after diagnosis, develop secondary progressive multiple sclerosis (SPMS), which is characterised by worsening disability in the absence or independent of relapses. Relapsing forms of multiple sclerosis (RMS) include patients with RRMS; and those with SPMS with superimposed relapses. Primary progressive multiple sclerosis (PPMS) is the presenting form of approximately 15% patients at diagnosis, characterised by chronic worsening of disability early in the disease and in the absence of relapses. A small subset of patients has chronic worsening of disability with some relapse activity at disease onset, referred to as progressive relapsing multiple sclerosis (PRMS).

Relapses, acute episodes of neurological dysfunction, are considered to represent the clinical sequelae of the inflammatory focal lesions, and progression is considered associated with demyelination, impaired remyelination, axonal loss and neuronal loss.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

The submitted clinical data package for Australia, United States (US; initial submission 22 December 2017, with a resubmission on 25 March 2019), Switzerland (submitted 6 May 2019) and European Union (EU; centralised procedure, submitted 6 March 2019) was the same, apart from differences due to local regulatory agency requirements.

The Australian submission has been adopted from the EU submission. The proposed indications in Australia, US and Switzerland were identical. The proposed EU indication was for adults with *relapsing-remitting* MS, not for all relapsing forms as proposed in other jurisdictions.

At the time the submission was under consideration, a similar application has been approved in the EU (approved on 20 May 2020) and the US (approved on 20 March 2020), and was under consideration in Switzerland and Canada.

[3] Sphingosine-1-phosphate (S1P) is a signaling sphingolipid (or lysosphingolipid), and can be referred to as a bioactive lipid mediator. Sphingolipids at large form a class of lipids characterised by a particular aliphatic aminoalcohol, which is sphingosine.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2019-02397-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2019
First round evaluation completed	27 February 2020
Sponsor provides responses on questions raised in first round evaluation	26 March 2020
Second round evaluation completed	15 April 2020
Delegate's Overall benefit-risk assessment	1 July 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	16 July 2020
Completion of administrative activities and registration on the ARTG	17 July 2020
Number of working days from submission dossier acceptance to registration decision*	218 days

*Statutory timeframe for standard applications is 255 working days

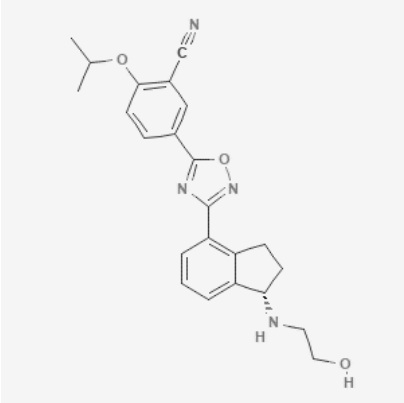
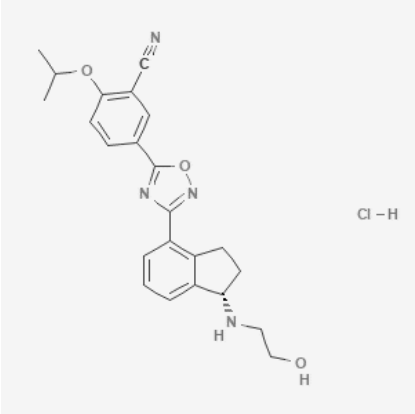
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Table 2, shown below, summarises the structures, molecular weights and formulae for both ozanimod and ozanimod hydrochloride.

Table 2: Ozanimod and ozanimod hydrochloride drug structure, molecular weights and formulae

Chemical information		
Structure	Ozanimod 	Ozanimod hydrochloride 
Molecular formula	Ozanimod: $C_{23}H_{24}N_4O_3$ Ozanimod hydrochloride: $C_{23}H_{24}N_4O_3.HCl$	
Molecular weight	Ozanimod: 404.5 g/mol Ozanimod hydrochloride: 440.9 g/mol	

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Overall, approval is recommended from a pharmaceutical chemistry and quality perspective.

Nonclinical

There are no major deficiencies in the nonclinical dossier provided by the sponsor.

The nonclinical evaluation provided the following overall summary:

- The submitted nonclinical dossier was in accordance with the relevant TGA-adopted International Conference on Harmonisation (ICH) guideline.[4] The overall quality of the nonclinical dossier was high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (oral capsule).
- The primary pharmacology studies support the proposed indication for ozanimod.
- Secondary pharmacodynamics and safety pharmacology studies did not identify clinically relevant hazards aside from the known transient bradyarrythmias;[5] that also occur with other members of the same drug class.[6]

[4] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, current Step 4 version dated 11 June 2009. Available from the ICH website.
[5] **Bradyarrythmia** (also known as bradycardia) is typically defined as a resting heart rate of < 60 beats per minute. The occurrence of bradycardia alone is not necessarily indicative of symptomatic problems.
[6] Drug class: Sphingosine-1-phosphate (S1P) receptor agonists; Anatomical therapeutic chemical (ATC) code: L04AA

- Changes in lymphocytes and lymphoid lesions in repeat dose studies were consistent with the pharmacological action of the drug. The lung was identified as a possible target organ in the repeat-dose toxicity studies. The effects seen did not cause clinical symptoms and were reversible. Due to the low relative exposure at the no-observed adverse effect level;[7] in monkeys, and to the chronic nature of treatment with ozanimod, monitoring of pulmonary function is recommended.
- Ozanimod is not considered to pose a genotoxic or carcinogenic hazard to patients.
- The sponsor has proposed Pregnancy Category D for ozanimod;[8] which is acceptable and consistent with the nonclinical data and the previous categorisation of other drugs in this class.

Overall, there are no nonclinical objections to the registration of ozanimod.

Clinical

Clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety studies. The submission contained the following clinical information:

Multiple sclerosis specific studies, summaries or general clinical pharmacology data

- 16 Phase I clinical pharmacology studies: 10 pharmacokinetic (PK) and/or pharmacodynamic (PD) studies and 6 drug-drug interaction (DDI) studies; and 1 population PK (PopPK) analysis.
- 3 controlled efficacy and safety studies:
  - Study RPC01-301 (Phase III, pivotal);[9]
  - Study RPC01-201A (Phase II dose-finding study with blinded extension: (Study RPC01-201A-Ext);[10] and
  - Study RPC01-201B (Phase III, pivotal).[10]
- 1 long-term open-label extension study:
  - Study RPC01-3001 (comprised of subjects who completed Studies RPC01-1001, 1 year of Study RPC01-201A-Ext, Study RPC01-301 and Study RPC01-201B).[11]
- 2 integrated summaries: 1 integrated summary of safety and 1 integrated summary efficacy.
- Literature references.

[7] The **no-observed adverse effect level (NOAEL)** denotes the highest level of exposure in an organism, found via experiment or observation, at which there is no biologically or statistically significant increase in the frequency or severity of any adverse effects of the tested protocol.
[8] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[9] Study RPC01-301; title: 'A Phase 3, multi-center, randomized, Double-Blind, double-dummy, active controlled, parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to relapsing multiple sclerosis patients.' EudraCT Number: 2014-002320-27; NCT identifier: NCT02294058.
[10] Study RPC01-201A; title: '(Part A) A Phase 2/3, Multi-center, Randomized, Double-blind, Placebo-controlled (Part A) and Double-Blind, Double-dummy, Active-controlled'; and Study RPC01-201 (Part B), Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients'. EudraCT Number: 2012-002714-40; NCT identifier: NCT01628393.
[11] Study RPC01-3001; title: 'A Multi-Site, Open-Label Extension Trial of Oral RPC1063 in Relapsing Multiple Sclerosis'. EudraCT number: 2015-002500-91; NCI identifier: NCT02576717.

Studies for other indications[12]

In ulcerative colitis:

- 3 controlled efficacy and safety studies:
  - Study RPC01-202 (Phase II);
  - Study RPC01-202 OLP (Phase II, open label period); and
  - Study RPC01-3102 (Phase III open label extension); and

In Crohn's disease:

- Study RPC01-2201 OL induction (Phase II, open label induction).

Pharmacology

Pharmacokinetics

In general, comprehensive data (several Phase I trials along with additional data from Phase II and III studies) was provided in the application dossier to support the proposed indication and proposed product information of oral ozanimod in adults with RMS. Model-estimated pharmacokinetic (PK) parameters (for example, half-life ($T_{1/2}$), time to steady state, apparent total clearance of the drug from plasma after oral administration (CL/F) and apparent volume of distribution during terminal phase after non-intravenous administration (VZ/F)) were consistent with the results from the designated PK studies.

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites. Ozanimod and its major active metabolites have similar activity and selectivity for S1P1 and S1P5. Following multiple dose administration of ozanimod in healthy subjects, ozanimod, and the metabolites CC112273 and CC1084037 each represented approximately 6%, 73% and 15% of circulating total active drug exposure, respectively.

The time to reach maximum (peak) plasma concentration following drug administration (T_{max}) of ozanimod is approximately 6 to 8 hours. T_{max} for the major active metabolites is variable with median values between 6 and 10 hours. Plasma protein binding of ozanimod, CC112273 and CC1084037 to human plasma proteins is approximately 98.2%, 99.8% and 99.3%, respectively. The $T_{1/2}$ of ozanimod is approximately 20 hours, while the $T_{1/2}$ of CC112273 and CC1084037 is about 236 to 308 hours, leading to accumulation of these active metabolites (relative to the parent) after multiple dosing. Metabolite-to-parent ratio for CC112273 is approximately 16 fold at steady state. Exposure of ozanimod and CC112273 increased dose-proportionally in the dose range of 0.5 mg to 1 mg. Ozanimod, CC112273, and CC1084037 concentrations in urine were negligible, indicating that renal clearance is not an important excretion pathway. Inter-subject variability (% CV) in the maximum (peak) plasma drug concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for ozanimod, CC112273 and CC1084037, in healthy and RMS subjects, and for single and repeated dosing regimens, ranged from 20% to 40%. No data was provided for administration of oral ozanimod for paediatrics, adolescents (< 18 years of age) or persons aged 55 years and over.

Generally, the PK of ozanimod were not significantly different between healthy adult subjects and adults with RMS. In addition, ozanimod can be taken without regard to food. No dose-adjustment should be necessary based on sex, adult age, bodyweight, mild or moderate hepatic impairment status, severe renal impairment status or the presence of RMS.

[12] These studies provided supportive safety information only.

Ozanimod is not recommended with MAO inhibitors;[13] strong CYP2C8 inhibitors;[14] strong CYP inducers, breast related cancer protein (BRCP) Inhibitors.

A few issues raised by the clinical evaluator needed further clarification. Despite some batch variability in some excipients used in the pivotal Phase III clinical studies, the fill-weight overages used in Formulation 2 compared to Formulation 3 (commercial product) did not adversely influence the bioavailability comparison between these formulations. Distribution and elimination of ozanimod and CC112273 did not appear to be affected by genetic polymorphism of enzymes, thereby indicating no significant racial differences in the treatment effect. PK information in the draft PI is generally satisfactory.

Pharmacodynamics

Generally, the pharmacodynamic (PD) data provided in the clinical dossier were sufficiently comprehensive to support the proposed indication of oral ozanimod in adults with RMS. Plasma concentration-effect relationships were defined for many important secondary PD effects, including effects on QT interval;[15] and dose-related effects on heart rate. Secondary PD effects were generally consistent with C_{max} and total exposure (AUC).

The thorough QT study;[16] did not reveal clinically meaningful effects of ozanimod treatment, or the major active metabolites, CC112273 and CC1084037, on QT prolongation. A transient dose-dependent negative chronotropic effect was demonstrated with ozanimod over the dose range 0.3 mg to 3 mg ozanimod in Study RPCS-001, on Day 1 of treatment. This effect is consistent with S1P receptor modulation. Introduction of a 7 day long dose escalation regimen across the Phase I studies, starting with 0.25 mg ozanimod on Day 1, helped to mitigate against most of the first-dose effect and the continued negative chronotropic effect observed during dose escalation.

Dose-and time-dependent reductions in absolute lymphocyte count (ALC);[17] were observed across the Phase I studies, which was an expected pharmacological effect reported with S1P receptor modulation. The time-course and magnitude of the ALC reductions were generally consistent with other marketed S1P receptor agonists.

[13] **Monoamine oxidase inhibitors (MAOIs)** are a class of drugs that inhibit the activity of one or both isoforms of the **monoamine oxidase (MAO)** enzymes: **monoamine oxidase A (MAO-A)** and **monoamine oxidase B (MAO-B)**. MAOIs act by inhibiting the activity of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters and thereby increasing their availability. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine. MAO-B preferentially deaminates phenethylamine and certain other trace amines; in contrast, MAO-A preferentially deaminates other trace amines, like tyramine, whereas dopamine is equally deaminated by both types.

[14] **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[15] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

[16] A thorough QT study examines the pharmacokinetic/pharmacodynamics potential for the pharmacologic prolongation of the QT interval that can be affected by some drugs. The **corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

[17] The **absolute lymphocyte count (ALC)** is the determination of the number of lymphocytes (or white blood cells) in a blood sample or biological specimen.

Major anticipated clinical safety concerns based on the claimed mechanism of action include immune-related events, bradycardia, hypertension (elevated systolic and/or diastolic blood pressure) and associated cardiovascular events (for example tachycardia;[18] and palpitations).

Overall, the PD information in the draft PI is generally satisfactory.

Dosing

The dosing regimens used in the pivotal efficacy studies were based on a combination of PK, efficacy and safety data derived from the Phase II dose finding Study RPC01-201A, as well as additional safety, PK and PD data obtained from the phase I clinical program. The introduction of a 7 day long dose-escalation regimen appeared to help mitigate potential cardiac effects of ozanimod. This was an acceptable approach to dose finding for the pivotal Phase III studies.

Efficacy

The indication for ozanimod in subjects with RMS is based on efficacy data from 1 placebo-controlled Phase II dose-finding study (Study RPC01-201A), 2 active-controlled pivotal phase III clinical studies (Studies RPC01-301 and RPC01-201B) that compared ozanimod against the well-established comparator, IFN β1a;[19] for up to 24 months, and maintenance of response in the long-term studies (the extension study, Study RPC01-201A Ext; and the ongoing study, Study RPC01-3001), for up to 68 months.

Statistical superiority and clinically meaningful reductions were demonstrated in the annualised relapse rate (primary endpoint);[20] for ozanimod treatments compared to IFN β1a treatment over 12 and 24 months, in a broad population of subjects with RMS (most with RMMS), including those without prior disease modifying treatments. These findings were supported by the results from subgroup and sensitivity analyses of the primary efficacy endpoint, as well as statistically significant and clinically meaningful reductions in the first two key secondary efficacy endpoints (number of new or enlarging hyper intense T2-weighted lesions and number of GdE T1 lesions).[21]

Ozanimod treatments also resulted in less reduction in brain volume measures compared to IFN β1a treatment and evidence of favourable effects on cognition, for example, processing speed. Generally, the 1 mg ozanimod dose group produced numerically larger, more clinically meaningful reductions in efficacy endpoint measures compared to the 0.5 mg ozanimod dose group.

Maintenance of response was demonstrated in subjects treated with ozanimod for up to 68 months (that is, over 5 years of exposure).

No superior benefit of ozanimod treatments over IFN β1a treatment was observed at 3 months and 6 months for disease progression (third key secondary efficacy endpoint), in either the individual studies, or pooled results from the pivotal studies. Subject numbers in each treatment group were too small to draw meaningful conclusions. Hence, the effect

[18] **Tachycardia** is an abnormally rapid heart rate, typically defined as a heart rate above 100 beats per minute, however, thresholds for different age, gender, and patient populations exist.
[19] **Interferon beta-1a (IFN β1a)** is a cytokine in the interferon family used to treat multiple sclerosis (MS).
[20] The average number of relapse a group of patients in a clinical study have in one year.
[21] **T1** and **T2** are technical terms applied to different magnetic resonance imaging (MRI) methods used to generate magnetic resonance images. Specifically, T1 and T2 refers to the time taken between magnetic pulses and the image is taken. These different methods are used to detect different structures or chemicals in the central nervous system. T1 and T2 lesions refers to whether the lesions were detected using either the T1 or T2 method. A T1 MRI image supplies information about current disease activity by highlighting areas of active inflammation. A T2 MRI image provides information about disease burden or lesion load (the total amount of lesion area, both old and new). **Gde** refers to the use gadolinium-enhanced images

of ozanimod exposure on disability progression in RMS has not been fully characterised at this first-round evaluation.

The pivotal studies lacked placebo-control, primarily to mitigate against worsening disability and disease progression over the duration of the studies (up to 24 months). Since IFN β1a is an accepted standard of care, with its own proven benefit as a disease modifying treatment in RMS, the 'additional benefit' that can be expected of ozanimod treatment versus placebo or 'no-treatment' in RMS patients would be much greater than that observed with its comparison with IFN β1a treatment alone. This is supported, in part, by the results of the placebo-controlled Phase II dose-finding Study RPC01-201A, in which favourable reductions in magnetic resonance imaging brain lesion endpoints occurred with ozanimod treatments, in the order of 84% to 94%, compared to the effect of placebo treatment.

The pooled results for the primary and first two key secondary efficacy endpoints in the pivotal studies, and their respective subgroup analyses, generally favoured ozanimod treatments over IFN β1a treatment, particularly for 1 mg ozanimod. There were too few subjects in the pooled subgroup analyses of MS treatment naïve subjects to demonstrate statistical superiority versus IFN β1a treatment. However, statistical superiority of ozanimod treatments was demonstrated, irrespective of prior disease modifying treatment status. On this basis, and the positive trend towards a treatment effect in the MS treatment naive 1 mg ozanimod group, this evaluator finds no compelling reason not to recommend ozanimod be used in MS treatment naïve patients.

In general, the pivotal studies were well designed and conducted, and complied with the TGA-adopted Guideline for MS.[22] The efficacy of ozanimod in RMS is generally consistent with other marketed S1P agonists approved for use in RMS and the submitted clinical efficacy data generally supports ozanimod as a first-line treatment as monotherapy, in all grades of disease severity.

Safety

The safety database provided by the sponsor is adequate because it contains approximately more than 1500 patients exposed to any dose of ozanimod for more than a year.

The safety profile of ozanimod has been established in a subject population of more than 3200 RMS subjects and more than 600 inflammatory bowel disease subjects, with total cumulative exposure to 0.5 mg or 1 mg ozanimod of 1628.9 and 6446.6 person years, respectively. Greater exposure to once daily 1 mg ozanimod reflects its selection as the proposed recommended dose. The number of RMS subjects who received 1 mg ozanimod was 2825, of whom 2565 received at least 6 months of ozanimod treatment and 2408 received at least 12 months ozanimod treatment.

Serious adverse events

In the safety data pool containing all treated patients with RMS, serious adverse events (SAEs) occurred in 7.2 % of ozanimod 1 mg treated patients and 5.2% of ozanimod 0.5 mg treated patients, versus 4.4% of interferon-treated patients.

Overall incidence of serious (SAEs) and severe adverse events (AEs) was similar across treatments, with no clear dose-dependent trends observed. Similarly, incidence of AEs that led to study drug discontinuation was similar across treatments. The most frequent reported AE that led to study drug discontinuation in the active-controlled studies was

[22] CHMP/771815/2011 Rev. 2: Clinical investigation of medicinal products for the treatment of multiple sclerosis. Effective from 1 October 2015.

alanine transaminase (ALT) increased (0.1% in the 0.5 mg ozanimod group versus 0.5% in the 1 mg ozanimod group versus 0.3% in the IFN β1a group, respectively).

Deaths

Twelve deaths (0.4%, 12 out of 2917 exposed to at least one dose) occurred in the clinical development program for ozanimod (FDA safety review 2020). Nine of these deaths occurred in patients with RMS who were on treatment during the active-controlled or open-label extension studies of ozanimod in RMS. One death in a patient with RMS from metastatic pancreatic carcinoma occurred more than 28 days after discontinuation from Study RPC01-301. Although, causes of death in the ozanimod development program were heterogeneous and confounded by factors outside of treatment. Infections and malignancies are known to be associated with treatment using other S1P modulators, and ozanimod therefore have information for these outcomes consistent with other S1P therapies in the PI.

Adverse events

The overall pattern and type of AEs reported in both the RMS and IBD programs were consistent with the results from the pooled active-controlled studies, and generally consistent with other S1P agonists. There were some differences in AE types and frequencies between RMS and inflammatory bowel disease study populations, which could be attributed to the underlying conditions being treated rather than to ozanimod exposure per se.

Cardiovascular safety

S1P receptors are expressed in cardiac tissue, as a result, initiation of S1P modulators can cause negative chronotropic effect (and associated conductance abnormalities). During the development of ozanimod, introduction of a 7 day long dose-escalation regimen was successfully in reducing the risk of serious cardiac arrhythmias in patients with no prior history of significant cardiac disease or who had first-degree atrioventricular block. Similarly, while effects on blood pressure, particularly an increase in supine systolic blood pressure (approximately 1 to 2 mmHg higher with 1 mg ozanimod than IFN β1a treatment) are not expected to be clinically meaningful, low incidence of hypertension was reported across the entire ozanimod program (3.4% of subjects who received 1 mg ozanimod), albeit with no clear time-dependent relationship observed. The long-term cardiovascular risk from ozanimod exposure, particularly in patients with known risk factors remains unknown. This is adequately reflected in the proposed risk management plan (RMP) and PI.

Liver enzymes

Ozanimod administration is associated with increased serum levels of liver transaminases. Pre-existing liver disease, for example, Gilbert's disease;[23] and underlying elevated bilirubin levels, or male gender, may be risk factors for the development of elevated hepatic enzymes when taking ozanimod. Most hepatic AEs were mild to moderate in intensity and resolved whilst on study treatment. There were no cases of severe drug-induced liver injury identified across the clinical development program for ozanimod and

[23] **Gilbert's disease**, also known as **Gilbert's syndrome** (GS) is a mild liver disorder in which the liver does not properly process bilirubin, a breakdown product of the haem component of haemoglobin. Many people never have symptoms; occasionally a slight yellowing colouration of the skin or whites of the eyes may occur, increased lethargy and abdominal pain. include feeling tired, weakness, and abdominal pain. Gilbert's syndrome is due to a mutation in the UGT1A1 gene which results in decreased activity of the bilirubin uridine diphosphate glucuronosyltransferase enzyme. It is typically inherited in an autosomal recessive pattern and occasionally in an autosomal dominant pattern depending on the type of mutation. Episodes of jaundice may be triggered by stress such as exercise, menstruation, or not eating. Diagnosis is based on higher levels of unconjugated bilirubin in the blood without either signs of other liver problems or red blood cell breakdown.

no cases met the full criteria for Hy's law.[24] These findings were consistent with other S1P agonists. The risk for drug-induced liver injury will be more fully characterised in the post-market setting. This risk is clearly reflected in the proposed RMP and PI.

Macular oedema

The incidence of macular oedema with ozanimod treatment was low (0.3%) and consistent with the reported incidence for other S1P agonists. All 9 ozanimod-related confirmed cases of macular oedema (by an external review panel) appeared to be associated with pre-existing risk factors and/or comorbid conditions known to cause macular oedema. At data cut-off, 8 cases had resolved following study drug discontinuation, with no permanent vision loss reported to date. The potential for an incremental risk in patients with predisposing comorbid conditions, for example, uveitis, diabetes mellitus, cannot be excluded which is reflected in the PI.

Psychiatric illness

Across the ozanimod program, the incidences of depression and suicidal behaviours were infrequent, balanced across treatments and consistent with MS background rates. There was no evidence for exacerbation or worsening of depression or suicidal ideation or behaviour after discontinuation of ozanimod. The proportion of subjects with AEs and SAEs of 'Psychiatric Disorders SOC';[25] were low in both ozanimod treatment groups and did not increase with longer term use of 1 mg ozanimod.

Pulmonary function

S1P receptor modulator therapies are known to cause symptoms consistent with restrictive airway disease and persistent changes in forced-expiratory volume over one second (FEV_1) and diffusion lung capacity for carbon monoxide. No clinically meaningful changes in pulmonary function tests, or respiratory-related AEs, were observed with ozanimod treatments across the RMS program.

Infections

Non-serious infections; for example, nasopharyngitis, pharyngitis, urinary tract infection and viral respiratory tract infection, occurred with 1 mg ozanimod. Overall incidence of SAEs in the Phase III RMS program was similar across treatments, with no dose-dependent trends observed. Although, dose and time-dependent reductions in ALC were observed across all phases and studies in the ozanimod clinical program, there were no clear correlations between ALC < 0.2 x 10^9/L values and serious or opportunistic infections. Incidence of AEs of infections that led to study discontinuation was low. Herpes zoster virus infections occurred in most treatment groups, across the clinical program. Cases were generally isolated, non-serious, infrequent and treated whilst continuing ozanimod treatment. However, modest dose- and time-dependent trends were observed.

While the incidence of serious or opportunistic infections was found to be low in the submitted data package, risk associated with ozanimod withdrawal and rebound were not assessed. Given the estimated 3 month period to clear ozanimod and its active metabolites from blood, and the prolonged ALC reductions over the same period, there is a risk, albeit

[24] **Hy's Law**: Evidence of hepatocellular injury with a rise in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

[25] **System Organ Classes (SOC)** are groupings or recorded or suspsected adverse events according to aetiology, used by **MedDRA,** the **Medical Dictionary of Regulatory Activities** developed by the **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**, a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans.

perhaps low based on what has been described in this evaluation report, of development of infections (as well as risk of MS relapse), including serious or opportunistic infections.

Risk associated with rare events for example, PML;[26] or cryptococcal infections;[27] will be more fully characterised with longer-term ozanimod exposure.

Malignancy

Malignancies are noted with other S1P receptor modulators, and it is biologically plausible that decreased immunosurveillance from sequestering lymphocytes in lymphoid tissue would increase the risk of malignancy.

Half of the neoplasms reported with ozanimod in active controlled clinical trials consisted of skin malignancies, with basal cell carcinoma presenting as the most common skin neoplasm and reported with a similar incidence in the combined ozanimod (0.2%, 3 patients) and IFN β1a (0.1 %, 1 patient) group.

Risk of malignancy is adequately addressed in the PI and the RMP.

Cumulative toxicity

The evidence provided in the clinical dossier indicated that prolonged ozanimod exposure is not generally associated with cumulative toxicity. However, risk associated with occurrence of rare events such as PML, autoimmune disorders, disseminated cryptococcal infections or events associated with a long-lag time, such as lymphoma and other malignancies, cannot be fully characterised until much longer periods of ozanimod exposure have occurred i.e. in the post-market setting. These potential risks should be included in the PI and RMP until such time they have been more fully characterised. In the 68 months safety data provided in the RMS (and the inflammatory bowel disease) program, no new safety signals were identified.

The clinical dossier did not provide safety data by disease activity (active versus highly active) in each active-controlled Phase III study. Since the proposed indication is for treatment of adults in all grades of severity of RMS, clinical evaluator requested this information. The sponsor's response provided for 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.

Overall, ozanimod demonstrated an acceptable safety profile in RMS, with good tolerability, for the proposed 1 mg ozanimod once daily dose regimen. Furthermore, ozanimod treatments (both 0.5 mg and 1 mg) demonstrated a favourable safety profile over IFN β1a treatment, a well-established standard of care treatment for RMS, in the Phase III active-controlled studies (up to 24 months), as well as a favourable safety profile over 68 months ozanimod exposure.

Risk management plan

The sponsor submitted EU-RMP version 0.1 (14 February 2019; data lock point (DLP) 30 June 2018) and Australia-specific annex (ASA) version 1.0 (28 June 2019) in support of this application. The sponsor has not submitted an updated EU-RMP or ASA at the second round of evaluation. The sponsor has submitted EU-RMP version 1.0 (23 April 2020; DLP

[26] **Progressive multifocal leukoencephalopathy (PML)** is a rare and potentially fatal viral disease characterised by progressive damage or inflammation of the white matter of the brain at multiple locations (multifocal). It is caused by the JC virus, which is normally present and kept under control by the immune system. The JC virus is harmless except in cases of weakened immune systems.
[27] **Cryptococcosis** is rare yet serious fungal infection.

30 June 2018) at the third round of evaluation. The sponsor has submitted ASA version 2.0 (10 June 2020) at the fourth round of evaluation.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.[28]

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	(none)	–	–	–	–
Important potential risks	Symptomatic bradycardia	ü Ω	ü*	ü	ü¶
	Severe liver injury	ü Ω	ü*†	ü	ü¶
	Serious opportunistic infections including Progressive multifocal leukoencephalopathy (PML) §	ü‡ Ω	ü*†	ü	ü¶
	Macular oedema	ü Ω	ü*†	ü	ü¶
	Posterior reversible encephalopathy syndrome (PRES)	ü Ω	ü*†	ü	–
	Embryo-fetal toxicity in exposed pregnant females	ü‡	ü*†	ü	ü¶α
	Malignancy	ü Ω	ü*†	ü	ü¶
Missing information	Long term risk of cardiovascular comorbidity	ü	ü*†	–	–
	Effects following withdrawal of drug	ü	ü*†	ü	–
	Use in patients over 55 years	ü	ü*†	ü	–

*PASS; †Long term follow up of Study RPC01-3001; ‡Follow-up form HCP checklist and Patient/caregiver guide; α Pregnancy-specific patient reminder card (EU-RMP only); Ω Core questions sent by sponsor safety team.

- The sponsor has included 'Use in patients over 55 years' as missing information in the ASA. As such, the summary of safety concerns is now acceptable.

[28] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- The sponsor has proposed routine pharmacovigilance activities for all safety concerns, including follow-up forms for PML and pregnancy. The sponsor has advised that core questions will be tailored on a case-by-case basis when investigating follow-up information for several safety concerns. The sponsor has proposed a PASS;[29] and long-term follow-up of Study RPC01-3001;[11] as additional pharmacovigilance activities to address all safety concerns. The pharmacovigilance plan proposed is acceptable
- The sponsor has proposed routine risk minimisation activities for the majority of safety concerns. The sponsor has proposed a Healthcare practitioner (HCP) checklist and patient/caregiver guide as additional risk minimisation activities to address the majority of the important risks. This is acceptable.
- At the fourth round of evaluation and following the sponsor's responses to recommendations, there are no outstanding recommendations.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The ozanimod EU-Risk Management Plan (RMP) (version 1.0, dated 23 April 2020, data lock point 30 June 2018), with Australian Specific Annex (version 1.0, dated 28 June 2019), included with submission PM-2019-02397-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.
>
> If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

[29] A **post-authorisation safety study (PASS)** is a study that is carried out after a medicine has been authorised to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures.

As Zeposia is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Zeposia (ozanimod) is to be included in the Black Triangle Scheme. The PI and CMI for Zeposia must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

Ozanimod is a S1P receptor modulator that binds selectively to the S1P1 and S1P5 receptors, proposed by the sponsor for the treatment of RMS. Therapies, which modulate S1P receptor modulators, reduce peripheral lymphocyte counts by preventing lymphocyte egress from lymph nodes.

Overall, the PK of ozanimod have been adequately characterised by the sponsor through several Phase I trials along with additional data from Phase II and III studies. The modelling strategy was considered acceptable and the PK models seemed to describe the data sufficiently. The proposed clinical dose of ozanimod 1 mg preceded by 7 days of dose escalation is acceptable to the delegate.

Two pivotal trials (Studies RPC01-201B and RPC01-301) form the basis of support for the effectiveness of ozanimod for the treatment of RMS. Both trials were randomised, double-blind, double-dummy, active-controlled, parallel group studies that compared 0.5 mg and 1 mg doses of ozanimod with IFN β1a (30 μg given intramuscularly weekly). The two trials were identical with a same set of the primary and key secondary endpoints with the exception of duration (Study RPC01-201B of 24 month duration and Study RPC01-301 of 12 month duration).

Dose-dependent statistical superiority of once daily oral ozanimod 0.5 mg and 1 mg over 30 μg IFN β-1a once weekly intramuscular injections (an accepted standard of care as disease modifying treatment in adult RMS patients) was demonstrated in both pivotal phase III efficacy studies.

Pivotal studies failed to demonstrate the superior benefit of ozanimod treatments over IFN β-1a treatment at the 3 months and 6 months' time point for disease progression (third key secondary efficacy endpoint), in either the individual studies, or pooled results from the pivotal studies. Subject numbers in each treatment group were too small to draw meaningful conclusions. Hence, the effect of ozanimod exposure on disability progression in RMS has not been fully characterised.

Maintenance of efficacy/sustained relapse prevention in adults was generally demonstrated for 1 mg ozanimod for up to 68 months, that is, over 5 years' ozanimod exposure; for example, an adjusted average relapse rate of 0.141 for treatment from first dose through to data cut-off (30 June 2018).

The safety profile of ozanimod in the RMS population did not present with any unexpected findings as compared to other S1P receptor modulators. Fingolimod was authorised more than 9 years ago in the Australia and risk minimisation measures proved efficacious for the indication of relapsing forms of MS. Siponimod was recently granted approval (November 2019);[30] for treatment of adult patients with SPMS. Siponimod, although

[30] AusPAR for Mayzent siponimod Novartis Pharmaceuticals Australia Pty Ltd PM-2018-04434-1-1; https://www.tga.gov.au/auspar/auspar-siponimod

indicated for treatment of a later stage of MS, presented with a qualitatively similar safety profile as compared to fingolimod and ozanimod.

The amount of clinical trial safety data of fingolimod and siponimod and post-marketing experience with fingolimod appears reassuring that the safety of ozanimod is likewise manageable with preventative measures in place in the PI and RMP. Patients with severe cardiac pre-morbid conditions were excluded from clinical studies and are likewise to be excluded from treatment with ozanimod (See: 'contraindication' in section 4.3 of the PI).

Similar to other S1P receptor modulators, there are other relevant safety concerns with chronic ozanimod use, that is, risk for serious/opportunistic infections, elevation of liver enzymes that may be problematic for patients with pre-existing hepatic conditions, and an increased risk of malignancies. The determination of the long-term safety risk is still outstanding and will be further addressed in the ongoing long-term open label extension of Study RPC01-3001 and in a real-world post marketing study.

The overall benefit risk profile of Zeposia is positive for the treatment of adult patients with relapsing forms of multiple sclerosis.

Deficiencies of the data

The Delegate listed the following as deficiencies of current data:

- long term risk of cardiovascular comorbidity;
- effects following withdrawal of drug;
- use in patients over 55 years;
- effect on confirmed disease progression; and
- long term risk of malignancy.

Conditions of registration

As Zeposia is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. With wording as shown in the '*Risk management plan*' section, above.

Proposed action

Overall, Zeposia is approvable as the quality, nonclinical and clinical evaluators (subjected to product information changes) have all recommended approval. The Delegate considers that sufficient data and justification have been provided to support the registration of Zeposia on quality, safety and efficacy grounds for the relapsing forms of multiple sclerosis.

Request for Advisory Committee on Medicines advice

This application was not referred to an Advisory Committee on Medicines (ACM) for review because this drug is not the first in its class; the safety profile is similar to that of the two other drugs in this class approved for MS. The clinical trials were well designed, the efficacy was clearly demonstrated, and the safety profile was acceptable. Additionally, there were no pending issues with clinical, quality or toxicology evaluators. Product information will make prescribers fully aware of the risks associated with ozanimod treatment, allowing them to inform patients and decide whether to use the drug.

Advisory Committee considerations[31]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of:

- Zeposia ozanimod 920 µg capsules blister pack; and
- Zeposia ozanimod 230 µg and 460 µg capsules blister wallet composite pack.

The approved indication for these therapeutic goods is:

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

Specific conditions of registration applying to these goods

- Zeposia (ozanimod) is to be included in the Black Triangle Scheme. The PI and CMI for Zeposia must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The ozanimod EU-Risk Management Plan (RMP) (version 1.0, dated 23 April 2020, data lock point 30 June 2018), with Australian Specific Annex (version 1.0, dated 28 June 2019), included with submission PM-2019-02397-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes.

[31] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Zeposia approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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