5.05 OZANIMOD, Capsule, 230 micrograms, 460 micrograms, 920 micrograms, Zeposia®, Celgene Proprietary Limited.

1 Purpose of submission

1.1 The submission requested an Authority Required listing for ozanimod for the treatment of clinically definite relapsing-remitting multiple sclerosis (RRMS).

1.2 Listing was requested on the basis of a cost-minimisation analysis versus fingolimod. The key components of the clinical issue addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with RRMS
Intervention	Ozanimod
Comparator	Fingolimod
Outcomes	Primary: Annualised relapse rate (ARR) Secondary: time to onset of disability progression; MRI outcomes; safety
Clinical claim	In patients with RRMS, ozanimod is non-inferior compared with fingolimod at reducing relapses and preventing disease progression and non-inferior (potentially superior) compared with fingolimod in terms of comparative safety

Source: Table 13, p2 of the submission.
Abbreviation: MRI = magnetic resonance imaging; RRMS = relapsing-remitting multiple sclerosis

2 Background

Registration status

2.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Round 1 Clinical Evaluation Report (CER) was available. The TGA Delegate's Overview is expected in May 2020.

3 Requested listing

3.1 See below for the requested listing. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
OZANIMOD					
Capsule, 0.23 mg, 4 capsules Capsule, 0.46 mg, 3 capsules	7	0	*$552.60* [a]	ZEPOSIA®	Celgene Pty Ltd
Capsule, 0.92 mg capsules	28	5	*$2,210.41*[a]		

Category/Program:	General Schedule
PBS indication:	Multiple sclerosis
Treatment phase:	Initial
Restriction:	~~Authority – Telephone, Electronic~~ *Authority - Streamlined*
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition, AND Patient must be ambulatory (without assistance or support). OR ~~Patients must have previously received PBS-subsided treatment with this drug for this condition, AND~~ Patient requires re-initiation of therapy following treatment interruption of more than 14 consecutive days
Prescriber Instructions:	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

[a] *Published DPMQ used in financial estimates based on daily treatment cost with fingolimod.*

Name, Restriction, Manner of administration and form	Max. Qty	№. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
Capsule, 0.92 mg capsules	28	5	*$2,210.41*[a]	ZEPOSIA®	Celgene Pty Ltd

Category/Program:	General Schedule
PBS indication:	Multiple sclerosis
Treatment phase:	Continuing
Restriction:	~~Authority – Telephone, Electronic~~ *Authority - Streamlined*
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND ~~Patient must be receiving benefit from treatment with this drug~~ *Patient must not show continuing progression of disability due to multiple sclerosis while on treatment with this drug* AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Prescriber Instructions:	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

[a] *Published DPMQ used in the financial estimates consistent with the published DPMQ of fingolimod.*

3.2 The submission requested listing on a cost minimisation basis with fingolimod. As fingolimod is subject to a special pricing arrangement (SPA), the requested price for ozanimod was based on the published price of fingolimod. The submission sought a SPA consistent with the effective price of fingolimod.

3.3 At its November 2019 meeting, the PBAC recommended changing the authority level of the current listings for dimethyl fumarate, fingolimod, teriflunomide and cladribine for the treatment of RRMS to Authority Required (Streamlined)[1]. The Pre-Sub-Committee Response (PSCR) agreed with the proposal to align the authority level of ozanimod with that of other oral RRMS therapies per the November 2019 PBAC recommendation.

3.4 The submission requested that prescribers be able to prescribe the seven-day titration pack and first 28-day pack with five repeats at the same time. The submission noted that this would provide a similar length of initiation treatment as the fingolimod listing and would be more convenient for prescribers and patients. The ESC considered that this approach was appropriate.

[1] http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2019-11/positive-recommendations-11-2019.docx.pdf

3.5 The submission proposed alternative text for the continuation criterion for fingolimod, 'Patient must not show continuing progression of disability while on treatment with this drug' with the wording: 'Patient must be receiving benefit from treatment with this drug'. The submission considered the existing criterion was ambiguous and may prevent subsidy for patients who have worsening disability due to other factors (such as age) rather than disease progression. The Secretariat proposed alternative wording to clarify the current criteria 'Patient must not show continuing progression of disability due to multiple sclerosis while on treatment with this drug'. The PBAC considered that no change to the continuation criteria was necessary.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Multiple sclerosis (MS) is an idiopathic neurodegenerative disease characterised by autoimmune degradation of myelin sheaths surrounding the nerve cells in the central nervous system (CNS), leading to impaired nervous conduction of electrical impulses. This is thought to be started by lymphocytes crossing the blood brain barrier. MS can cause a range of symptoms which may include numbness and weakness in the legs, difficulty walking, loss of sensation, vision loss, loss of coordination, cognitive dysfunction, fatigue, pain, bladder and bowel disturbance, and neuropsychological symptoms such as depression.

4.2 RRMS is the most common type of MS and is estimated to affect 85% of newly diagnosed MS patients. Patients with RRMS experience exacerbations ('flare-ups' or relapses) of symptoms, followed by remission of symptoms. Patients with RRMS typically develop irreversible disability over time. The clinical course of MS is varied. The symptoms of MS and accumulation of disability progressively reduce the quality of life for people with MS.

4.3 Ozanimod is a selective sphingosine 1-phosphate (S1P) receptor (S1PR) modulator. The mechanism of action for ozanimod is not fully understood; however, the submission stated that ozanimod reduces the movement of activated lymphocytes into the brain, reducing the autoimmune attack on nerve cells. Ozanimod and fingolimod have a similar mechanism of action; but ozanimod demonstrates greater receptor specificity (S1PR2 and S1PR5 receptor subtypes) compared with fingolimod (S1PR1, S1PR3, S1PR4, S1PR5 receptor subtypes). The PBAC noted there are a number of S1P inhibitor drugs undergoing clinical trials, and that newer generation drugs are more selective for specific S1P receptor subtypes, whilst fingolimod is relatively non-selective.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated fingolimod as the comparator. This was based on both drugs being pharmacological analogues that target the S1P receptor pathway, fingolimod having the largest market share of RRMS treatments, and both treatments being oral DMTs. This was reasonable. However, in practice, ozanimod could substitute for all PBS subsidised RRMS medicines. If PBS-listed, ozanimod would be one of more than 10 DMTs available on the PBS for patients with RRMS.

5.2 Based on the randomised head-to-head trials presented in the submission, ozanimod demonstrated statistically significant reductions in annualised relapse rate (ARR) compared with IFN-β1a. Other PBS-listed treatments for RRMS listed on a cost-minimisation basis with IFN-β1a include the other ABCR therapies (subcutaneous IFN-β1a, intramuscular IFN-β1a, IFN-β1b, peginterferon-β1a and glatiramer acetate), teriflunomide and dimethyl fumarate.

5.3 Fingolimod and natalizumab were recommended on a cost-effectiveness basis compared with IFN-β1a and IFN-β1b, respectively. Ocrelizumab and cladribine were listed on a cost minimisation basis with fingolimod and alemtuzumab was listed on a cost minimisation basis with both fingolimod and natalizumab.

5.4 Under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from MS Australia and MS Research supporting the listing of ozanimod for RRMS. The submissions noted the importance of having a range of treatment options for RRMS and highlighted the results of the SUNBEAM and RADIANCE trials supported the effectiveness of ozanimod.

Clinical trials

6.3 No head-to-head trials comparing ozanimod to fingolimod were available. The submission was based on two indirect treatment comparisons (ITCs) between ozanimod and fingolimod using IFN-β1a as the common comparator:

- The main ITC compared ozanimod (SUNBEAM) with fingolimod (TRANSFORMS). These trials were nominated for the main ITC due to similar trial durations (at least 12 months, and 12 months, respectively); and
- A sensitivity analysis of the ITC compared ozanimod (meta-analysis of SUNBEAM and RADIANCE B [24 months]) with fingolimod (TRANSFORMS).

6.4 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trials comparing ozanimod with IFN-β1a		
SUNBEAM	A Phase 3, Multi-Centre, Randomised, Double-Blind, Double-Dummy, Active-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients.	CSR
	Comi G, Kappos L, *et al.* Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multi-centre, randomised, minimum 12-month, Phase 3 trial.	Lancet Neurol. 2019 Sep 3. pii: S1474-4422(19)30239-X. doi: 10.1016/S1474-4422(19)30239-X
RADIANCE B	A Phase 3, Multi-Centre, Randomised Double-Blind, Double-Dummy, Active-Controlled (Part B), Parallel Group Study To Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients.	CSR
	Cohen JA, Comi G, *et al.* Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multi-centre, randomised, 24-month, Phase 3 trial.	Lancet Neurol. 2019 Sep 3. pii: S1474-4422(19)30238-8. doi: 10.1016/S1474-4422(19)30238-8.
Trial comparing fingolimod with IFN-β1a		
TRANSFORMS	Cohen JA, Barkhof F, *et al.* (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis.	New England Journal of Medicine 362: 402-415.
	Barkhof F, De Jong R, *et al.* (2014). The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs. FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), a Phase 3 study of fingolimod in multiple sclerosis.	Multiple Sclerosis 20: 1704-1713.
	Khatri BO, Pelletier J, *et al.* (2014). Effect of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod vs. interferon β-1a intramuscular: Subgroup analyses of the Trial Assessing Injectable Interferon vs. Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS).	Multiple Sclerosis and Related Disorders 3: 355-363.
	Cohen JA, Barkhof F, *et al.* (2013). Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS.	Journal of Neurology 260: 2023-2032.

Source: Table 26, p29 of the submission.
CSR = clinical study report

6.5 The key features of the direct randomised trials used in the ITC are summarised in the table below.

Table 3: Key features of the included evidence – indirect treatment comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Ozanimod vs. IFN-β1a					
SUNBEAM	1,346	DB, MC, R ≥ 12 months	Low	Adult, RMS	Relapse rate [a] Disability progression MS related lesions
RADIANCE B	1,313	DB, MC, R 24 months	Low	Adult, RMS	Relapse rate [a] Disability progression MS related lesions
Fingolimod vs. IFN-β1a					
TRANSFORMS	1,292	DB, MC, R 12 months	Low	Adult, RRMS	Relapse rate [b] Disability progression MS related lesions

Source: Sections 2.2-2.4, pp24-43 of the submission.
DB = double blind; EDSS = Expanded Disability Status Scale; FS = functional system; IFN = interferon; MC = multi-centre; OL = open label; PRMS = Primary progressive multiple sclerosis; R = randomised; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis
Note: The ozanimod trials, SUNBEAM and RADIANCE B, included a small proportion of participants with SPMS (five and one participant, respectively) and PRMS (19 and 23 participants, respectively).
[a] A relapse was defined as new or worsening neurological symptoms (≥ 0.5 EDSS point, or ≥ 2 points on a single FS, or ≥ 1 point on ≥ 2 FS).
[b] A relapse was defined as new or worsening neurological symptoms (≥ 0.5 EDSS point, or ≥ 2 points on a single FS, or ≥ 1 point on ≥ 2 FS excluding changes in bowel or bladder function and cognition) attributable to MS and immediately preceded by a relatively stable or improving neurological state of ≥ 30 days.

6.6 There were differences across the trials in treatment durations; the SUNBEAM and TRANSFORMS trials had a one-year duration; and the RADIANCE B trial had a two-year duration. The submission addressed this by presenting two ITCs: a main ITC that compared the one-year trials and an ITC sensitivity analysis that included both ozanimod trials with the key fingolimod trial.

6.7 The ozanimod trials (SUNBEAM and RADIANCE B) and the fingolimod trial (TRANSFORMS) differed with respect to the key eligibility criteria as outlined in Table 4 below. Key differences between the 2005 and 2010 McDonald criteria relate to changes to requirements for demonstrating dissemination of lesions in space (DIS) and time (DIT) as part of the diagnosis of MS[2].

[2] Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292–302. doi:10.1002/ana.22366

Table 4: Key differences in the eligibility criteria across the randomised trials

	SUNBEAM	RADIANCE B	TRANSFORMS
Diagnosis	Diagnosis of MS using 2010 McDonald criteria	Diagnosis of MS using 2010 McDonald criteria	Diagnosis of MS using the 2005 McDonald criteria
Disease course	Relapsing clinical course and history of brain lesions consistent with MS	Relapsing clinical course and history of brain lesions consistent with MS	RRMS course of disease only
Disease progression	EDSS score of 0 to 5.0	EDSS score of 0 to 5.0	EDSS score of 0 to 5.5
Relapse history	≥ 1 relapse in the last 12 months OR 1 relapse in the last 24 months and evidence of ≥ 1 Gde brain lesion in the last 12 months	≥ 1 relapse in the last 12 months OR 1 relapse in the last 24 months and evidence of ≥ 1 Gde brain lesion in the last 12 months	1 relapse in the last 12 months OR 2 relapses in previous 24 months

Source: Table A 1, Appendix A, p3 of the submission.
EDSS = Expanded Disability Status Scale; Gde = gadolinium enhanced; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.

6.8 The submission considered the differences in the baseline characteristics of participants in the trials in terms of prior treatment history, presence and volume of magnetic resonance imaging (MRI) lesions, relapse history, disability, and region did not affect the transitivity assumption. However, there were differences in disability progression rates in the IFN-β1a arm of the trials (refer to paragraph 6.12). The submission argued that patients in the ozanimod trial had a greater MRI disease burden, based on fewer gadolinium-enhanced (Gde) T1 lesions, greater mean volume of T2 lesions, and a lower normalised brain volume. The submission did not present evidence to support its claim that MRI disease burden affected treatment response. A post-hoc analysis of fingolimod trials reported that lower normalised brain volume was found to be predictive of disability worsening (Sormani et al. 2017). There were also differences in the definition of a relapse as the fingolimod trial (TRANSFORMS) did not consider changes in the bowel and bladder or cognition functional systems. The differences in the assessment of relapses was a transitivity issue of the indirect comparison of ARR, with an unclear direction of bias.

6.9 The PSCR argued that the SUNBEAM trial had a higher mean baseline Expanded Disability Status Scale (EDSS) score and higher MRI burden than TRANFORMS, which biased against ozanimod in the indirect comparison. The ESC considered that differences in patient baseline characteristics, differences in 3-month confirmed disability progression in the comparator (IFN-β1a) arms in the clinical trials and differences in the definition of relapse were all potential transitivity issues, which had an unknown effect on outcomes and uncertain direction of bias. In particular, the ESC noted that a greater proportion of patients in the TRANSFORMS trial had prior treatment with DMT at baseline (56.7%) compared to the SUNBEAM and RADIANCE B trials (30.5% and 28.9% respectively).

Comparative effectiveness

6.10 The results for the key direct and indirect comparisons presented in the submission are presented in Table 5.

Table 5: Key relapse, disability, and MRI outcomes between ozanimod, fingolimod and IFN-β1a

Trial	Ozanimod	IFN-β1a	Fingolimod	Treatment difference (95% CI)
Annualised relapse rate, RR (95% CI)				
SUNBEAM	0.18 (0.14, 0.24)	0.35 (0.28, 0.44)	-	**0.52 (0.41, 0.66)**
RADIANCE B	0.17 (0.14, 0.21)	0.28 (0.23, 0.32)	-	**0.62 (0.51, 0.77)**
Meta-analysis of ozanimod trials (Chi2= 1.26; I2 = 21%; p= 0.26)				**0.58 (0.48, 0.69)**
TRANSFORMS	-	0.33 (0.26, 0.42)	0.16 (0.12, 0.21)	**0.48 (0.37, 0.64)**
Main ITC (ozanimod [SUNBEAM] vs. fingolimod)				1.08 (0.75, 1.56)
ITC sensitivity analysis (ozanimod [meta-analysis] vs. fingolimod)				1.21 (0.88, 1.66)
Confirmed 3-month disability progression, HR (95% CI)				
SUNBEAM	13 (2.91%)	19 (4.24%)	-	0.69 (0.34, 1.40)
RADIANCE B	54 (12.47%)	50 (11.34%)	-	1.05 (0.71, 1.54)
Meta-analysis of ozanimod trials (Chi^2= 1.02; I^2 = 2%; P= 0.31)				0.95 (0.67, 1.34)
TRANSFORMS		34 (7.89%)	25 (5.83%)	0.71 (0.42, 1.21)
Main ITC (ozanimod [SUNBEAM] vs. fingolimod)				0.97 (0.40, 2.35)
ITC sensitivity analysis (ozanimod [meta-analysis] vs. fingolimod)				1.34 (0.71, 2.52)
Number of new or enlarging hyperintense lesions on T2 weighted images, RR (95% CI)				
SUNBEAM	1.47 (1.20, 1.78)	2.84 (2.33, 3.45)	-	**0.52 (0.43, 0.63)**
RADIANCE B	1.84 (1.52, 2.21)	3.18 (2.64, 3.84)	-	**0.58 (0.47, 0.71)**
Meta-analysis of ozanimod trials (Chi2= 0.60; I2 = 0%; P= 0.44)				**0.54 (0.47, 0.62)**
TRANSFORMS	-	2.60 (2.00, 3.20)	1.70 (1.30, 2.10)	**0.65 (0.49, 0.87)**
Main ITC (ozanimod [SUNBEAM] vs. fingolimod)				0.79 (0.56, 1.12)
ITC sensitivity analysis (ozanimod [meta-analysis] vs. fingolimod)				0.83 (0.60, 1.14)

Source: Table 66, p107; Table 67, p108; and Table 68, p109 of the submission.
HR = hazard ratio; IFN = interferon; ITC = indirect treatment comparison; MRI = magnetic resonance imaging; RR = rate-ratio; vs. = versus
Note: Bolded values indicate statistically significant difference
Note: Rate-ratio or hazard ratio < 1 favours ozanimod/fingolimod in the direct comparisons or ozanimod in the ITC.

6.11 Treatment with ozanimod was associated with a statistically significant reduction in ARR and a reduction in the number of new or enlarging hyperintense lesions on T2 weighted images on MRI (referred to hereafter as "MRI outcomes") compared with IFN-β1a. There was no statistically significant difference in confirmed 3-month disability progression events between ozanimod and IFN-β1a. The hazard ratio for confirmed 3-month disability progression favoured ozanimod in the SUNBEAM trial (hazard ratio: 0.69 over 12 months) but was neutral in the RADIANCE B trial (hazard ratio: 1.05 over 2 years). The submission argued disability progression may take several years to accumulate and as such it is challenging to measure in trials due to limitations of the EDSS instrument and relatively shorter trial durations. This claim was reasonable as the trials were not powered to detect differences in disability progression and the low sensitivity of the EDSS (Uitdehaag, 2018). However, the proportion of patients with 3-month confirmed disability progression in the longer RADIANCE B trial was similar in the ozanimod and IFN-β1a arms. The ESC considered that, on balance, the evidence supported ozanimod having superior effectiveness compared to IFN-β1a.

6.12 The main ITC between ozanimod and fingolimod found no statistically significant difference in ARR, disability progression, or MRI outcomes, with the point estimates numerically favoured ozanimod marginally for two of the three outcomes (disability

progression and MRI outcomes). The ITC sensitivity analysis, which included both ozanimod trials, also found no statistically significant difference in ARR, disability progression, or MRI outcomes, however the point estimates shifted further in favour of fingolimod for ARR, favoured fingolimod for disability progression, and continued to favour ozanimod for MRI outcomes. The disability progression rates differed between the IFN-β1a arms of the SUNBEAM and TRANSFORMS trials (4.2% vs. 7.9%, respectively) although the trials were of a similar duration. This may suggest patients in the TRANSFORMS trial were at a greater risk of worsening disability. The ESC noted patients in the TRANSFORMS trial had a higher use of prior DMTs at baseline (paragraph 6.9) which may further indicate these patients are at a greater risk of worsening disability.

6.13 The submission argued the lack of statistically significant differences across ARR, 3-month confirmed disability progression and lesion outcomes in the ITC supported the claim of non-inferiority. The submission did not nominate a non-inferiority margin. The ESC noted the confidence intervals in the ITC were wide and greater than the minimal clinically important differences (MCIDs) for RRMS previously presented to the PBAC.

6.14 The ESC noted the PBAC has not previously specified an acceptable non-inferiority margin for ARR for RRMS. MCIDs for ARR previously considered, but not formally accepted by the PBAC for RRMS included 1.46 (paragraph 6.3, cladribine PSD, July 2018 PBAC meeting) and 1.23 (paragraph 6.14, ocrelizumab PSD, July 2017 PBAC meeting).

6.15 The ESC agreed with the PSCR that the results from the main ITC of the SUNBEAM and TRANSFORMS trials were the most reliable basis upon which to consider the comparative effectiveness of ozanimod and fingolimod. The ESC noted there were no statistically significant differences in any of the primary or secondary efficacy outcomes in the main ITC or the sensitivity analysis using the meta-analysed SUNBEAM and RADIANCE-B trials.

Comparative harms

6.16 Table 6 presents a summary of key adverse events (AEs) from the ozanimod trials.

Table 6: Summary of key adverse events in the ozanimod trials

	SUNBEAM (at least 12 months)			RADIANCE B (24 months)		
	Ozanimod 0.92 mg	IFN-β1a 30 µg	RD (95%CI)	Ozanimod 0.92 mg	IFN-β1a 30 µg	RD (95%CI)
N	448	445	-	434	440	-
Follow up, median days (range)	413 (4, 671)	414 (5, 639)	-	729 (3, 745)	729 (1, 743)	-
Summary of adverse events, n (%)						
At least one AE	268 (59.8)	336 (75.5)	**-0.16 (-0.22, -0.10)**	324 (74.7)	365 (83.0)	**-0.08 (-0.14, -0.03)**
At least one moderate or severe AE	138 (30.8)	182 (40.9)	**-0.10 (-0.16, -0.04)**	170 (39.2)	235 (53.4)	**-0.14 (-0.21, -0.08)**
At least one severe AE	7 (1.6)	10 (2.2)	-0.01 (-0.02, 0.01)	15 (3.5)	19 (4.3)	**-0.01 (-0.03, -0.02)**
Influenza-like illness	17 (3.8)	227 (51.0)	**-0.47 (-0.52, -0.42)**	27 (6.2)	215 (48.9)	**-0.43 (-0.48, -0.37)**
Pyrexia	5 (1.1)	28 (6.3)	**-0.05 (-0.08, -0.03)**	11 (2.5)	28 (6.4)	**-0.04 (-0.07, 0.01)**
Increased ALT	21 (4.7)	8 (1.8)	**0.03 (0.01, 0.05)**	26 (6.0)	20 (4.5)	0.01 (-0.02, 0.04)
Increased GGT	15 (3.3)	2 (0.4)	**0.03 (0.01, 0.05)**	25 (5.8)	9 (2.0)	**0.04 (0.01, 0.06)**

Source: Table 49, p83; Table 42, p75; Table 48, p82; Table 56, p92 of the submission.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; IFN = interferon; NR = not reported; RD = risk difference; ULN = upper limit of normal
Note: RD< 0 is associated with fewer events in the ozanimod treatment group
Note: Bolded values indicate statistical significance based on 95% CI

6.17 In both trials, ozanimod was associated with fewer AEs than IFN-β1a, including fewer instances of influenza-like illness and pyrexia. Patients in the ozanimod arms were more likely to have raised alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT). The ESC considered the evidence supported ozanimod having a superior safety profile compared to IFN-β1a.

6.18 The submission presented a naïve comparison of AEs across the ozanimod and fingolimod trials (Table 7). The submission considered an ITC for safety was not appropriate given the potential confounding differences in the proportion of participants who had received DMT prior to baseline. This was not consistent with the use of an ITC for effectiveness outcomes.

Table 7: Summary of adverse events reported during ozanimod and fingolimod trials (Safety population)

	SUNBEAM (≥ 12 months)		RADIANCE B (24 months)		TRANSFORMS (12 months)	
	OZ 0.92 mg *N = 448*	IFN-β 30 µg *N = 445*	OZ 0.92 mg N = 434	IFN-β 30 µg N = 440	FING.5 mg N = 429	IFN-β 30 µg N = 431
Summary of adverse events reported during trials, n (%)						
At least one AE	268 (59.8)	336 (75.5)	324 (74.7)	365 (83.0)	369 (86.0)	395 (91.6)
At least one serious AE	13 (2.9)	11 (2.5)	28 (6.5)	28 (6.4)	30 (7.0)	25 (5.8)
Discontinuation of study drug due to AE	13 (2.9)	16 (3.6)	13 (3.0)	18 (4.1)	24 (5.6)	16 (3.7)
Key adverse events, n (%)						
Bradycardia	1 (0.2)	0	0	0	2 (0.5)	0
AV-block (1st degree)	2 (0.2)	0	0	0	1 (0.2)	0
AV-block (2nd degree)	0	0	0	0	1 (0.2)	0
Mean change in heart rate following first dose, BPM (SD) [a]	0.6 (7.85)	8.2 (9.54)	0.4 (7.47)	8.9 (10.67)	-8 (NR)	NR
Maximum mean change in heart rate following first dose, BPM	-1.8	NR	1.7	NR	8.0	NR
ALC< 0.5 x 10^9/L, n (%)	231 (51.8)	8 (1.8)	249 (57.8)	6(1.4)	NR	NR
ALC< 0.4 x 10^9/L, n (%)	NR	NR	NR	NR	308 (71.8)	11 (2.6)
Infections (serious)	5 (1.1)	3 (0.7)	4 (0.9)	4 (0.9)	NR (0.2% to 1.7%)	
Increased ALT [b]	19/447 (4.3)	10/445 (2.2)	29/431 (6.7)	17/434 (3.9)	32/380 (8.4)	9/378 (2.3)
Increased AST	3/447 (0.7)	7/445 (1.6)	6/431 (1.4)	12/434 (2.8)	8/380 (2.1)	7/377 (1.9)
Increased GGT	15 (3.3)	2 (0.4)	25 (5.8)	9 (2.0)	NR All fingolimod trials: 6.0% [c]	

Source: Table 69, p111, and Table 70, p113 of the submission; Table 77, p168 of the fingolimod AUSPAR; Table 14.3.2.1 of the SUNBEAM CSR; Table 14.3.2.1 of the RADIANCE B CSR.

AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AV = atrioventricular; BPM = beats per minute; CSR = clinical study report; GGT = gamma-glutamyltransferase; IFN = interferon; NR = not reported; SD = standard deviation

[a] First-dose heart rate measurements were conducted from baseline to six hours in SUNBEAM and RADIANCE B. The duration of first-dose heart rate measurements was not reported in TRANSFORMS; however, maximum mean changes in heart rate were observed four to five hours after baseline

[b] Greater than or equal to 3 times of upper limit of normal range.

[c] Data from all patients in double-blind, randomised, and placebo or active-controlled studies fingolimod studies at 12 months with GGT greater than three times upper level of normal.

6.19 The submission considered the naïve comparison of AEs suggested the safety profile of ozanimod was similar to fingolimod, with the exception of ozanimod having fewer first dose cardiac events such as bradycardia or decreased heart rate, and atrioventricular block. Ozanimod was also associated with lower reductions in absolute lymphocyte count (ALC), fewer increases in liver enzymes (ALT and AST), and fewer discontinuations due to AEs. Bradycardia and atrioventricular block both occurred with ozanimod and fingolimod but not with IFN-β1a. However, the mean change in heart rate appeared lower in the ozanimod trials compared with the TRANSFORMS trial. The submission's claim that ozanimod was associated with lower reductions in ALC compared with fingolimod appeared reasonable over the trial durations. The submission considered lower reductions in ALC may be clinically important, since ALC in peripheral blood is associated with protection against infection and immune surveillance against cancer cells. However, the incidence of serious

infections were similar between the ozanimod and fingolimod treatment arms compared with IFN-β1a. Ozanimod had numerically lower proportions of patients with increases in ALT and AST; however, it was not clear whether these differences were clinically meaningful.

6.20 The submission stated ozanimod does not require first-dose cardiac monitoring. The ESC noted the TGA CER) received during evaluation supported this claim, with the evaluator stating that, 'introduction of a 7-day dose escalation regimen…was not associated with any clinically meaningful HR [heart rate] reductions, conduction or rhythm abnormalities or cardiac AEs [adverse events]. Hence, first-dose cardiac monitoring is not necessary in patients who do not have significant cardiovascular condition'.

Clinical claim

6.21 The submission described ozanimod as non-inferior in terms of effectiveness compared to fingolimod. The submission's claim of non-inferiority may not be fully supported as:

- the 95% confidence intervals were wide and the upper limit for ARR was higher than MCID values presented in previous RRMS submissions (although these values were not accepted by the PBAC); and
- differences in the rates of 3-month confirmed disability progression in the IFN-β1a arms in the SUNBEAM and TRANSFORMS trials and differences in the baseline proportion of patients with prior treatment with DMTs suggested there may be underlying differences in the patient populations and a possible transitivity issue, with an unknown effect on outcomes.

6.22 The submission described ozanimod as non-inferior (potentially superior) in terms of safety compared with fingolimod. The ESC considered that the claim of non-inferior safety was adequately supported.

6.23 The PBAC considered that, on balance, the claim of non-inferior comparative effectiveness was reasonable.

6.24 The PBAC considered that the claim of non-inferior comparative safety was reasonable overall and that ozanimod may have a modest safety advantage at the time of initiation due to lower risk of first-dose cardiac adverse events.

Economic analysis

6.25 The submission presented a cost minimisation analysis based on a claim of non-inferiority compared with fingolimod (Table 8). The equi-effective doses were estimated as ozanimod 0.92 mg once daily and fingolimod 0.5 mg once daily.

6.26 Based on the cost-minimisation analysis presented in the submission (using the published fingolimod DPMQ), the DPMQ for ozanimod was calculated to be $2,210.41

for the 28-day pack. Cost-minimisation analyses should be conducted using the ex-manufacturer price (AEMP). However, given both standard pack sizes for ozanimod and fingolimod provide 28-days' therapy and no other costs were included, the cost minimisation using the AEMP would not change the cost-minimised price of ozanimod. The DPMQ for the titration pack of ozanimod is $577.81 based on the AEMP of seven days of ozanimod treatment.

Table 8: Cost minimisation analysis

Row	Parameter	Value	Source / Reference
A	FING maximum quantity	28	PBS item 5262Y
B	FING PBS price (published DPMQ)	$2,210.41	PBS item 5262Y
C	FING total cost per day	$78.94	= B / A
D	OZA maximum quantity	28	Proposed item
E	OZA price per day	$78.94	= C
F	OZA 28-tablet pack price (published DPMQ)	$2,210.41	D x E
G	OZA 28-tablet pack price (ex-manufacturer)	$2,058.29	Calculated from F
H	Ozanimod titration pack price (ex-manufacturer)	$514.57 [a]	G / 28 × 7
I	Ozanimod titration pack price (published DPMQ)	$577.81 [a]	Calculated from H

Source: Table 87, p152 of the submission.
DPMQ = dispensed price maximum quantity; FING = fingolimod; OZA = ozanimod; PBS = Pharmaceutical Benefits Scheme
Note: The published price for fingolimod is used as a proxy for ozanimod published price in the submission. The final published and net list price will be determined during the listing process.
[a] Recalculated during the evaluation based on 7 days cost of ozanimod at ex-manufacturer price. Calculated at DPMQ price in submission.

6.27 The ESC considered the base case cost minimisation approach (when applied to effective prices of fingolimod) was reasonable and potentially conservative, given the base case approach did not include a cost-offset for first-dose cardiac monitoring required for fingolimod.

Drug cost/patient/year: $28,814.27

6.28 Ozanimod would cost $28,814.27 per year for each patient based on a 0.92 mg daily dose and costs derived from the published price of fingolimod. The mean dose for ozanimod considered in the cost-minimisation and financial estimates was appropriate and consistent with the SUNBEAM trial, given the compliance rate for ozanimod 0.92 mg was 99.9% during SUNBEAM.

Table 9: Drug cost per patient for ozanimod and fingolimod drug

	Ozanimod trial dose and duration	Ozanimod economic evaluation	Proposed drug financial estimates	Fingolimod trial dose and duration	Fingolimod economic evaluation	Fingolimod financial estimates
Mean dose	0.92 mg/day			0.5 mg/day		
Mean duration	412.4 days	-	-	NR	-	-
Cost/patient/ 28 days	$2,210.41			$2,210.41		
Cost/patient/ year	$28,814.27			$28,814.27		

Source: Table 31, p49-50 of the submission.
CSR = clinical study report
Note: The trial dose and duration data were based on the SUNBEAM and TRANSFORMS trials for ozanimod and fingolimod, respectively. The cost/patient/28 days for ozanimod based on the RADIANCE B trial was also $2,210.41.
Note: The mean dose for ozanimod is based on the maintenance dose only. The cost/patient/28 days would remain the same if also considering the titration pack as the cost per tablet for the titration and 28-day packs were the same.
Note: Compliance data for TRANSFORMS was not available, hence the cost/patient/28 days and cost/patient/year for fingolimod was based on an assumed 100% compliance.

Estimated PBS usage & financial implications

6.29 This submission was not considered by DUSC.

6.30 The estimated market size was based on PBS data for fingolimod. The proportion of patients requiring titration packs was determined based on 10% sample PBS data for fingolimod. The key inputs for the financial impact analysis are presented in Table 10.

6.31 The submission calculated financial estimates based on the fingolimod market only. The submission considered that since ozanimod is a pharmacological analogue of fingolimod, it will not affect treatment strategies used by clinicians to treat RRMS.

6.32 The financial impact analysis assumed there would be no growth in the total RRMS market as a result of listing ozanimod. The ESC considered that there may be patients who were ineligible for fingolimod due to cardiac issues who would be eligible for ozanimod.

Table 10: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Market size	Market size of fingolimod. Projected based on historical PBS data for fingolimod	Appropriate. The submission could have also considered substitution for other RRMS DMTs
Uptake rate of ozanimod	The submission assumed a fingolimod to ozanimod substitution rate of 10%, 20%, 30%, 40%, 50%, and 50%, respectively each year.	Uncertain given the uptake rate was speculative. However, given the cost-minimisation approach, this is not likely to affect the predicted cost-neutrality.
Proportion of patients requiring titration packs	Based on 10% sampled PBS data for fingolimod in equivalent year of listing. Commissioned by Prospection Pty Ltd.	Appropriate
Dose	Based on the trial data and the Product Information	Appropriate

Source: Section 4.1, pp153-161 of the submission.
DMT = disease modifying treatment; PBS = Pharmaceutical Benefits Scheme; RRMS = relapsing-remitting multiple sclerosis

6.33 The financial impact analysis, based on the published price of fingolimod, is presented in Table 11. The PBS/RPBS financial implications less co-payments resulted in a marginal cost saving. This was due to the additional patient co-payments associated with the 7-day titration pack script for ozanimod.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use for ozanimod						
Number of titration pack scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of 28-day pack scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated costs and offsets associated with ozanimod						
Estimated net cost of ozanimod to the PBS/RPBS less co-payments						
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net offsets for ozanimod (due to fingolimod substitution) to the PBS/RPBS less co-payments						
Cost to PBS/RPBS less co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications of listing ozanimod						
PBS/RPBS total, less co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

Source: Table 95 and 96, pp160-161; Table 97, p162; and Table 98, p163 of the submission.
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
Note: Values used in the financial impact calculations were not rounded.
Note: The published price for fingolimod is used as a proxy for ozanimod published price in this submission. The final published and net list price will be determined during the listing process.

6.34 While the submission assumed that ozanimod would only substitute for fingolimod, in practice, ozanimod could take market share from several other RRMS treatments, some of which may be cheaper than fingolimod.

6.35 The submission noted that further cost-savings may be possible for ozanimod due to improved tolerability profile and reduced need for first-dose cardiac monitoring, fewer cardiac AEs, fewer infections due to higher ALCs, and fewer hepatic abnormalities compared with fingolimod. The submissions claim for fewer cardiac AEs and hepatic abnormalities was uncertain as ozanimod and fingolimod appeared to have similar safety profiles.

6.36 At year 6, the estimated number of patients was 500 to < 5,000 and estimated number of scripts was 20,000 to < 30,000; and was net cost saving to the PBS. The PBAC noted these costs were based on the published price of the comparator.

Financial Management – Risk Sharing Arrangements

6.37 The submission did not propose a risk-sharing arrangement (RSA). An RSA with shared subsidisation caps is currently in place for fingolimod and cladribine. In its Pre-PBAC Response, the Sponsor indicated a willingness to join the existing RSA for fingolimod. The PBAC noted that this was appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of ozanimod on the PBS as the TGA Delegate's Overview was not available at the time of consideration.

However, the PBAC was of a mind to recommend the Authority Required (STREAMLINED) listing of ozanimod for the treatment of relapsing remitting multiple sclerosis (RRMS) on a cost minimisation basis with fingolimod

7.2 The PBAC considered the nominated comparator of fingolimod was reasonable, however also considered ozanimod may substitute for a number of other RRMS therapies currently listed on the PBS.

7.3 Based on the results of two direct, randomised head-to-head trials (SUNBEAM, RADIANCE-B) of ozanimod and interferon-β1a (IFN-β1a), the PBAC was satisfied that ozanimod provides, for some patients, a significant improvement in effectiveness and safety over IFN-β1a for the purposes of Section 101 (3B) of the *National Health Act 1953*.

7.4 The PBAC considered that while the clinical need for an additional treatment with the same mechanism of action as other PBS listed treatment options was low, the addition of another option may be useful for some patients.

7.5 The PBAC noted alemtuzumab, cladribine and ocrelizumab were recommended for listing on a cost minimisation basis compared to fingolimod and could be considered alternative therapies to ozanimod. The PBAC considered that, as no evidence was provided to demonstrate ozanimod provided a significant improvement in efficacy and/or reduction of toxicity over these alternative therapies, it should not be more costly.

7.6 Based on the results of the indirect comparison presented, the PBAC considered the claim that ozanimod was of non-inferior effectiveness compared to fingolimod was uncertain given the transitivity issues identified (paragraph 6.8) and further noted the upper bound of the 95% confidence interval was greater than MCID values presented in previous submissions for RRMS (paragraph 6.13). However, on balance, the PBAC considered the claim of non-inferior comparative effectiveness was reasonable.

7.7 Based on the presented evidence, the PBAC considered that ozanimod was likely to be of non-inferior safety to fingolimod. The PBAC noted the TGA CER supported the claim that ozanimod may have an additional safety benefit of reduced cardiac toxicity meaning that first-dose cardiac monitoring is not required for ozanimod, in comparison to fingolimod.

7.8 When it is in a position to recommend ozanimod, the PBAC considered it would be appropriate to list under the same circumstances for which fingolimod is currently listed as an Authority Required (STREAMLINED) listing. The PBAC did not recommend amending the wording of, 'Patient must not show continuing progression of disability while on treatment with this drug,' as there was no reason to conclude there was misunderstanding or misinterpretation of the current criterion among prescribers.

7.9 The PBAC considered it would be appropriate to list the 7-day titration pack as both initial and continuing therapy, with a maximum quantity of one pack and no repeats, to allow first use and re-titration for patients who have a treatment break of more

than 14 days not associated with disease progression. The PBAC also considered it would be appropriate to list the standard pack as initial and continuing therapy with a maximum quantity of one pack with 5 repeats. The PBAC noted that it would be possible for both packs to be prescribed at the same time.

7.10 The PBAC considered that based on the available information, it would be reasonable to list ozanimod on a cost minimisation basis with the effective price of fingolimod and it would also be appropriate that ozanimod join the existing risk sharing arrangement for fingolimod and cladribine. The PBAC advised the equi-effective doses are ozanimod 0.92 mg once daily and fingolimod 0.5 mg once daily.

7.11 The PBAC considered the assumptions in the utilisation estimates were reasonable.

7.12 The PBAC advised in principle that ozanimod is not suitable for prescribing by nurse practitioners as other RRMS DMTs are restricted to prescribing by medical practitioners only.

7.13 The PBAC advised in principle that the Early Supply Rule should apply.

7.14 The PBAC advised it was appropriate to consider ozanimod at a future opportunity following receipt of the TGA Delegate's Request for ACM Advice.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.