Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Zeposia

Active ingredient: Ozanimod

Sponsor: Celgene Pty Limited

September 2022

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 therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The 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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate aminotransferase
$AUC_{0\text{-last}}$	Area under concentration time curve from time zero to the last measurable concentration
CD4	Cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use (European Union, European Medicines Agency)
CI	Confidence interval
C_{max}	Maximum serum concentration
CMI	Consumer Medicines Information
CPMP	Committee for Proprietary Medicinal Products (European Union, European Medicines Agency)
DLP	Data lock point
EC_{50}	Half maximal (50%) effective concentration
EMA	European Medicines Agency (European Union)
EMEA	European Medicines Evaluation Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
GGT	Gamma-glutamyltransferase
GVP	Good Pharmacovigilance Practices
IL	Interleukin
ITT	Intention-to-treat
OR	Odds ratio

Abbreviation	Meaning
PI	Product Information
PSUR	Periodic safety update report
RMP	Risk management plan
SOC	System Organ Class
S1P	Sphingosine 1-phosphate receptor
S1P1/5	Sphingosine 1-phosphate receptor subtype 1/5
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_h	T-helper cell
TNBS	Trinitrobenzenesulphonic acid
TNF	Tumour necrosis factor
UC	Ulcerative colitis
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	Extension of indications
Product name:	Zeposia
Active ingredient:	Ozanimod
Decision:	Approved
Date of decision:	16 March 2022
Date of entry onto ARTG:	18 March 2022
ARTG numbers:	318800 and 318801
, *Black Triangle Scheme:*	Yes. This product will remain in the scheme for 5 years, starting on the date the new indication was approved.
Sponsor's name and address:	Celgene Pty Limited Level 2, 4 Nexus Court Mulgrave, VIC 3170
Dose form:	Capsule
Strengths:	230 µg and 460 µg capsules (composite pack) 920 µg capsule (blister pack)
Containers:	Blister pack and 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:	***Ulcerative colitis*** *Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*
Route of administration:	Oral
Dosage:	Treatment should be initiated under the supervision of a physician experienced in the management of multiple sclerosis or ulcerative colitis. 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 recommended dose of Zeposia for adults is 920 µg once daily taken orally, following an initial 7-day dose escalation regimen:

- Days 1 to 4: 230 µg capsule, once daily
- Days 5 to 7: 460 µg capsule, once daily

Following the 7-day dose escalation, the once daily dosage is 920 µg taken orally starting on Day 8.

Initiation of Zeposia without dose escalation may result in greater reductions in heart rate (see Section 4.4 of the Product Information).

For further information regarding dosage, refer to the Product Information.

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.

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 submission by Celgene Pty Limited (the sponsor) to register Zeposia (ozanimod) 230 µg and 460 µg capsules (composite pack), 920 µg capsule (blister pack) for the following proposed extension of indications:

> *Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.*

Ulcerative colitis is a chronic gastrointestinal inflammatory disorder that involves the surface mucosa, including the infiltration of neutrophils and other inflammatory cells into the epithelium and submucosa of the colon. The aetiology of ulcerative colitis is multifactorial, but likely includes a dysregulated mucosal immune response against commensal non-pathogenic bacteria of the colon, resulting in bowel inflammation.

Management involves first treating the acute symptoms of ulcerative colitis and induction of disease remission, followed by long-term management to maintain remission and prevent disease relapse.

Aminosalicylates such as mesalazine, olsalazine, sulfasalazine and balsalazide have long been the mainstay of maintaining remission but are also a first-line therapy used to treat

symptoms in active mild to moderate ulcerative colitis.[1,2] These medications reduce inflammation in the lining of the gut and maintain remission. They are most effective for reducing inflammation in the large intestine and taken orally as tablets, but can be used rectally as enemas or suppositories, particularly in disease affecting the rectum, sigmoid or descending colon. Corticosteroids (oral prednisolone) may also be used in the short-term for their immunosuppressive properties, but use is limited to acute flares in active moderate to severe disease, or in patients too sick, or patients who do not respond to (or cannot tolerate) adequate doses of 5-aminosalicylate agents.[1]

Drugs that modulate or suppress the immune system (especially azathioprine, 6-mercaptopurine and less commonly, methotrexate) are commonly used to help control inflammation, maintain long term disease remission and prevent or reduce corticosteroid dependence; however, they are not ideal agents for induction of remission due to their slow onset of action.[1]

Anti-tumour necrosis factor inhibitors are a group of biological agents that block the pro-inflammatory effect of tumour necrosis factor (TNF), a pro-inflammatory cytokine implicated in ulcerative colitis. These include infliximab (Remicade);[3] and adalimumab (Humira);[4] and their biosimilars, along with golimumab (Simponi)[5].

Another monoclonal antibody, vedolizumab (Entyvio)[6] binds to integrin α4β7 (LPAM-1, lymphocyte Peyer's patch adhesion molecule 1, a dimer of integrin alpha-4 and integrin beta-7), resulting in gut-specific anti-inflammatory activity.

Ustekinumab (Stelara);[7] is another approved biologic, targeting interleukin (IL)-12 and IL-23 by binding to the p40 protein subunit that IL-12 and IL-23 use, thereby modulating the immune response and help controlling immune-mediate inflammation in ulcerative colitis.

Golimumab (Simponi), vedolizumab (Entyvio) and ustekinumb (Stelara) are used in more severe disease, and along with all such biologics, are approved for injection only, either via intravenous infusion or subcutaneous injection.

Tofacitinib (Xeljanz) is an approved agent for use in ulcerative colitis. It is a small molecule drug and not a biological, and is a Janus kinase (JAK) inhibitor. Xeljanz[8] oral tablets are listed on the Australian Register of Therapeutic Goods (ARTG), indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.

The sponsor's rationale for developing ozanimod (Zeposia) is that there is an unmet need for highly effective oral therapies with a novel mechanism of action that provides a favourable safety and tolerability profile, and with the convenience of once daily dosing for patients with moderate to severe ulcerative colitis who are intolerant to or fail conventional therapy, and those who are naïve to or who had primary or secondary nonresponse to an anti-tumour necrosis factor (anti-TNF) or other biologic therapy or were intolerant to either treatment.

[1] GESA Australian Guidelines for General Practitioners and Physicians: Inflammatory Bowel Disease 4th Edition (updated 2018). *Gastroenterological Society of Australia* (2018).
[2] van der Woude CJ, Ardizzone S, Bengtson MB, et al. The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease. Journal of Crohn's and Colitis 2015;9(2):107–24.
[3] Remicade was first registered on the ARTG on 2 August 2000 (ARTG number: 73827).
[4] Humira was first registered on the ARTG on 28 August 2012 (ARTG numbers: 199410, 199411 and 199412).
[5] Simponi was first registered on the ARTG on 13 November 2009 (ARTG numbers: 153181 and 153767).
[6] Entyvio was first registered on the ARTG on 27 June 2014 (ARTG number: 210048).
[7] Stelara was first registered on the ARTG on 28 July 2009 (ARTG number: 149549).
[8] Xeljanz was first registered on the ARTG on 5 February 2015 (ARTG numbers: 196987 and 233439).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 July 2020;[9] for the following indication:

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

At the time the TGA considered this submission, similar submissions had been approved in European Union (EU) on 18 November 2021 and United States of America (USA) on 27 May 2021. Similar submissions were under consideration in Canada (submitted on 29 January 2021) and Switzerland (submitted on 21 December 2020).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	24 November 2020	Approved on 18 November 2021	*Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.*
United States of America	30 November 2020	Approved on 27 May 2021	*Zeposia (ozanimod) is indicated for the treatment of: moderately to severely active ulcerative colitis (UC) in adults.*
Canada	29 January 2021	Under consideration	Under consideration
Switzerland	21 December 2020	Under consideration	Under consideration

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 PI/CMI search facility.

[9] Further information on the initial approval/registration of this medicine is available via the following: AusPAR for Zeposia (ozanimod), new chemical entity, published on 2 December 2020. Available at: https://www.tga.gov.au/resources/auspar/auspar-ozanimod-hydrochloride.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2021-00444-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2021
First round evaluation completed	2 September 2021
Sponsor provides responses on questions raised in first round evaluation	17 November 2021
Second round evaluation completed	23 November 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 January 2022
Sponsor's pre-Advisory Committee response	18 January 2022
Advisory Committee meeting	3 and 4 February 2022
Registration decision (Outcome)	16 March 2022
Completion of administrative activities and registration on the ARTG	18 March 2022
Number of working days from submission dossier acceptance to registration decision*	196

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis, CHMP/EWP/18463/2006 Rev.1, 28 June 2018.
- European Medicines Evaluation Agency (EMEA), Committee for Proprietary Medicinal Products (CPMP), ICH Topic E1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, Step 5, Note for Guidance on Population Exposure: the Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95, June 1995.

Quality

A full quality evaluation was conducted at the time this product received initial registration.[9]

Nonclinical

In support of the proposed extension of indication, the sponsor submitted five *in vivo* pharmacology studies. Two additional *in vitro* metabolite bindings studies were also submitted to address gaps in the nonclinical evaluation in the original submission of new chemical entity.

Ozanimod hydrochloride (RPC1063)[10] is a sphingosine 1-phosphate receptor (S1P) agonist, which binds with high affinity to S1P receptor subtype 1 (S1P1) and subtype 5 (S1P5), which are G-protein coupled receptors activated by binding to S1P, and regulate various processes, including migration of lymphocytes , and thus by extension, inflammation and infection.[11] There are five isoforms (S1P1 to S1P5), and the activation of S1P1 facilitates the egress of lymphocytes from lymphoid organs during an immune response.

A pro-inflammatory role of S1P/S1P receptor signalling has been proposed to be associated with ulcerative colitis pathogenesis.[12] To this end, previous studies have reported attenuation of symptoms and histopathological findings in nonclinical models of colitis when the number of circulating and colonic lymphocytes are reduced with activation of S1P1 or S1P1/S1P5 with small molecules.[13,14,15,16] Since S1P1 and S1P5 agonism has been shown experimentally to trigger enhanced neuronal and oligodendrocyte precursor cell survival, and maintenance of blood brain barrier integrity,[17] the sponsor hypothesised that it is possible for S1P1 and S1P5 agonism to exert effects on local tissue cells and circulating inflammatory cells and also to modulate vascular barrier integrity, thus providing an analogous mechanism to achieve efficacy in the treatment of ulcerative colitis using a S1P receptor agonist.

In support of the proposed hypothesis, the sponsor submitted two *in vivo* studies in the rat model of inflammatory bowel disease (induced with trinitrobenzenesulphonic acid (TNBS) and three studies in the mouse model of cluster of differentiation 4 (CD4)+ inflammatory bowel disease (adoptive transfer model of colitis). While the TNBS colitis model does not recapitulate the aetiopathogenesis of inflammatory bowel disease per se, the histopathology of TNBS-induced colitis has broad comparability with clinical disease presentation, and thus presents as a reasonable model to assess the attenuation of pathological presentation. In contrast, the CD4+ inflammatory bowel disease model colonic inflammation develops as a result of enteric antigen-driven activation, polarisation, and homeostatic expansion of the naive (CD4+CD45RB^{high}) T-cells to produce

[10] RPC1063 is ozanimod HCl (0.92 mg ozanimod = 1 mg ozanimod HCl).
[11] Tiper, I. et al. Sphingosine 1-Phosphate Signaling Impacts Lymphocyte Migration, Inflammation and Infection, *Pathog Dis*, 2016; 74(6): ftw063.
[12] Izzo, R. et al. Sphingosine-1-Phosphate Receptor: a Novel Therapeutic Target in Ulcerative Colitis, *Expert Rev Clin Immunol*, 2016; 12(11): 1137-1139.
[13] Debien, E. et al. S1PR5 is Pivotal for the Homeostasis of Patrolling Monocytes, *Eur J Immunol*, 2013; 43(6): 1667-1675.
[14] Drouillard, A. et al. S1PR5 is Essential for Human Natural Killer Cell Migration Toward Sphingosine 1 Phosphate, *J. Allergy Clin. Immunol*, 2018; 141: 2265-2268.
[15] van Doorn, R. et al. Sphingosine 1-Phosphate Receptor 5 Mediates the Immune Quiescence of the Human Brain Endothelial Barrier, *J. Neuroinflammation*, 2012; 9: 133.
[16] Walzer, T. et al. Natural Killer Cell Trafficking *in vivo* requires a Dedicated Sphingosine 1-Phosphate Receptor, *Nat Immunol*, 2007; 8(12): 1337-1344.
[17] Groves, A. et al. Fingolimod: Direct CNS Effects of Sphingosine 1-Phosphate (S1P) Receptor Modulation and Implications in Multiple Sclerosis Therapy, *J Neurol Sci*, 2013; 328: 9-18.

colitogenic effector cells such as T-helper cell (T_h)1 and/or T_h17.[18] As a result, inflammatory tissue damage and dysfunction may occur in multiple tissues, in addition to the colon, potentially confounding interpretation of pathological findings. However, the model is adequately suited to investigate attenuation of colitis pathology following ozanimod administration.

In the TNBS rat model, ozanimod, doses up to 1 mg/kg (taken orally daily) resulted in improvement of the inflammatory parameters, such as attenuation of body weight loss, decreases in adhesions, strictures, ulcer score, colon wall thickness and colonic scores. While the reduction in the number of ulcers was small compare to untreated control, a dose-related decrease in the size of ulcers was observed. At 1 mg/kg functional recovery (as determined by presence of faecal pellets compare to controls or lower doses) and increased playing function was also noted. In the mouse CD4+ inflammatory bowel disease model, doses up to 1.2 mg/kg showed reductions in total colon inflammation, gland loss, hyperplasia, neutrophil scores, mucosal thickness, erosion, cytokine expression (interleukin (IL)-10, IL-12 p70, IL-1β, IL-6 and TNF-α). The efficacious doses (3.6 mg/m^2 in mice and 6 mg/m^2 in rats) are above the intended clinical dose on a mg/m^2 basis (0.6 mg/m^2 in a 50 kg individual). Taken together, the rat and mouse inflammatory bowel disease model findings lend some support for the efficacy claim for ozanimod to attenuate pathological effects of ulcerative colitis, but at doses higher than that proposed clinically.

In Chinese hamster ovary cell lines expressing monkey S1P1 to S1P5, ozanimod and its downstream metabolites CC112273, CC1084037, RP101124, RP101075, RP101988, RP101442, RP112289 and RP112509, demonstrated preferential binding to S1P1 (half maximal (50%) effective concentration (EC_{50}) = 0.49 nM to 17.27 nM) and S1P5 (EC_{50} = 10.10 nM to 86.40 nM), with the exception of metabolite RP101124, which appeared inactive across S1P1 to S1P5. These observations were consistent with those previously observed for human S1P1 to S1P5. The activity of ozanimod and its metabolites in rat S1P5 was reduced compare to the human homologue, most likely due to the greater difference in amino acid sequence. Ozanimod had a potency of > 1,111 nM for rat S1P5. As with human and monkey S1P1 and S1P5 no appreciable levels of activity were associated with metabolite RP101124.

There are no nonclinical objections to proposed extension of indication.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- four Phase I studies: Study RPC-1063-CP-001 and Study RPC01-1915 (clinical pharmacology studies); Study CLG-Certara-UC-358-1 and Study CLG-Certara-UC-358-2 (population pharmacokinetic analyses);
- two Phase II studies: Study RPC01-202 and Study RPC01-202 open label phase;
- two Phase III studies: Study RPC01-3101 (pivotal efficacy and safety study) and Study RPC01-3102 open label extension.

[18] Ostanin, D. et al. T Cell Transfer Model of Chronic Colitis: Concepts, Considerations, and Tricks of the Trade. *Am J Physiol Gastrointest*, *Liver Physiol*, 2008; 296: G135-G146.

Pharmacology

Primary pharmacology studies were evaluated in Submission PM-2019-02397-1-1.[9] Clinical pharmacology studies provided in the current submission reported the following outcomes:

- After multiple dosing of ozanimod 1.84 mg once daily for up to 28 days (preceded by 10-day dose escalation of 0.23 mg for 4 days, 0.46 mg for 3 days, and 0.92 mg for 3 days), absolute lymphocyte count appeared to return to Baseline by 65 to 85 days after the last dose of ozanimod.

  Overall, no new safety findings were observed in this extension study compared to the parent Studies RPC01-1912, RPC01-1913, and RPC01-1914.

- There was no significant difference in exposure of ozanimod or its metabolites CC112273, and CC1084037 with or without cyclosporine coadministration.

  Cyclosporine significantly increased maximum serum concentration (C_{max}) and area under concentration time curve from time zero to the last measurable concentration ($AUC_{0\text{-}last}$) for ozanimod metabolite RP101988. Because this is a minor active metabolite (accounting for approximately 5% of active moieties at steady state exposure to ozanimod and metabolites), this increase is not considered clinically meaningful.

- Population pharmacokinetic analysis indicated no meaningful differences in pharmacokinetic parameters in patients with relapsing multiple sclerosis or ulcerative colitis.

Efficacy

Study RPC01-3101 was a multicentre, randomised, double blind, placebo controlled study of ozanimod as induction (up to 10 weeks) and maintenance therapy (from 10 to 52 weeks) for subjects with moderate to severe ulcerative colitis.

The study was conducted from 12 August 2015 to 27 March 2020 at sites in North America, Europe, Australia, South America, and South Africa.

A total of 1012 participants were enrolled into the induction period study, and of these 526 responders at Week 10 were re-randomised into the maintenance period study.

Moderate to severe ulcerative colitis was defined based on a 4-component Mayo score;[19]of 6 to 12 inclusive, with endoscopic subscore of at least 2, a rectal bleeding score of at least one, and a stool frequency score of at least one.

[19] The Mayo Score for Ulcerative Colitis was developed at the Mayo Clinic in 1987 to standardise the severity of a patient's ulcerative colitis, useful in research and clinically to assess response to treatment over time. In clinical trials, 'response to therapy' and 'remission' may be defined differently in each trial.
The Mayo Score is comprised of four components: assessment of rectal bleeding; assessment of stool frequency; endoscopic mucosal assessment; and the physician's global assessment (a measure of the physican's assessment of disease severity including abdominal pain, extra-abdominal signs/symptoms and the patient's overall well-being).
Each component is given a subscore from between 0 and 3 points, with 0 indicative of no signs/symptoms or normal function, and 3 indicative of the most severe disease.
A 'Total' (4-component) Mayo score is composite of the subscores of all four components, and may score a minimum of 0 (no signs/symptoms), and a maximum (most severe) of 12 points.
A '3-component' Mayo score is a composite of 3 component subscores (the rectal bleeding, stool frequency, and endoscopic assessment subscores), and without a physicians global assessment subscore.
higher overall composite scores are indicative of increased disease severity.
A 'Partial' Mayo score is an alternate composite of 3 component subscores (the rectal bleeding, stool frequency, and the physician's global assessment subscores) and without an endoscopic assessment subscore.

Clinical remission was determined using the 3-component Mayo score (unless otherwise stated in the clinical study report).

Clinical remission, when determined using the 3-component Mayo score, was defined as:

- a rectal bleeding subscore of zero;
- a stool frequency subscore of one or less, (and a decrease of at least one point from the baseline stool frequency subscore); and
- an endoscopy subscore or one or less.

Clinical remission, when determined using the 4-component Mayo score, was defined as:

- a complete Mayo score of 2 or less points with no individual subscore of more than one point.

Clinical response determined using the 3-component Mayo score was defined as:

- a reduction from Baseline in the 3-component (9-point) Mayo score of
  - at least 2 points and at least 35% overall; and
  - a reduction from Baseline in the rectal bleeding subscore of at least one point, or an absolute (end of study) rectal bleeding subscore of no more than one point.

Clinical response determined by 4-component (12-point) Mayo score was defined as:

- a reduction from Baseline in the complete Mayo score of:
  - at least 3 points and at least 30% overall; and
  - a reduction from Baseline in the rectal bleeding subscore of at least one point; or an absolute (end of study) rectal bleeding subscore of no more than one point.

In the induction period two cohorts of participants were treated for a total of 10 weeks and evaluated for clinical response and remission:

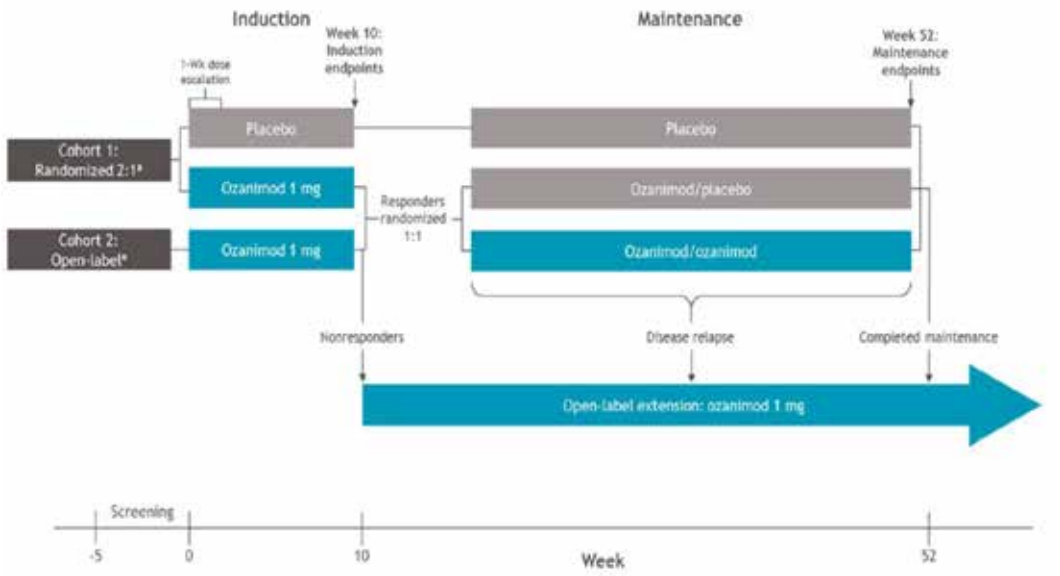
- Cohort 1: participants were randomised in a 2:1 ratio to receive either ozanimod 1 mg or placebo once daily in a double blind fashion, stratified by corticosteroid use at screening (yes or no), and prior anti-TNF therapy (yes or no)
- Cohort 2: participants received open label ozanimod 1 mg once daily. Cohort 2 was enrolled to ensure that sufficient responders could be enrolled into the maintenance period study.

All participants in the induction period had to be on stable current treatment comprised of taking at least one of oral 5-aminosalicylate agent; or either oral prednisone (≤ 20 mg per day, or equivalent) or oral budesonide multi-matrix formulation, which was to be continued during the induction period.

In the maintenance period participants who satisfied requirements for a clinical response or remission by either 3-component or 4-component Mayo definition at 10 weeks were re-randomised to receive either ozanimod 1 mg or matching placebo in a 1:1 ratio in a blinded fashion. Participants who were randomised to placebo in the induction period and had at least a clinical response at Week 10 continued to receive placebo in the maintenance period in a double blind manner. Participants re-randomised in the maintenance period were stratified prior to randomisation by clinical remission status at Week 10 (yes or no) and corticosteroid use at Week 10 (yes or no).

Original publication: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987 Dec 24;317(26):1625-9.

Figure 1: Study RPC01-3101 Study schematic for Cohort 1 and Cohort 2



Abbreviation: wk = week.

a Subjects stratified by prior tumour necrosis factor exposure (yes/no) and corticosteroid use (yes/no) at screening. The randomisation in the maintenance period stratified by clinical remission status at Week 10 (yes/no) and corticosteroids use at Week 10 (yes/no).

Subjects in Cohort 1 were randomised to receive ozanimod or placebo in a 2:1 ratio in a double blinded manner. Subjects in Cohort 2 received ozanimod in an open label manner. Subjects in clinical response at Week 10 of the induction period who were randomized to placebo (Cohort 1) continued to receive placebo in the maintenance period in a double blind manner. Only responders assigned to ozanimod (Cohort 1 and 2) in the induction period were randomized to receive ozanimod or placebo in a 1:1 ratio in a double blinded manner when entering the maintenance period.

The primary objective for both the induction and maintenance periods was to demonstrate the efficacy of ozanimod versus placebo therapy on clinical remission in adults.

The clinical study report included analyses for multiple secondary and other endpoints in both the induction and maintenance periods. Patient reported outcomes included the health related quality of life assessments SF-36;[20] and EQ-5D,[21] health resource utilisation and work productivity, which were not included in the hierarchical statistical analysis framework. Only the results of the primary (the proportion of patients in clinical remission after 10 weeks in the induction period; the proportion of participants in clinical remission at 52 weeks in the maintenance period) and the key secondary endpoints for each period are considered in this overview. A protocol variation changed the hierarchical order for statistical testing of the endpoints in the maintenance period, which did not affect the first three objectives. Statistical methods were appropriate, applying 2-sided Cochran-Mantel-Haenszel tests at the 5% level of significance on the intention-to-treat

[20] The **SF-36** is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

[21] Developed by EuroQol, **EQ-5D** is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

(ITT)[22] population, and applying a closed hierarchical testing procedure to the primary and key secondary endpoints to control Type 1 error. Changes expressed as changes from Baseline were analysed using analysis of covariance models.

Induction period

For the induction period, baseline demographics were comparable between Cohort 1 placebo (n = 216), Cohort 1 ozanimod (n = 429) and Cohort 2 ozanimod (n = 367) groups, although moderately more men were enrolled in the placebo group (66.2%) compared to ozanimod groups (57.1% male for Cohort 1, 58.3% for Cohort 2). Between 4.4% and 6.5% of participants in each arm were aged 65 years or over (total 54 participants). Disease characteristics and treatment history at Baseline were also comparable between the treatment arms. Concomitant corticosteroids for systemic use (predominantly prednisone) were used in 27.7% of subjects in the Cohort 1 ozanimod group, 32.4% of subjects in the placebo group, and 33.8% of subjects in Cohort 2 ozanimod group. Approximately 30% of participants in Cohort 1 had received prior anti-TNF therapy,[23] whereas approximately 43% of participants in Cohort 2 had received prior anti-TNF therapy.

A statistically significantly greater proportion of participants achieved clinical remission in the Cohort 1 ozanimod group (18.4%) compared to the Cohort 1 placebo group (6.0%) at Week 10 of the induction period ($p < 0.0001$, see Table 3 below). Sensitivity analyses supported the result. Key secondary outcomes were also significantly better in the ozanimod treatment arm compared to placebo (see Table 4 below).

Table 3: Studies RPC01-3101 Proportion of participants in clinical remission (3-component Mayo definition using 7-day scoring algorithm) at Week 10 of induction period (intention-to-treat population, non-responder imputation)

	Cohort 1		Cohort 2
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Ozanimod 1 mg (N = 367)
Subjects in clinical remission, n (%)[a]	79 (18.4)	13 (6.0)	77 (21.0)
Odds ratio (95% CI)[b]	3.586 (1.938, 6.636)		-
Difference in proportions (95% CI)[b]	0.124 (0.075, 0.172)		-
p-value[b]	< 0.0001		-

Abbreviations: CI = confidence interval; N = number of subjects; n = number of subjects in group.

a Clinical remission is defined as: rectal bleeding subscore = 0 point and stool frequency subscore ≤ 1 point (and a decrease of ≥ 1 point from the Baseline stool frequency subscore) and endoscopy subscore ≤ 1 point without friability.

b Odds ratio (active to placebo), treatment difference, and 2-side 95% Wald CI and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the Cochran-Mantel-Haenszel test, stratified by corticosteroid use at screening and prior anti-tumour necrosis factor use (yes or no).

Subjects with any of rectal bleeding subscore, stool frequency subscore, and endoscopy subscores missing at Week 10 are classified as non-remitters.

[22] Randomised clinical trials analysed by the **intent-to-treat (ITT)** approach provide the unbiased comparisons among the treatment groups. In the ITT population, none of the patients are excluded and the patients are analysed according to the randomisation scheme.
[23] Defined as had received prior anti-tumour necrosis factor therapy and had primary non-response (persistently active disease despite an adequate trial of induction therapy), secondary non-response (recurrence of symptoms during maintenance dosing following prior clinical benefit) or developed intolerance (inability to achieve doses, dose levels or treatment durations because of treatment related side effects).

Table 4: Study RPC01-3101 Results for secondary efficacy outcomes (induction period)

	Ozanimod 1 mg (N = 429) n (%)	Placebo (N = 216) n (%)	Odds ratio (95% CI)	Difference in proportions (95% CI)	p-value
Clinical response at Week 10	205 (47.8)	56 (25.9)	2.670 (1.858, 3.836)	0.219 (0.144, 0.293)	< 0.0001
Endoscopic improvement at Week 10	117 (27.3)	25 (11.6)	2.876 (1.802, 4.591)	0.157 (0.097, 0.217)	< 0.0001
Mucosal healing at Week 10	54 (12.6)	8 (3.7)	3.767 (1.759, 8.068)	0.089 (0.049, 0.129)	< 0.001

Abbreviations: CI = confidence interval; N = number of subjects; n = number of subjects in group.

The clinical evaluation concluded that the statistical significance and clinical relevance of the primary and key secondary endpoints provided acceptable evidence of efficacy of ozanimod, over placebo in initiating remission and clinical response. The evaluation noted that subgroup analyses other than those considering experience with anti-TNF therapies and use of corticosteroids should be considered exploratory.

Maintenance period

Between 88.3% and 93.5% of participants in the different arms of the induction period study completed the induction period. Adverse events or withdrawal by subject were the most common reasons for study withdrawal, and lack of efficacy also contributed to withdrawal in the placebo treatment group.

Of the participants who completed the induction period, 233 (54.3%) in the Cohort 1 ozanimod arm, 69 (31.9%) in the placebo arm, and 224 (61%) in Cohort 2 achieved at minimum a clinical response at Week 10 of the induction period and enrolled into the maintenance period study. Patients in the placebo group were continued on double blinded placebo treatment (placebo/placebo group), whereas the 257 responders in the two ozanimod cohorts were re-randomised to placebo (n = 227, ozanimod/placebo group) or ozanimod (n = 230, ozanimod/ozanimod group) for a further 42-weeks treatment.

Baseline demographics were broadly similar in the three groups, although men represented a moderately greater proportion of participants in the placebo/placebo group (46, 66.7%) than in the ozanimod/placebo (122, 53.7%) or ozanimod/ozanimod group (117, 50.9%). Between 5.3% and 8.7% of participants in each treatment group were aged 65 years or over (total 31 participants). Regarding concomitant corticosteroid use, 26.1% of the placebo/placebo group, 26.4% of the ozanimod/placebo group, and 31.7% of the ozanimod/ozanimod group were taking concomitant systemic steroids at entry to the maintenance period. Approximately 20% of participants re-randomised to ozanimod/ozanimod or ozanimod/placebo and 13 (6%) of participants in the placebo/placebo group were in complete remission at the commencement of the maintenance period, with the balance having a clinical response.

A statistically significantly greater proportion of participants in the ozanimod/ozanimod group (37.0%) were in clinical remission at Week 52 compared to participants in the ozanimod/placebo group (18.5%, p < 0.0001, non-responder imputation, see Table 5 below). Key secondary outcomes were also achieved by higher proportions of participants

in the ozanimod/ozanimod group than in the ozanimod/placebo group (see Table 6 below).

Table 5: Study RPC01-3101 Proportion of subjects in clinical remission (3-component Mayo definition using 7-day scoring algorithm) at Week 52 of total treatment in the maintenance period (intention-to-treat population, non-responder imputation)

	Placebo (N = 69)	Rerandomized Subjects	
		Ozanimod 1 mg – Placebo (N = 227)	Ozanimod 1 mg – Ozanimod 1 mg (N = 230)
Subjects in clinical remission, n (%)[a]	17 (24.6)	42 (18.5)	85 (37.0)
Odds ratio (95% CI)[b]	-	2.755 (1.767, 4.294)	
Difference in proportions (95% CI)[b]	-	0.186 (0.108, 0.264)	
p-value[b]	-	< 0.0001	

Abbreviations: CI = confidence interval; N = number of subjects; n = number of subjects in group.

a Clinical remission is defined as: rectal bleeding subscore = 0 point and stool frequency subscore ≤ 1 point (and a decrease of ≥ 1 point from the Baseline stool frequency subscore) and endoscopy subscore ≤ 1 point without friability.

b Odds ratio (active to placebo), treatment difference, and 2-sided 95% Wald CI and p-value for comparison between the ozanimod 1 mg - ozanimod 1 mg and ozanimod 1 mg - placebo groups are based on the Cochran-Mantel-Haenszel test, stratified by remission status at Week 10 and corticosteroid use at Week 10 (yes or no). Subjects with any of rectal bleeding subscore, stool frequency subscore, and endoscopy subscores missing at Week 52 are classified as non-remitters.

Table 6: Study RPC01-3101 Results for secondary efficacy outcomes – maintenance period

	Ozanimod/ Placebo (N = 227) n (%)	Ozanimod/ Ozanimod (N = 230) n (%)	Odds ratio (95% CI)	Difference in proportions (95% CI)	p-value
A clinical response at Week 52	93 (41.0)	138 (60.0)	2.266 (1.542, 3.331)	0.192 (0.104, 0.280)	< 0.0001
Endoscopic improvement at Week 52	60 (26.4)	105 (45.7)	2.476 (1.650, 3.716)	0.194 (0.110, 0.277)	< 0.0001
Durable clinical remission[a]	22 (9.7)	41 (17.8)	2.646 (1.384, 5.061)	0.082 (0.028, 0.136)	0.0030
Clinical remission at Week 52 of participants in remission at Week 10	22 (29.3)	41 (51.9)	2.881 (1.447, 5.738)	0.239 (0.091, 0.386)	0.0025
Corticosteroid-free remission	38 (16.7)	73 (31.7)	2.557 (1.598, 4.093)	0.152 (0.078, 0.226)	< 0.001
Mucosal healing at Week 52	32 (14.1)	68 (29.6)	2.643 (1.642, 4.256)	0.156 (0.082, 0.229)	< 0.001

a The endpoint of durable remission was moved to sixth in the hierarchy of key secondary endpoints (formerly third in hierarchy). Protocol clarification letter (4 March 2020, that is, just before completion of the study).

Statistical comparisons were not presented between the placebo/placebo group and the re-randomised ozanimod/placebo and ozanimod/ozanimod populations. At Week 52, 27 (39.1%) of participants in the placebo/placebo group had a clinical response, 20 (29.0%) had endoscopic improvement, 17 (24.6%) had corticosteroid-free remission, 7 (10.1%) had mucosal healing and 5 (7.2% of all placebo treated patients in the maintenance phase) had durable clinical remission (clinical remission at both Week 10 and Week 52). This was also presented as 41.7% of 12 patients in clinical remission in the placebo/placebo arm at the beginning of the maintenance period.

The clinical evaluation concluded that the statistical significance and clinical relevance of the primary and first two secondary endpoints in the maintenance phase provided acceptable evidence of efficacy of ozanimod over placebo.

In both the induction and maintenance period studies, participants who were anti-TNF naïve appeared to respond to ozanimod better than those who had experienced previous treatment with anti-TNF agents. Similarly, participants who had not been treated with corticosteroids previously appeared to respond to ozanimod better than those who had been treated with corticosteroids earlier.

Study RPC01-3102 is an ongoing open label extension study in patients with moderately to severely active ulcerative colitis who had been enrolled in Study RPC01-3101 at minimum to Week 10 of the induction period, had relapsed during the maintenance period or had completed the maintenance period of that study, and in patients with moderately to severely active ulcerative colitis who completed at least one year in the open label period of the Phase II Study RPC01-202. At the time of the interim report for Study RPC01-3102 efficacy data was only available from patients who had participated in Study RPC01-3101. Efficacy data were consistent with the reported outcomes of Study RPC01-3101.

Study RPC01-202 was a randomised double blind, placebo controlled parallel group study that enrolled 199 participants with moderately to severely active ulcerative colitis with the primary objective to compare the efficacy of ozanimod titrated to 0.5 mg daily over one week or to 1.0 mg daily over one week with placebo for the induction of remission after 8 weeks at maximum dose. Secondary objectives were to compare the efficacy of ozanimod versus placebo at Weeks 8 and 32 as measured by clinical response, clinical remission and mucosal healing, and to compare the overall safety and tolerability of ozanimod. Exclusion and inclusion criteria were broadly similar to Study RPC01-3101.

The proportion of patients in clinical remission at Week 8 was statistically significantly higher with ozanimod 1 mg (16.4%) compared with placebo (6.2%, p = 0.0482). As the 1 mg comparison to placebo was the primary comparison in the pre-specified statistical hierarchy, the trial met its primary endpoint. A higher remission rate was also observed with ozanimod 0.5 mg (13.8%) compared with placebo (the second comparison in the hierarchy), but this difference did not reach statistical significance (p = 0.1422). Most of the sensitivity analyses supported the primary analysis endpoint.

Safety

Safety data in ulcerative colitis was collected from Studies RPC01-202, RPC01-3101 and RPC01-3102 (ongoing open label study). The sponsor's summary of clinical safety also included safety data from studies with patients with Crohn's disease and with multiple sclerosis. Pooled safety data from patients with ulcerative colitis were described as:

- Pool F, comprised of patient data from controlled ulcerative colitis studies;

- Pool G, comprised of patient data from controlled and uncontrolled ulcerative colitis studies; and
- Pool D, comprised of patient data from controlled and uncontrolled studies in ulcerative colitis, Crohn's disease, and multiple sclerosis.

Table 7: Study RPC01-3101 Overall exposure to ozanimod (safety populations)

Safety Pool Treatment Group	N	Mean (SD) Duration of Exposure[a]	Total Subject-years of Exposure[b]
Pool F Induction Period[c], weeks			
Placebo	281	10.01 (2.101)	53.9230
Ozanimod 1 mg	496	10.25 (1.764)	97.4700
RPC01-3101 Cohort 1 Induction Period[d], weeks			
Placebo	216	10.278 (2.163)	NC
Ozanimod 1 mg	429	10.446 (1.692)	NC
RPC01-3101 Maintenance Period[e], weeks			
Placebo[f]	69	33.437 (14.165)	NC
Ozanimod 1 mg - Placebo	227	30.84 (14.849)	134.1554
Ozanimod 1 mg - Ozanimod 1 mg	230	37.55 (11.307)	165.5286
Pool G[g], months			
Placebo	508	5.785 (3.8564)	242.8216
Ozanimod 1 mg	1158	19.323 (17.2913)	1841.6699
Pool D[h], months			
Placebo	596	5.831 (3.5756)	283.9518
Ozanimod 1 mg	4057	34.171 (20.2939)	11610.2840

Abbreviations: N = number of subject; NC = not calculated; SD = standard deviation.

a For the integrated summary of safety (ISS) safety analysis pools (Pool F, G, and D), total duration of exposure (weeks) = (date of last dose - date of first dose + 1)/7. Total duration exposure (months) = (date of last dose - date of first dose + 1)/(number of days in one month). Number of days in one month may be defined differently in each study.

b Subject years of exposure is calculated as ((date of last dose - date of first dose) + 1)/365.25.

c Pool F induction analysis includes controlled safety data from Study RPC01-202 induction period and Study RPC01-3101 Cohort 1 induction period.

d Defined as the total number of days from the date of first dose to the date of last dose as reported on the End of Study electronic case report form for patients who did not enter the maintenance period, or the total number of days from the date of first dose to the date before onsite dosing for maintenance period for patients who entered maintenance period.

e Pool F maintenance analysis includes analysis of Study RPC01-3101 maintenance period (Cohorts 1 and 2) but did not include subjects receiving placebo in both Study RPC01-3101 induction and maintenance periods.

f Data from subjects who received placebo in both Study RPC01-3101 induction and maintenance periods were not analysed as part of Pool F. Treatment duration defined in the Study RPC01-3101 statistical analysis plan was defined as the total number of days from the date of first dose of maintenance period to the date of last dose as reported on the end of study electronic case report form.

g Pool G comprised controlled and uncontrolled data from ulcerative colitis Studies RPC01-202, RPC01-3101, and RPC01-3102. A total of 227 subjects who were treated with ozanimod 1 mg in Study RPC01-3101 induction period and were re-randomised to placebo in Study RPC01-3101 maintenance period are also included in the total count of the 'placebo' group for Pool G displays.

h Pool D comprised data from all controlled and uncontrolled data from ulcerative colitis studies (Studies RPC01-202, RPC01-3101 and RPC01-3102), Crohn's disease (Studies RPC01-2201 and RPC01-3204), and multiple sclerosis (Studies RPC01-201A, RPC01-201B, RPC01-301, RPC01-3001 and RPC01-1001). A total of 227 subjects who were treated with ozanimod 1 mg in Study RPC01-3101 induction period and were re-randomised to placebo in Study RPC01-3101 maintenance period are also included in the total count of the 'placebo' group for Pool D displays.

At completion of the maintenance period of Study RPC01-3101, 250 participants with moderate to severe ulcerative colitis had been exposed to ozanimod 1 mg daily for at least 42 weeks.

During the induction periods of controlled studies included in Pool F, reports of severe treatment-emergent adverse events (TEAEs), serious TEAEs, or TEAEs leading to permanent discontinuation of study drug or leading to study withdrawal were infrequent and comparable between placebo and ozanimod populations. No deaths were reported in this population pool. By System Organ Class (SOC) the participants treated with ozanimod more frequently reported TEAEs in the Investigations SOC than participants treated with placebo (alanine aminotransferase (ALT) increased: 2.4% versus 0%, aspartate aminotransferase (AST) increased: 1.2% versus 0%, and gamma-glutamyltransferase (GGT) increased: 1.2% versus 0%, respectively). By Preferred Term, headache, nasopharyngitis, nausea, pyrexia, ALT increased, and arthralgia were reported by ≥ 2% of participants in ozanimod groups and more frequently than in placebo groups, but anaemia (5.7% versus 3.6%) and ulcerative colitis (2.8% versus 1.6%) were reported for ≥ 2% of participants in the placebo groups and more frequently than in ozanimod groups.

In the maintenance period of Study RPC01-3101, serious TEAEs affected 5.8% of placebo/placebo patients, 7.9% of ozanimod/placebo patients and 5.2% of ozanimod/ozanimod patients. Severe TEAEs, TEAEs leading to interruption of study drug and TEAEs leading to discontinuation of study drug were reported by 4.0% or fewer participants. There were no deaths reported in the maintenance period. The most frequently reported TEAEs affecting ≥ 2% in the ozanimod/ozanimod group were ALT increased, headache, arthralgia, nasopharyngitis, GGT increased, oedema peripheral, and herpes zoster. The TEAEs of colitis ulcerative and upper respiratory tract infection were reported more frequently in the ozanimod/placebo treatment group (4.4% and 1.8%, respectively) than the ozanimod/ozanimod treatment group (0.4% and 0.9%, respectively). Infections and infestations were more frequent in patients treated with ozanimod throughout induction and maintenance period. Severe TEAEs were uncommon. A single death of a 43-year-old woman with mucinous adenocarcinoma after 911 days of treatment was considered possibly related to study drug by the investigator and unrelated by the sponsor.

The reported adverse events in the ulcerative colitis studies were consistent with the known safety profile of ozanimod (lymphopenia and associated signs and symptoms, elevated serum transaminases) in multiple sclerosis.

The clinical evaluation considered that the benefit-risk balance of ozanimod in the treatment of ulcerative colitis was marginally favourable, highlighting that ozanimod may increase the risk of infections and the severity of hepatic disease both of which are separately associated with ulcerative colitis.

Clinical recommendation

The TGA's clinical evaluation recommended authorisation of ozanimod for a modified indication, subject to negotiation of the PI. The modified indication proposed as a result of the clinical evaluation is:

For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.

Risk management plan

The most recently evaluated EU-risk management plan (RMP) was EMA approved version 1.0 (dated 23 April 2020; data lock point (DLP) 30 June 2018) and Australia specific annex (ASA) version 2.0 (dated 10 June 2020). In support of the extended indications, the sponsor has submitted EU-RMP version 3.0 (dated 18 October 2021; DLP 7 May 2021) and ASA version 4.0 (dated 23 November 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 8: 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	ü[2,3]	ü	ü[3]
	Severe liver injury	ü	ü[2,3,4]	ü	ü[3]
	Serious opportunistic infections including progressive multifocal leukoencephalopathy;[a]	ü[1]	ü[2,3,4,5]	ü	ü[3]
	Macular oedema	ü	ü[2,3,4]	ü	ü[3]
	Malignancy	ü	ü[2,3,4,5]	ü	ü[3]
	Posterior reversible encephalopathy syndrome	ü	ü[2,3,4]	ü	–
	Embryofetal toxicity in exposed pregnant females	ü[1]	ü[2,3,4]	ü	ü[3]
Missing information	Long term risk of cardiovascular effects	ü	ü[2,3,4]	–	–
	Effects following withdrawal of drug	ü	ü[2,3,4]	ü	–
	Use in patients over 65 years	ü	ü[2,3,4]	ü	–

a Additional studies listed are not powered to assess leukoencephalopathy but will provide safety information in conjunction with enhanced pharmacovigilance.

1 Follow-up questionnaire

2 the ORION trial (multiple sclerosis)

3 Study RPC01-3102 (ulcerative colitis)

4 Long-term follow-up of Study RPC01-3001 (multiple sclerosis)

5 ulcerative colitis post-authorisation safety study (PASS)

3 Healthcare practitioner checklist and patient/caregiver guide

- The summary of safety concerns are the same as for the existing multiple sclerosis indication and there are no differences between EU-RMP and ASA concerns. Since the time of last RMP evaluation sponsor has updated a safety concern for the missing information; 'use in patients aged over 55 years' to 'use in patients aged over 65 years' to reflect results of ulcerative colitis study findings in elderly cohort. No Australia specific safety concerns are proposed. From an RMP perspective, the summary of safety concerns is acceptable.
- The sponsor has proposed routine pharmacovigilance activities for all safety concerns, including continued use of follow-up forms for leukoencephalopathy and pregnancy in ulcerative colitis patient cohort. 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 and an ongoing clinical Study RPC01-3102 (ulcerative colitis) as additional pharmacovigilance activities to address all safety concerns for ulcerative colitis indication. From an RMP perspective, the proposed pharmacovigilance plan is acceptable.
- The sponsor has proposed routine risk minimisation activities for the majority of safety concerns. The sponsor has proposed a healthcare practitioner checklist and patient/caregiver guide as additional risk minimisation activities to address all important risks, with exception of posterior reversible encephalopathy syndrome which is addressed by routine measures alone. The activities are in line with other S1P receptor modulators and the existing multiple sclerosis indication of Zeposia. Proposed activities are considered a requirement of Zeposia for ulcerative colitis indication as there will be a different prescriber population and patient cohort. Prescribers in both Australia and Europe for multiple sclerosis treatments (including ozanimod) are neurologists and for ulcerative colitis therapies (including ozanimod) are specialist gastroenterologists. From an RMP perspective, the proposed pharmacovigilance plan is considered acceptable overall.

Risk-benefit analysis

Delegate's considerations

The clinical evaluation concluded that the sponsor had demonstrated the efficacy and safety of ozanimod in the treatment of moderate to severe ulcerative colitis,[24] but challenged whether the benefits identified in the population of patients with ulcerative colitis included in the pivotal and supportive studies should be generalised to all patients with moderate to severe ulcerative colitis. One pivotal question was whether study participants, who according to the protocol were required to continue with 5-aminosalicylate agents, or moderate doses of either oral corticosteroids (≤ prednisone 20 mg/day or equivalent) or budesonide multi-matrix, should be considered to '*have had an inadequate response, lost response, or were intolerant to conventional therapy*'. The sponsor's definition of conventional therapy included '*5-aminosalicylates, corticosteroids, immunomodulators*'. Of Cohort 1 patients who were randomised to ozanimod,

[24] As defined by Mayo scores at commencement of treatment.

approximately 70% were receiving concomitant mesalazine, approximately 16% were receiving concomitant sulfasalazine, and approximately 33% were receiving concomitant corticosteroids. A proportion may have had concomitant treatment with both 5-aminosalicylate agents and corticosteroid therapies. In pre-defined subgroup analyses corticosteroid-naïve participants appeared to respond to ozanimod better than those who had been treated with corticosteroids.

The clinical evaluation proposed that a total Mayo score;[19] of 6 to 12 at Baseline despite 5-aminosalicylate or systemic corticosteroid treatment confirms either inadequate or lost response to these two conventional modalities of treatment and therefore this should be reflected in the indication, and the Delegate concurs.

The reverse issue then lies with whether a population restriction in the indication should also include failure to respond or intolerance to other 'conventional' immunomodulators. The inclusion and exclusion criteria regarding previous and concomitant medications in the ozanimod ulcerative colitis trials are included in Table 9. As previously discussed, azathioprine, methotrexate and 6-mercaptopurine have a long history of use in the treatment of ulcerative colitis despite no specific indication. The sponsor argued based on *post hoc* analyses that 49.0% of participants in the induction phase of the pivotal study were naïve to both conventional immunomodulators and anti-TNF or other biological medicines, and therefore could not be considered to have failed these treatments. In the opinion of the sponsor, a restriction to having failed 'conventional' immunotherapies would imply that ozanimod should not be commenced before methotrexate, 6-mercaptopurine or azathioprine have been trialled. The sponsor also contends that as 67.0% of participants in the pivotal induction study were naïve to biological medicines including anti-TNFs and vedolizumab, it would not be correct to require failure of or intolerance to biological therapies prior to trialling ozanimod.

Table 9: Study RPC01-3101 Summary of key criteria pertaining to prior and/or concomitant ulcerative colitis medication (5-aminosalicylates, corticosteroids, immunomodulators, and anti-tumour necrosis factors and other biologics)

Biologics / anti-TNFs
· **Eligibility:** – Prior therapy allowed – Excluded if: used within 8 weeks or 5 elimination half-lives (whichever is less) prior to randomisation; *or* if primary nonresponder to 2 or more biologic agents approved for the treatments of ulcerative colitis – Concomitant use prohibited · **Failed/inadequate response** (per protocol and designated on eCRF): considered after at least 4 weeks (approved for marketing at an approved labelled dose) for induction therapy, or recurrence of disease activity despite scheduled maintenance therapy – **Primary nonresponse** (designated on eCRF): signs and symptoms of persistently active disease despite an adequate trial of induction treatment with an anti-TNF agent (per country's approved label). – **Secondary nonresponse** (designated on eCRF): recurrence of symptoms during maintenance dosing following prior clinical benefit · **Intolerance** (per protocol and designated on eCRF): unable to achieve doses, dose levels, or treatment durations because of treatment-related side effects and/or laboratory abnormalities

Immunomodulators (AZA, 6-MP, MTX)

- **Eligibility:**
  - Prior therapy allowed
  - Excluded: Planned use anytime on or after randomisation
  - Concomitant use prohibited
- **Failed/inadequate response** (per-protocol and designated on eCRF): considered after at least 8 weeks of oral AZA ≥ 1.5 mg/kg or 6-MP ≥ 0.75 mg/kg or MTX ≥ 12.5 mg/week
- **Intolerance** (per protocol and designated on eCRF): unable to achieve doses, dose levels, or treatment durations because of treatment-related side effects and/or laboratory abnormalities

Required concomitant medication (corticosteroids and/or 5-ASA)

- **Eligibility**
  - Required to be on concomitant therapy with either corticosteroids until Week 10 or oral 5-ASAs until Week 52
    - If on corticosteroids, a stable dose for at least 2 weeks prior to screening endoscopy (for example, prednisone ≤ 20 mg per day or equivalent; budesonide MMX: dose not specified for eligibility) was required.
    - If on 5-ASA, a stable dose at least 3 weeks prior to screening endoscopy (for example, mesalamine, sulfasalazine, olsalazine, balsalazide ≥ 2.4 g/day) was required.
  - **Excluded**: topical rectal 5-ASA or topical rectal steroids within 2 weeks prior to screening endoscopy

Required concomitant medication (corticosteroids and/or 5-ASA)

Corticosteroids

- **Failed/inadequate response** (per protocol and designated on eCRF): considered after at least 2 weeks of oral prednisone ≥ 30 mg or budesonide MMX ≥ 9 mg or intravenous corticosteroids for one week.
- **Tapering:**
  - **Induction**: maintain stable dose through Week 10
  - **Maintenance**: taper upon entering the maintenance period (Week 10)
    - Prednisone > 10 mg/day (or equivalent): reduced at a rate of 5 mg per week until a 10 mg/day dose (or equivalent) is achieved.
    - Prednisone 10 mg/day (or equivalent), or once a 10 mg/day dose (or equivalent) is achieved by tapering, should have their dose reduced at a rate of 2.5 mg/week until discontinuation.
    - Budesonide MMX ≥ 9 mg every day reduced to 9 mg every other day for 2 weeks and then discontinued.
  - For subjects who cannot tolerate the corticosteroid taper, the corticosteroid dose may be increased (up to the dose at trial entry if required), but tapering should begin again within 2 weeks.

Aminosalicylates (5-ASAs)

· **Failed/inadequate response** (per protocol and designated on eCRF): considered after at least 8 weeks of oral therapy ≥ 2.4 g/day	
Considerations for statistical analysis	
Biologics/anti-TNFs	Prior anti-TNFs use: stratified at induction (yes/no) Treatment failure if initiated during study
Immunomodulators (AZA, 6-MP, MTX)	Treatment failure if initiated during study
Corticosteroids	Stratified in induction (yes/no based on steroids at screening) and maintenance (yes/no based on steroids at Week 10)[a] Treatment failure if: · initiated during study (oral or rectal) or increased dose above Baseline · systemic steroids used for > 14 days for treatment other than ulcerative colitis
5-ASAs	Treatment failure if initiated during study (oral or rectal) or increased dose above Baseline

Abbreviations: 5-ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; AZA = azathioprine; eCRF = electronic case report form; MMX = multi-matrix; MTX = methotrexate; TNF = tumour necrosis factor.

a Maintenance was also stratified by clinical remission status at Week 10 (yes, no).

Of the recently registered biological and targeted immunotherapies for ulcerative colitis only ustekinumab;[7] has been approved in Australia without population restriction. However, the study information in the ustekinumab PI states that failure of conventional therapy or at least one biological therapy was required:

> Concomitant use of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least one prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least one anti-TNFα therapy and vedolizumab.

For the other registered treatments for moderate to severe ulcerative colitis, failure or inadequate response to conventional immunomodulators and/or biological immunomodulators were enrolment requirements. While the Delegate acknowledges that failure of conventional and biological immunomodulators was not a requirement of the pivotal and supportive studies, the benefits of ozanimod should nevertheless be weighed against relatively scarce long-term safety data.

Proposed action

Ozanimod is approved by the US Food and Drug Administration (FDA) for an open indication, but the description of the clinical trials includes 'who had an inadequate response or were intolerant to any of the following: oral aminosalicylates, corticosteroids, immunomodulators (for example, 6-mercaptopurine and azathioprine), or a biologic (for example, TNF blockers and/or vedolizumab).' This approach aligns with usual FDA

practice. More recently, the EU has also restricted use to patients with moderately to severely active ulcerative colitis who 'had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.'

The decision regarding the indication for ozanimod in the treatment of ulcerative colitis requires this Delegate to consider the benefits and risks of immunomodulatory agents that have a long history of use, against the benefits and potential risks of a new therapy, with apparent safety benefits in the short term, but relatively less long-term safety data in any population. Therefore, pending advice from the Advisory Committee for Medicines (ACM), the Delegate proposes to approve the registration of ozanimod hydrochloride for the following indication, subject to conditions as recommended by the clinical and risk management plan evaluators and agreement on an appropriate PI:

> *For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please indicate what proportion of participants in Study RPC01-3101 were naïve to corticosteroids, and anti-tumour necrosis factor or other biological medicines, and other 'conventional' immunomodulators, that is, participants who had only experienced systemic treatment with oral 5-aminosalicylates.***

To address this request, the sponsor assessed the number and proportion of subjects in the induction period of Study RPC01-3101 who were naïve to corticosteroids, anti-TNF or other biological medicines, and other 'conventional' immunomodulators, that is, subjects who had only experienced systemic treatment with oral 5-aminosalicylates [based treatment]. These subjects did not have any prior treatment with corticosteroids, biologics, or immunomodulators (such as 6-mercaptopurine, azathioprine, methotrexate) before enrolment in Study RPC01-3101 and were not being treated with concomitant corticosteroids at the time of study entry. Within the randomised Cohort 1 study population, there were 89/429 (20.7%) subjects in the ozanimod 1 mg cohort and 44/216 (20.4%) subjects in the placebo cohort who had experienced only systemic treatment with oral 5-aminosalicylates. To provide additional information regarding this population, the sponsor performed efficacy analyses for the induction period primary and key secondary endpoints (see Table 10 below). Similar to that observed in the overall population, a consistent treatment effect that favoured ozanimod 1 mg versus placebo was observed in all pre-specified primary and key secondary endpoints in the induction period in subjects who had experienced only systemic treatment with oral 5-aminosalicylates.

Table 10: Study RPC01-3101 Analysis of the primary and key secondary endpoints for the induction period Cohort 1 in subjects who had only experienced systemic treatment with oral 5-aminosalicylates

	Overall Population				Subjects Who Had Only Experienced Systemic Treatment with Oral 5-ASA			
	Ozanimod 1 mg (N = 429)	Placebo (N = 216)	Difference in Proportions (95% CI)[a]	P-value[a]	Ozanimod 1 mg (N = 89)	Placebo (N = 44)	Difference in Proportions (95% CI)[b]	P-value[b]
Primary endpoint (Week 10)								
Clinical remission (3-component Mayo)[c]	79 (18.4)	13 (6.0)	0.124 (0.075, 0.172)	< 0.0001	23 (25.8)	7 (15.9)	0.099 (-0.042, 0.241)	0.1972
Key secondary endpoints (Week 10)								
Clinical response (3-component Mayo)[d]	205 (47.8)	56 (25.9)	0.219 (0.144, 0.293)	< 0.0001	47 (52.8)	13 (29.5)	0.233 (0.063, 0.403)	0.0112
Endoscopic improvement[e]	117 (27.3)	25 (11.6)	0.157 (0.097, 0.217)	< 0.0001	33 (37.1)	8 (18.2)	0.189 (0.037, 0.341)	0.0264
Mucosal healing (endoscopic improvement with histologic remission)[f]	54 (12.6)	8 (3.7)	0.089 (0.049, 0.129)	< 0.001	14 (15.7)	2 (4.5)	0.112 (0.014, 0.209)	0.0621

Abbreviations: 5-ASA = 5-aminosalicylate; CI = confidence interval; N = number of subjects.

a Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the active and placebo groups are based on the Cochran-Mantel-Haenszel test, stratified by corticosteroid use at Screening and prior anti- tumour necrosis factor use (yes or no).

b Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the active and placebo groups are based on the Chisquare test.

c Clinical remission is defined as: rectal bleeding subscore = 0 point and stool frequency subscore ≤ 1 point (and a decrease of ≥ 1 point from the Baseline stool frequency subscore) and endoscopy subscore ≤ 1 point.

Subjects with any of rectal bleeding subscore, stool frequency subscore, and endoscopy subscores missing at Week 10 are classified as non-remitters.

d Clinical response is defined as: A reduction from Baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from Baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point. Subjects with any of rectal bleeding subscore, stool frequency subscore, and endoscopy subscores missing at Week 10 are classified as non-responders.

e Endoscopic improvement is defined as: Endoscopy subscore of ≤ 1 point. Subjects with missing endoscopy subscore at Week 10 are classified as non-responders.

f Mucosal healing is defined as: endoscopy subscore of ≤ 1 point and Geboes index score < 2.0. Subjects with missing endoscopy subscore or Geboes index score at Week 10 are classified as non-responders.

Three-component Mayo (range of zero to 9 points): Sum of the rectal bleeding subscore, stool frequency subscore, and the endoscopy subscore.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***a. What is the understanding of the Committee regarding the role of conventional immunomodulators (not including 5-aminosalicylates and corticosteroids) in the treatment of ulcerative colitis in Australia?***

The ACM advised that the current treatment algorithm is to start with 5-aminosalicylates, then move to immunomodulators azathioprine/mercaptopurine if the patient has an inadequate response to 5-aminosalicylates.

The ACM commented that immunomodulators azathioprine/mercaptopurine is effective in maintaining moderate ulcerative colitis. The ACM noted a metanalysis of randomised control trials comparing immunomodulators azathioprine/mercaptopurine with placebo/5-aminosalicylates.[25] From the thirty non-controlled studies, the mean efficacy of immunomodulators azathioprine/mercaptopurine was 65% for induction and 76% for maintenance of the remission. From the seven controlled studies, mean efficacy for induction of remission was 73% versus 64% in controls (odds ratio (OR) = 1.59; 95% confidence interval (CI): 0.59, 4.29) and for maintenance of remission it was 60% versus 37% in controls (OR = 2.56; 95% CI: 1.51, 4.34).

b. What is the understanding of the Committee regarding the role of biological medicines (monoclonal antibodies, fusion proteins) and targeted immunomodulators (for example, Janus kinase inhibitors), compared to conventional immunomodulators in the treatment of ulcerative colitis in Australia?

The ACM commented that in clinical practice if patients do not have a response or are intolerant to immunomodulators azathioprine/mercaptopurine then they would be eligible for a biological therapy or a targeted immunomodulator.

Currently available therapies for moderate to severe ulcerative colitis include TNF inhibitors (infusion/injections), integrin inhibitors (infusion), interleukin (IL)-12 and 23 inhibitors (infusion/injection), and Janus kinase inhibitors (oral). These therapies have variable remission rates of 15% to 60%. In addition, 23% to 46% of patients who achieve remission with TNF inhibitors will lose response over time, possibly because of the development of antibodies.

2. What is the opinion of the Committee regarding the risk-benefit profile of ozanimod in patients with ulcerative colitis who are naïve to alternative immunomodulators compared to those who have not responded to, lost response to, or been intolerant to alternative immunomodulators?

For ulcerative colitis patients that have not responded to, lost response to, or been intolerant to either conventional therapy or a biological therapy, the ACM was of the view that Zeposia provides a useful oral treatment option with a novel mechanism of action, rapid absorption, and a good bioavailability.

The ACM advised that while Zeposia is reasonably efficacious it does not resolve the need for ulcerative colitis treatment options with higher efficacy rates, which should be used first in the treatment algorithm.

The ACM noted the sponsor's pre-ACM analyses of 20% of the study population who had received only 5-aminosalicylates prior to commencing the induction study, as well as the sponsor's rationale for a broader indication. The ACM commented that this was a post hoc analysis that was underpowered with small numbers and was not a predefined subset for the study. The ACM was strongly in favour of the narrower indication at this time and advised that further studies would be required to determine if this novel agent is appropriate following 5-aminosalicylates only.

The ACM noted a recent indirect analysis comparing the efficacy and safety of ozanimod versus adalimumab and vedolizumab in ulcerative colitis patients where subjects treated with ozanimod achieved significantly higher rates of clinical response (OR: 1.53,

[25] Gisbert, J.P. et al. Meta-Analysis: the Efficacy of Azathioprine and Mercaptopurine in Ulcerative Colitis, *AP&T*, 2009; 30, 126-137.

$p < 0.01$).[26] The ACM advised that head-to-head studies with existing treatment options would assist in the development of treatment algorithms.

The ACM was of the view that the safety profile of Zeposia may narrow its utility across the ulcerative colitis population and highlighted the importance of doing a thorough baseline assessment before prescribing, particularly in the older age group. The ACM commented that long term data on safety for this therapy is important. The ACM noted that Zeposia has been approved in Australia for use in multiple sclerosis since 2020. The ACM was of the view that it was not ideal to extrapolate the post market experience of Zeposia in multiple sclerosis to ulcerative colitis and that the post market experience with Zeposia is relatively new.

3. Other Advice.

The ACM discussed concurrent use of 5-aminosalicylates with Zeposia, noting that the majority of the trial participants were receiving concurrent 5-aminosalicylates and that in clinical practice all patients are started on 5-aminosalicylates.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Zeposia (ozanimod) 230 µg and 460 µg capsule (composite pack), 920 µg capsule (blister pack), for the following extension of indications:

> ***Ulcerative colitis***
>
> *Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*

As such, the full indications at this time were:

> ***Multiple sclerosis***
>
> *Zeposia is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis.*
>
> ***Ulcerative colitis***
>
> *Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*

Specific conditions of registration applying to these goods

- Zeposia (ozanimod) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Zeposia must include the black triangle

[26] Dubinsky, M. et al. S694 Comparative Efficacy and Safety of Ozanimod vs Adalimumab and Vedolizumab in Patients with Moderately to Severely Active Ulcerative Colitis, *Am J Gastroenterol,* 2021; 116: S314.

symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

- The Zeposia EU-risk management plan (RMP) (version 1.1, dated 3 November 2020, data lock point 31 March 2020), with Australian specific annex (version 3.0, dated 5 February 2021), included with Submission PM-2021-00444-1-1, and any subsequent revisions, as agreed with 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).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs 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. Note that submission of a PSUR does not constitute an application to vary the registration.

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 PI/CMI search facility.

Therapeutic Goods Administration

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