5.10 OCRELIZUMAB, Solution concentrate for I.V. infusion 300 mg in 10 mL, Ocrevus®, Roche Products Pty Limited

1 Purpose of Application

1.1 The submission requested a Section 100 (Highly Specialised Drugs Program) PBS listing for ocrelizumab for the treatment of relapsing-remitting multiple sclerosis (RRMS).

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Adult patients with relapsing-remitting multiple sclerosis
Intervention	Ocrelizumab (600 mg IV infusion every 6 months)
Comparators	Alemtuzumab, natalizumab, fingolimod
Outcomes	Suppress clinical relapses, delay disability progression, reduce subclinical measures (based on MRI) of disease activity
Clinical claim	Ocrelizumab is non-inferior in terms of efficacy and similar (possibly superior) in terms of safety compared to alemtuzumab, natalizumab and fingolimod

Abbreviations: IV, intravenous; MRI, magnetic resonance imaging
Source: Constructed during the evaluation

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	DPMQ	Proprietary Name and Manufacturer	
OCRELIZUMAB 300 mg/10 mL injection, 1 x 10 mL vial	2	0	Public: $[redacted] Private: $[redacted]	Ocrevus®	Roche

Category / Program:	Section 100 (Highly Specialised Drugs program)
PBS Indication:	Relapsing-remitting multiple sclerosis[a]
Treatment phase:	Initial/Continuation
Restriction:	Public hospital Authority Required (Streamlined) Private hospital Authority Required
Treatment criteria:	Must be treated by a neurologist. Treatment with this drug must cease if there is continuing progression of disability whilst the patient is being treated with this drug. For continued treatment the patient must demonstrate compliance with, and an ability to tolerate, this drug.

Clinical criteria:	The treatment must be as monotherapy, AND Patient must be ambulatory (without assistance or support), 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, AND The condition must be confirmed by magnetic resonance imaging of the brain and/or spinal cord; OR Patient must be deemed unsuitable for magnetic resonance imaging due to the risk of physical (not psychological) injury to the patient.
Prescriber Instructions	The date of the magnetic resonance imaging scan must be included in the patient's medical notes, unless written certification is provided, in the patient's medical notes, by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.

a The requested PBS listing in the submission was for "multiple sclerosis (MS)", which was broader than current PBS listings for other multiple sclerosis treatments, which include a criterion that specifically limits treatment to RRMS. The Pre-Sub-Committee Response (PSCR, p 1) agreed to align the restriction with existing listings and changed the proposed restriction criteria from MS to RRMS.

2.1 The evaluation noted that there is potential for leakage outside the restriction to patients with primary progressive multiple sclerosis (PPMS) given the high clinical need for treatments in this population. The PSCR (p4) states the sponsor is planning to submit an application for ocrelizumab for PPMS for consideration at the November 2017 PBAC meeting.

2.2 Ocrelizumab was administered as a 600 mg IV infusion every 24 weeks in the trials. The TGA approved Product Information (PI) recommends a dosing interval of every 6 months, however specifies a minimum interval of 5 months between each dose. (The initial dose is administered as two separate 300 mg infusions two weeks apart; this is consistent between the ocrelizumab trials and the PI). Ocrelizumab is anticipated to be used as a chronic treatment for multiple sclerosis.

2.3 The sponsor proposed a Special Pricing Arrangement for the listing of ocrelizumab. Under usual practice, a Special Pricing Arrangement can only apply to a cost-minimised drug when the drug to which it is cost-minimised also has a Special Pricing Arrangement. Fingolimod and alemtuzumab have special pricing arrangements. Natalizumab does not have a Special Pricing Arrangement.

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

3 Background

3.1 Ocrelizumab was submitted under the TGA/PBAC parallel process. The proposed TGA indication is for:

The treatment of patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity).

The treatment of patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.

3.2 TGA Status at time of PBAC consideration: The second round TGA clinical evaluation report and Delegate's Request for ACM advice were available at the time of PBAC consideration.

3.3 The PBAC has not previously considered ocrelizumab.

3.4 Other PBS listed drugs for the treatment of RRMS include subcutaneous and intramuscular forms of interferon (IFN) β-1a, IFN β-1b, glatiramer acetate, pegylated IFN β 1a (Peg-IFN β-1a), dimethyl fumarate (DMF), teriflunomide, fingolimod, natalizumab and alemtuzumab and daclizumab. Older treatments for RRMS, including both forms of IFN β-1a, IFN β-1b and glatiramer acetate are often termed 'ABCR' or 'BRACE' therapies.

4 Population and disease

4.1 Multiple sclerosis is a progressive, chronic, autoimmune disease of the central nervous system in which the myelin sheath protecting axons is damaged resulting in distorted nerve signals and pathways. Multiple sclerosis is associated with a complex range of symptoms including visual disturbance, fatigue, pain, reduced mobility and coordination, cognitive impairment and mood changes.

4.2 The submission positions ocrelizumab as a first-line alternative to fingolimod, natalizumab and alemtuzumab for RRMS in patients with moderate to high disease activity as well as a second-line alternative to these agents after failure of other disease modifying therapies in patients with mild disease activity.

5 Comparator

5.1 The submission nominated fingolimod, natalizumab and alemtuzumab as the main comparators. The main argument provided in support of this nomination is that ocrelizumab is a high efficacy treatment and is therefore most likely to replace other treatments used for patients with moderate to high disease activity.

5.2 For the requested population, numerous PBS medicines could be displaced in practice.

5.3 Interferon beta-1b has the lowest cost (as the result of a statutory price reduction), whilst the remaining ABCR/BRACE therapies, dimethyl fumarate and teriflunomide were all listed on a cost-minimisation basis with interferon beta. Randomised head-to-head trials were presented in the submission demonstrating statistically

significant reductions in relapse rate and progression of disability with ocrelizumab compared with SC interferon beta-1a (see section 6 below).

5.4 Natalizumab and fingolimod were listed on a cost-effectiveness basis with interferon beta. Alemtuzumab was listed on a cost-minimisation basis with fingolimod and natalizumab. Fingolimod and alemtuzumab have Special Pricing Arrangements. Natalizumab does not have a Special Pricing Arrangement.

5.5 The submission did not consider daclizumab as a potential comparator. Daclizumab was listed on the PBS on 1 May 2017. The recommendation for listing was on the basis that the presented direct comparison of IM interferon β-1a and indirect comparisons of daclizumab and fingolimod supported a conclusion that daclizumab is likely to be superior to interferon beta-1a and may be non-inferior to fingolimod with regard to comparative efficacy, but may be inferior to interferon beta-1a with regard to comparative safety. The PBAC recommended that although the superior comparative efficacy over IFN β-1a justified the cost of daclizumab per patient per course being higher than IFN β-1a, there were insufficient grounds for the cost per patient per course to be as high as fingolimod because of the substantial uncertainty about the indirect comparisons with fingolimod.

5.6 The submission claimed early use of ocrelizumab and therefore significant substitution of low to moderate efficacy agents, will not occur until clinicians gain more experience and confidence with the product. The ESC considered given the superior efficacy and similar overall incidence of adverse events with ocrelizumab compared with SC interferon beta-1a, and convenience in administration (twice a year), it is likely that ocrelizumab will replace ABCR/BRACE therapies in addition to high efficacy treatments.

5.7 The pre-PBAC response (p1) stated that a small proportion (5%) of substitution of other RRMS therapies (glatiramer acetate, dimethyl fumarate, teriflunomide, pegylated interferon beta 1a) were included in the budget impact estimates. The pre-PBAC response (p1-2) argued that due to the decline in use of interferon beta 1a subcutaneous and intramuscular, and interferon beta 1b, no patients are projected to receive these therapies in the first five years of the ocrelizumab PBS listing.

5.8 The PBAC considered that the decline in use of the older ABCR/BRACE therapies may be in part attributed to the availability of newer higher efficacy therapies, of which ocrelizumab represents an additional treatment option. The PBAC therefore agreed with the ESC that ocrelizumab will likely replace ABCR/BRACE therapies in addition to high efficacy treatments.

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 individuals (10), and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ocrelizumab, including the ability to continue paid employment, a reduction in disability progression and the advantages of an effective new treatment option for multiple sclerosis with fewer side effects.

6.3 The PBAC noted input received from MS Australia and MS Research Australia in support of subsidising ocrelizumab through the PBS. The organisations highlighted the significance of a new effective treatment option for multiple sclerosis, which will allow increased choice for patients and clinicians. The organisations also noted the favourable safety profile of ocrelizumab compared to some existing PBS medicines for multiple sclerosis.

6.4 Representatives of the PBAC met with MS Australia prior to the PBAC meeting. The following points provide a summary of the perspectives presented by MS Australia to the PBAC representatives:

- Ocrelizumab represents an additional treatment option for patients with RRMS.
- Patients and clinicians value the availability of multiple treatment options that are safe, effective, affordable and provide equitable access across the spectrum of multiple sclerosis types and severities.

Clinical trials

6.5 No head-to-head trials comparing ocrelizumab to fingolimod, natalizumab or alemtuzumab were available. The submission was based on a series of indirect comparisons against the nominated comparators:

- Indirect comparison of ocrelizumab vs. alemtuzumab:
    - Single step indirect analysis using SC interferon beta-1a as the common comparator (OPERA-I, OPERA-II, CAMMS223, CARE MS-I, CARE MS-II).
- Indirect comparison of ocrelizumab vs. fingolimod:
    - Indirect analysis of ocrelizumab vs. IM interferon beta-1a (OPERA-I, OPERA-II; EVIDENCE, Etemadifar 2006) linked to a meta-analysis of direct (TRANSFORMS) and indirect (BRAVO, MSCRG, FREEDOMS-I, FREEDOMS-II) comparisons of IM interferon beta-1a vs. fingolimod;

- Three step indirect analysis using SC interferon beta-1a/teriflunomide/placebo as bridging comparators (OPERA-I, OPERA-II, TENERE, TEMSO, TOWER, FREEDOMS-I, FREEDOMS-II).

- Indirect comparison of ocrelizumab vs. natalizumab:
  - Three step indirect analysis using SC interferon beta-1a/IM interferon beta-1a/placebo as bridging comparators (OPERA-I, OPERA-II, EVIDENCE, Etemadifar 2006, BRAVO, MSCRG, AFFIRM);
  - Three step indirect analysis using SC interferon beta-1a/teriflunomide/placebo as bridging comparators (OPERA-I, OPERA-II, TENERE, TEMSO, TOWER, AFFIRM).
- Meta-regression of combined indirect analysis results of ocrelizumab vs. alemtuzumab, fingolimod and natalizumab.
- Supportive network meta-analysis of treatments for relapsing-remitting multiple sclerosis (McCool 2016, unpublished).

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports included in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ocrelizumab trials		
OPERA-I	Roche Clinical Study Report (2016). A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis	Internal study report
OPERA-II	Roche Clinical Study Report (2016). A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis	Internal study report
Pooled OPERA analysis	Roche Clinical Study Report (2016). Randomized, double-blind, double-dummy, parallel-group studies to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis.	Internal study report
	Hauser et al (2017). Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis	New England Journal of Medicine 376: 221-234
Comparator trials		
CAMMS223	Coles et al (2008). Alemtuzumab vs. Interferon Beta-1a in Early Multiple Sclerosis	New England Journal of Medicine 359: 1786-1801
CARE MS-I	Cohen et al (2012). Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial	Lancet 380: 1819-1828
CARE MS-II	Coles et al (2012). Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial	Lancet 380: 1829-1839
FREEDOMS-I	Kappos et al (2010). A placebo-controlled trial of oral fingolimod in	New England Journal of

Trial ID	Protocol title/ Publication title	Publication citation
	relapsing multiple sclerosis.	Medicine 362: 387-401
FREEDOMS-II	Calabresi et al (2014). Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis: a double-blind, randomised, placebo controlled, phase 3 trial	Lancet Neurology 13: 545-56
TRANSFORMS	Cohen et al (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis.	New England Journal of Medicine 362:402-415
AFFIRM	Polman et al (2006). A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis	New England Journal of Medicine 354: 899-910
TENERE	Vermersch et al (2014). Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial.	Multiple Sclerosis 20: 705-716
TEMSO	O'Connor et al (2011). Randomized trial of oral teriflunomide for relapsing multiple sclerosis.	New England Journal of Medicine 365: 1293-303
TOWER	Confavreux et al (2014). Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial.	Lancet Neurology 13: 247-256
BRAVO	Vollmer et al (2014). A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis	Journal of Neurology 261: 773-783
MSCRG	Jacobs et al (1996). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis.	Annals of Neurology 39: 285-294
EVIDENCE	Panitch et al (2002). Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial.	Neurology 59: 1496-1506
Etemadifar (2006)	Etemadifar et al (2006). Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis.	Acta Neurologica Scandinavica 113: 283-287
Network meta-analyses		
McCool (2016)	McCool et al (2016). Systematic review and network meta-analysis of treatments for relapsing-remitting multiple sclerosis	Unpublished report

Source: Table B.2.6 (p 10-13) of the submission
Note: Only includes the main publications for each trial

6.7 The key features of the OPERA trials (ocrelizumab vs. SC interferon beta-1a) are summarised in the table below.

Table 3: Key features of the included evidence (ocrelizumab vs. SC interferon beta-1a)

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes
OPERA-I	821	MC, R, DB, PG (96 weeks)	Low	RMS patients with active disease	Relapse rates, disability progression, MRI measures
OPERA-II	835	MC, R, DB, PG (96 weeks)	Low	RMS patients with active disease	Relapse rates, disability progression, MRI measures
Pooled OPERA analysis	1,656	Pooled analysis of individual patient data from the OPERA-I and OPERA-II trials			

Abbreviations: DB, double blind; MC, multi-centre; MRI, magnetic resonance imaging; PG, parallel group; R, randomised; RMS, relapsing forms of multiple sclerosis.
Source: compiled during the evaluation

6.8 There were major exchangeability/transitivity issues between the OPERA trials and the other studies included in the indirect analyses and network meta-analyses. There

were differences in study duration, disease type, diagnostic criteria, baseline disease activity, baseline disability, disease duration, use of prior therapies and outcome definitions.

Comparative effectiveness

6.9 The results of the direct comparison of key relapse and disability outcomes between ocrelizumab and SC interferon beta-1a in the OPERA trials are summarised in the table below.

Table 4: Key relapse and disability outcomes between ocrelizumab and SC interferon beta-1a

Trial	Ocrelizumab	SC interferon beta-1a	Treatment difference (95% CI)
Protocol-defined annualised relapse rate (relapse rate, 95% CI)			
OPERA-I	0.156 (0.122, 0.200) N = 410	0.292 (0.235, 0.361) N = 411	Rate ratio: 0.536 (0.400, 0.719)
OPERA-II	0.155 (0.121, 0.198) N = 417	0.290 (0.234, 0.361) N = 418	Rate ratio: 0.532 (0.397, 0.714)
Pooled analysis	0.156 (0.131, 0.186) N = 827	0.291 (0.250, 0.339) N = 829	Rate ratio: 0.535 (0.435, 0.659)
Confirmed 3-month disability progression (proportion with event, n/N)			
OPERA-I	7.6% (31/410)	12.2% (50/411)	Hazard ratio: 0.57 (0.37, 0.90)
OPERA-II	10.6% (44/417)	15.1% (63/418)	Hazard ratio: 0.63 (0.42, 0.92)
Pooled analysis	9.1% (75/827)	13.6% (113/829)	Hazard ratio: 0.60 (0.45, 0.81)
Confirmed 6-month disability progression (proportion with event, n/N)			
OPERA-I	5.9% (24/410)	9.5% (39/411)	Hazard ratio: 0.57 (0.34, 0.95)
OPERA-II	7.9% (33/417)	11.5% (48/418)	Hazard ratio: 0.63 (0.40, 0.98)
Pooled analysis	6.9% (57/827)	10.5% (87/829)	Hazard ratio: 0.60 (0.43, 0.84)

Abbreviations: CI, confidence interval; SC, subcutaneous
Source: Table 17 (p 109-110), Table 22 (p 119), Table 24 (p 125) and p 903 of the OPERA-I trial report; Table 17 (p 108-109), Table 22 (p 118), Table 24 (p 125) and p 928 of the OPERA-II trial report; Table 7 (p 52-53), Table 10 (p 57), Table 12 (p 63) of the OPERA I & II Pooled Analysis 2016

6.10 Treatment with ocrelizumab was associated with a statistically significant reduction in relapses and was associated with a statistically significant delay in disability progression compared to SC interferon beta-1a. The OPERA trial reports noted that there were some differences in treatment effects across patient subgroups with ocrelizumab associated with larger relapse reductions in younger patients and patients with Gd-enhancing lesions. However, it was less effective in delaying relapses for patients with higher baseline weight and BMI (no apparent difference

from SC interferon beta-1a). The PSCR (p1) argued that the subgroup analyses were exploratory and that there was no evidence to suggest that response to therapy was dependent on age, weight, or the presence of Gd-enhancing lesions.

6.11 The results of the indirect comparison of key relapse and disability outcomes between ocrelizumab and nominated main comparators (alemtuzumab, fingolimod and natalizumab) are summarised in the table below.

Table 5: Key relapse and disability outcomes between ocrelizumab, alemtuzumab, fingolimod and natalizumab

Trial	Annualised relapse rate	Confirmed 3-month disability progression	Confirmed 6-month disability progression
Ocrelizumab vs. alemtuzumab			
Single-step indirect comparison	[redacted]	[redacted]	[redacted]
Ocrelizumab vs. fingolimod			
Multi-step indirect comparison (IM interferon beta-1a bridge)	[redacted]	[redacted]	[redacted]
Multi-step indirect comparison (Teriflunomide bridge)	[redacted]	-	-
Ocrelizumab vs. natalizumab			
Multi-step indirect comparison (IM interferon beta-1a bridge)	[redacted]	[redacted]	[redacted]
Multi-step indirect comparison (Teriflunomide bridge)	[redacted]	-	-
Ocrelizumab vs. combined main comparators			
Meta-regression assuming equal weight between comparators	[redacted]	[redacted]	[redacted]
Meta-regression weighted based on predicted utilisation between comparators	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IM, intramuscular
Source: Table B.8.1 (p 115-116) of the submission

6.12 The evaluation and the ESC commented that these comparisons should be interpreted with caution due to the inherent uncertainty of multi-step indirect comparisons as well as substantial transitivity issues between trials.

6.13 The PSCR (p1) argued that in the absence of head-to-head data, the PBAC has previously accepted indirect comparisons to support positive recommendations for RRMS therapies, such as for alemtuzumab, which was recommended in July 2014. The ESC considered that although multi-step indirect comparisons had been used the alemtuzumab submission, they are inherently uncertain and remained an issue in this submission. The ESC noted that, for example, the analysis of disability progression at six months between ocrelizumab and fingolimod was based on a three step indirect analysis and included trials spanning 21 years.

6.14 There was no statistically significant difference in relapse outcomes between ocrelizumab and alemtuzumab (results favoured alemtuzumab). The indirect estimate of effect for annualised relapse rate did not meet the nominated non-inferiority margin (the upper CI exceeded 1.23). There was no statistically significant difference in disability outcomes between treatments (results favoured alemtuzumab). The PBAC noted the results of the single-step indirect comparison with alemtuzumab exceeded the nominated non-inferiority margin.

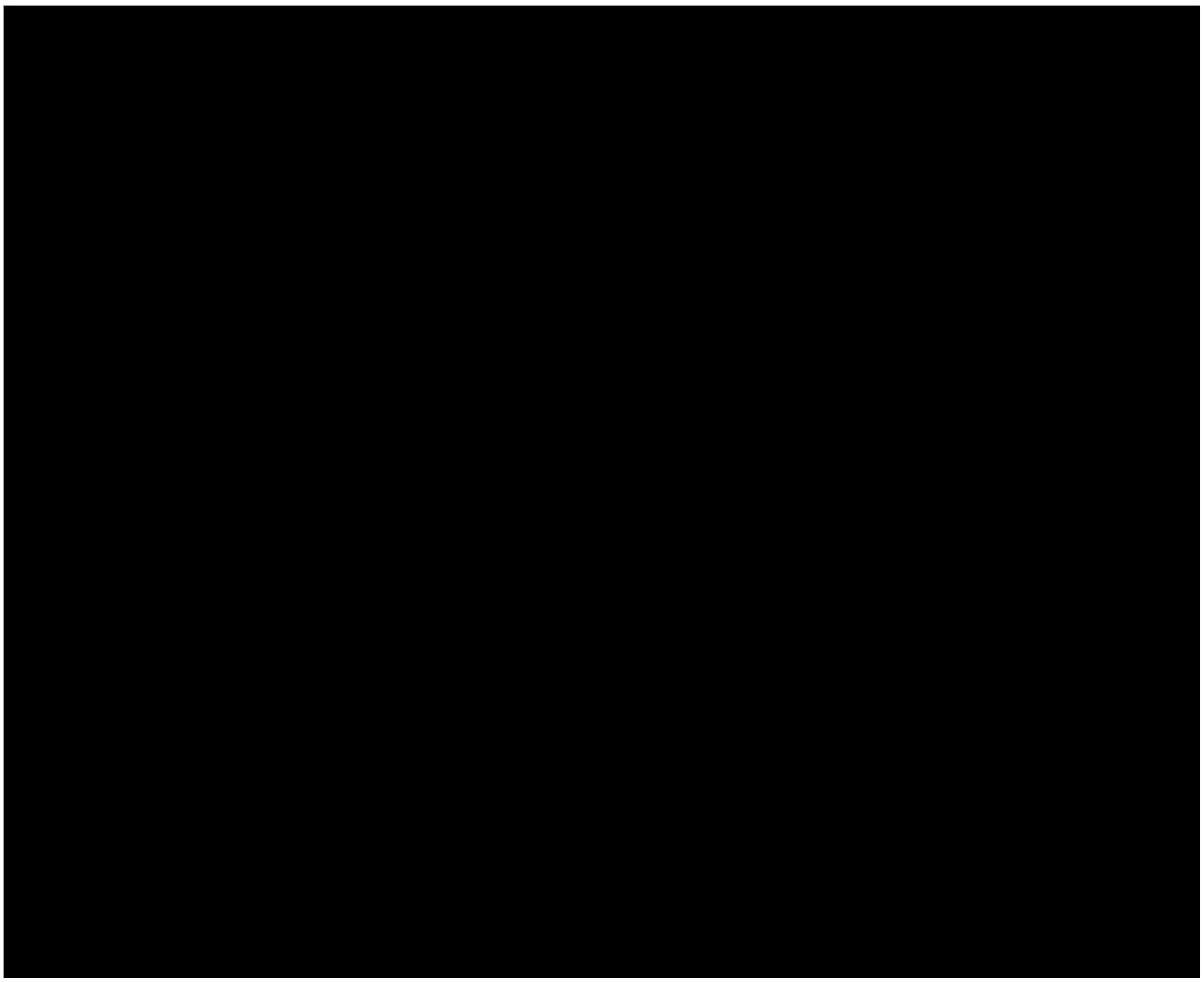
6.15 There was no statistically significant difference in relapse outcomes between ocrelizumab and fingolimod (results favoured ocrelizumab). The indirect estimate of effect for annualised relapse rate met the nominated non-inferiority margin (the upper CI was less than 1.23) for one comparison but failed in the other comparison. Treatment with ocrelizumab was associated with a statistically significant delay in the time to six-month confirmed disability progression but not three-month confirmed disability progression compared to fingolimod.

6.16 There was no statistically significant difference in relapse outcomes between ocrelizumab and natalizumab (results favoured ocrelizumab). The indirect estimate of effect for annualised relapse rate did not meet the nominated non-inferiority margin (the upper CI exceeded 1.23). There was no statistically significant difference in disability outcomes between treatments (results favoured ocrelizumab).

6.17 The evaluation contended that the combined analyses of all nominated main comparators are largely non-informative as alemtuzumab, fingolimod and natalizumab are separate drugs with their own profiles (comparative efficacy needs to be demonstrated against each individually).

6.18 Network meta-analyses of key relapse and disability outcomes between ocrelizumab other multiple sclerosis treatments are summarised in the figures below.

Figure 1: Comparison of annualised relapse rate between ocrelizumab and other treatment for multiple sclerosis

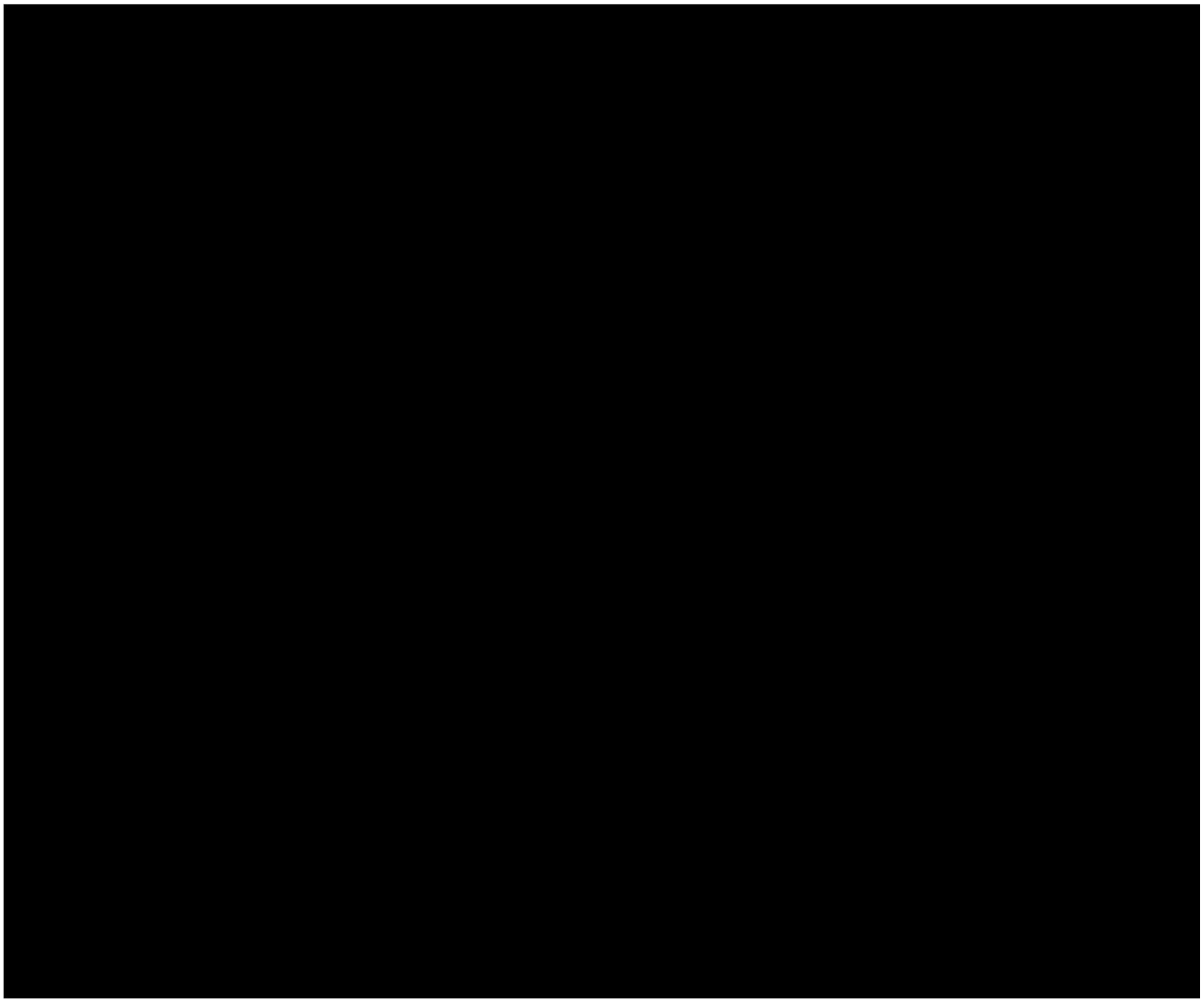


Source: Figure G.18 (p 212) of the unpublished McCool 2016 report
Note: Avonex is the brand name for IM interferon beta-1a, Rebif is the brand same of SC interferon beta-1a

6.19 Based on the network meta-analysis, treatment with ocrelizumab was associated with a statistically significant decrease in relapses compared to interferon beta-1b, IM interferon beta-1a, SC interferon beta-1a, peginterferon beta-1a, glatiramer acetate and teriflunomide. There was no statistically significant difference between ocrelizumab and other treatments. Results were within the specified non-inferiority margin for comparisons with dimethyl fumarate, daclizumab and fingolimod but exceeded the margin for comparisons with natalizumab and alemtuzumab.

6.20 The ESC considered that based on the results of the head-to-head comparison of ocrelizumab and interferon beta-1a, that ocrelizumab was superior in terms of reduction in annualised relapse rate over interferon beta-1a. The ESC also considered that based on the indirect comparisons presented, that ocrelizumab may also be superior for annualised relapse rate to teriflunomide. The ESC noted that the indirect estimate of effect for annualised relapse rate did not meet the nominated non-inferiority margin of 1.23 for natalizumab or alemtuzumab.

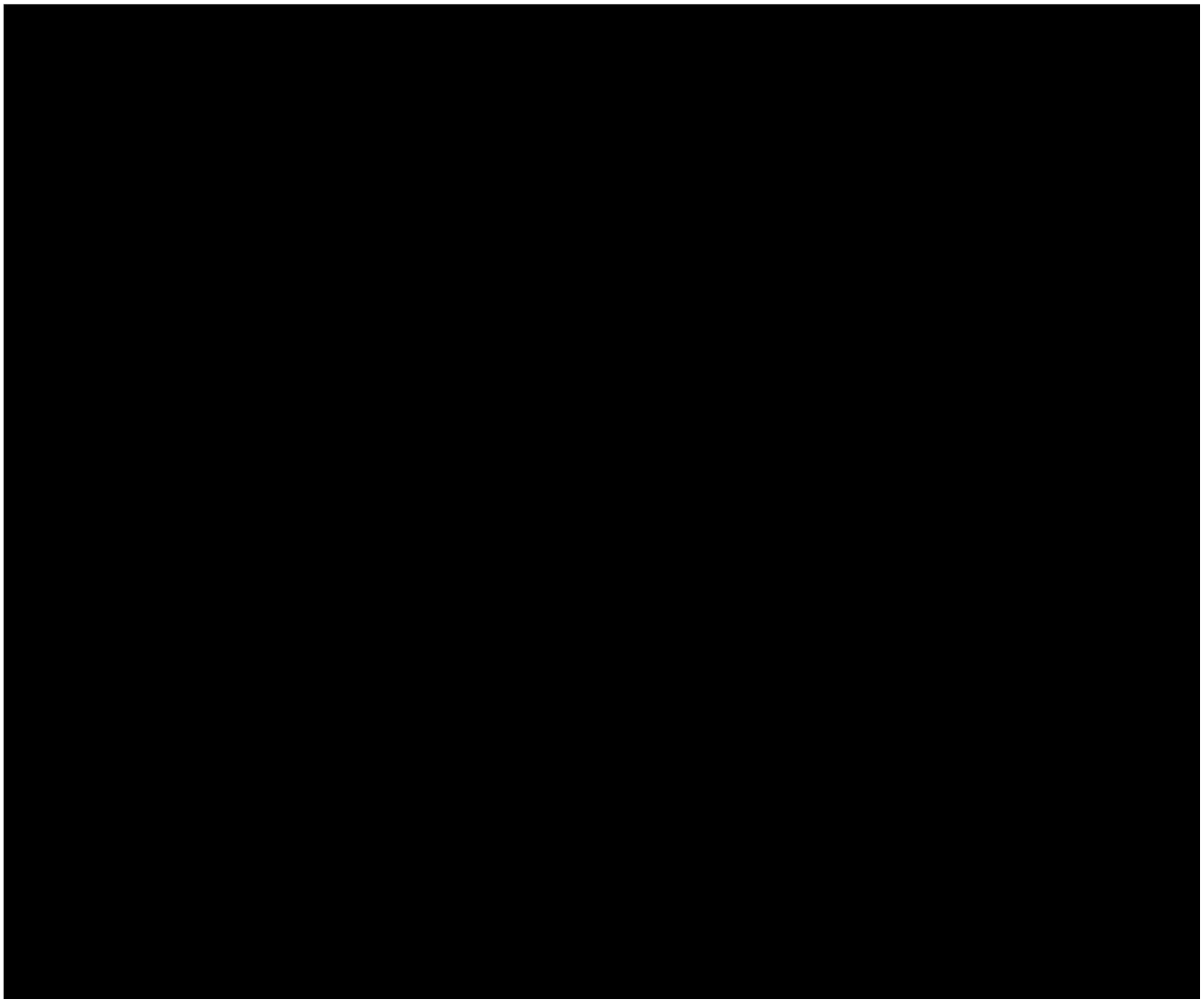
Figure 2: Comparison of 3-month confirmed disability between ocrelizumab and other treatment for multiple sclerosis



Source: Figure G.52 (p 266) of the unpublished McCool 2016 report
Note: Avonex is the brand name for IM interferon beta-1a, Rebif is the brand same of SC interferon beta-1a

6.21 Treatment with ocrelizumab was associated with a statistically significant delay in the time to 3-month confirmed disability progression compared to interferon beta-1b, IM interferon beta-1a, SC interferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod. There was no statistically significant difference between ocrelizumab and other treatments (alemtuzumab, daclizumab, natalizumab and peginterferon beta-1a).

Figure 3: Comparison of 6-month confirmed disability between ocrelizumab and other treatment for multiple sclerosis



Source: Figure G.94 (p 334) of the unpublished McCool 2016 report
Note: Avonex is the brand name for IM interferon beta-1a, Rebif is the brand same of SC interferon beta-1a

6.22 Treatment with ocrelizumab was not associated with a statistically significant delay in the time to 6-month confirmed disability compared to most treatments (with the exception of SC interferon beta-1a).

6.23 Overall, the indirect (single-step and multi-step) comparisons and network meta-analyses appear to support the non-inferiority efficacy claim against fingolimod but due to inherent uncertainty associated with these analyses they cannot exclude the potential for ocrelizumab to be inferior to natalizumab and alemtuzumab.

6.24 The PSCR (p 1) argued that 9 of the 11 point estimates in the indirect comparisons favoured ocrelizumab, and that despite the upper limit of the 95% CI exceeding the post-hoc non-inferiority margin in 8 of these comparisons, the sample sizes were not calculated in order to satisfy non-inferiority criteria.

6.25 The PBAC considered there were transitivity issues with the trials, and uncertainty with the multi-step indirect comparisons presented in the submission. The PBAC noted the pooled results of the OPERA trials showed an approximately 46% reduction in annualised relapse rate and a 40% reduction in hazard of disability progression at 3 and 6 months.

6.26 Based on the evidence presented in the submission, the PBAC was satisfied that ocrelizumab was superior to interferon beta-1a with regards to comparative efficacy. The PBAC accepted that ocrelizumab was likely to be non-inferior to fingolimod with regards to comparative efficacy, however considered that there were insufficient evidence to support a claim of non-inferiority of ocrelizumab to natalizumab or alemtuzumab.

Comparative harms

6.27 Based on data from the OPERA trials, treatment with ocrelizumab was associated with a similar overall incidence of adverse events compared to SC interferon beta-1a. The incidence of serious adverse events was relatively low in both treatment arms.

6.28 The most frequently reported events associated with ocrelizumab treatment were mild-to-moderate infections and infusion-related reactions. Serious adverse events occurring in more than one patient in the ocrelizumab arm included appendicitis, cellulitis, pyelonephritis, gastritis, cholecystitis, cholelithiasis, seizure, depression, invasive ductal breast carcinoma, thyroid adenoma and chest pain.

6.29 The submission presented a series of naïve indirect comparisons of common adverse events and serious adverse events associated with ocrelizumab, alemtuzumab, fingolimod and natalizumab. The submission noted that ocrelizumab was associated with a numerically lower overall incidence of adverse events and serious adverse events compared to the other treatments. The naïve indirect comparisons do not account for between trial differences and are insufficient to adequately inform the comparative assessment of safety between treatments.

6.30 The PSCR (p2) argued that in the absence of head-to-head data, the PBAC has previously accepted the results of naïve indirect comparisons to support listing decisions, and that the qualitative comparisons between ocrelizumab and its three nominated comparators showed lower rates of adverse events and less monitoring requirements for ocrelizumab.

6.31 There are limited long-term safety data on the use of ocrelizumab as a chronic treatment for multiple sclerosis. The PSCR (p 2) stated that the TGA Delegate's Overview has not mandated any changes to the proposed risk management program and that the risk of progressive multifocal leukoencephalopathy (PML) and malignancy with ocrelizumab remains unclear and will be monitored over time. The PBAC noted that the draft Product Information recommends that patients should be monitored for signs and symptoms of PML.

6.32 The PBAC considered that the naïve indirect comparisons presented in the submission provided insufficient evidence to draw meaningful conclusions on the comparative safety of ocrelizumab with its nominated comparators.

Clinical claim

6.33 The submission described ocrelizumab as non-inferior in terms of efficacy and non-inferior (possibly superior) in terms of safety compared to fingolimod.

6.34 The submission described ocrelizumab as non-inferior in terms of efficacy and non-inferior (possibly superior) in terms of safety compared to natalizumab.

6.35 The submission described ocrelizumab as non-inferior in terms of efficacy and non-inferior (possibly superior) in terms of safety compared to alemtuzumab.

6.36 The PBAC considered that the claim of non-inferior comparative effectiveness may be reasonable for fingolimod but could not exclude the potential for ocrelizumab to be inferior to natalizumab and alemtuzumab.

6.37 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.38 The sponsor proposed listing on a cost-minimisation basis versus natalizumab or fingolimod or alemtuzumab.

6.39 The equi-effective doses in the submission were based on the recommended dosing regimens outlined in the relevant product information documents.

6.40 The evaluation considered that estimated equi-effective doses may not be reasonable as the ocrelizumab trials used a dosage regimen of 600 mg every 24 weeks (simplified to every 6 months in the product information). The PSCR (p 3) stated that given that the product information proposes administration every six months it can be anticipated that clinicians will prescribe ocrelizumab in half yearly intervals, and that it is not expected that the clinical trial results would have been significantly different if ocrelizumab would have been administered every 6 months rather than every 24 weeks. The PSCR (p3) therefore argued that the equi-effective doses proposed in the submission are reflective of the anticipated utilisation of ocrelizumab in clinical practice and thus represent an appropriate basis for the cost-minimisation analysis.

6.41 The PBAC considered that the evidence supported a claim of non-inferior comparative efficacy with fingolimod, and therefore recommended that ocrelizumab be listed on a cost minimisation basis with fingolimod.

6.42 The PBAC noted that the TGA approved PI recommends a dosing interval of every 6 months, however specifies a minimum interval of 5 months between each dose. On this basis the PBAC considered it appropriate to use the clinical trial dosing interval of 24 weeks for establishing the equi-effective doses of ocrelizumab and fingolimod.

Drug cost/patient over 2 years: $[redacted]

6.43 The above cost per patient is based on two years of treatment at the dispensed price for maximum quantity (DPMQ) for public hospitals, with one infusion of 600 mg ocrelizumab every 6 months.

Estimated PBS usage & financial implications

6.44 This submission was not considered by DUSC.

6.45 The submission used a market share to estimate the utilisation/financial implications associated with the PBS listing of ocrelizumab.

6.46 There were a number of calculation errors in the submission that were corrected during the evaluation (e.g. the submission incorrectly estimated the average monthly patient number rather than the annual patient number for alemtuzumab. The PSCR (p5) presented revised financial estimates that accounted for these calculation errors and applied further updated PBS items data (to March 2017). The calculation errors appear to have been corrected; however, the updated data has not been evaluated. The pre-PBAC response (p4) corrected some of the financial figures presented in the ESC Advice, which are incorporated below. The financial estimates based on the proposed published price of ocrelizumab are presented in the table below.

Table 6: Estimated utilisation and cost to the PBS in the first five years of listing

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Total ocrelizumab market						
Patients treated with ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of ocrelizumab – published PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total published cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost offsets (drug costs based on published DPMQ less patient co-payment)						
Alemtuzumab substitution	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Fingolimod substitution	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Natalizumab substitution	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Other substitution	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost of hospital treatment (reduced IV infusion costs)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost of other medical resources (MBS)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Total costs						
Net published cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net published cost to government (PBS/RPBS/MBS)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: DPMQ, dispensed price for maximum quantity; MBS, Medicare Benefits Schedule; MS, multiple sclerosis; PBS, Pharmaceutical Benefits Scheme; RPBS Repatriation Pharmaceutical Benefits Scheme
Source: 'Financial cost to the PBS' Excel spreadsheet

6.47 The redacted table shows that at year 6, the estimated number of patients was less than 10,000, and the net cost to the PBS would be $30 - $60 million per year.

6.48 The evaluation considered that the budget impact estimate was highly uncertain due to the rapidly changing dynamics of the PBS multiple sclerosis market and the use of published rather than effective prices (due to the presence of Special Pricing Arrangements for a number of multiple sclerosis therapies). Some of the reasons for the high uncertainty were:

- The submission assumed that ocrelizumab will not grow the market (i.e. through capture of previously untreated patients or through providing an additional line of therapy) as the submission argued there is already a wide range of treatment options available to patients with multiple sclerosis. The assumption may not be reasonable given the substantial growth in the market that has been associated with other recent listings for multiple sclerosis treatments. The PSCR (p3) referred to the 2015 DUSC review that found expenditure on RRMS medicines continued to grow, but that this "was mainly driven by an increasing utilisation of the oral therapies fingolimod and dimethyl fumarate with a decline in the use of injectable therapy." The PSCR stated that newer RRMS therapies have become less burdensome for patients through more convenient administration, which has meant that patients are more likely to commence treatment earlier, leading to a growth in the overall market. The PSCR argued that this shift in the RRMS treatment paradigm is historical and the impact is unlikely to continue specifically with the listing of IV ocrelizumab.
- The forecast utilisation of alemtuzumab and peginterferon beta-1a indicated rapid growth in the use of these treatments on the PBS but estimates were based on limited actual data (alemtuzumab was listed in April 2015; peginterferon beta-1a was listed in March 2015) and it was unclear whether

these growth rates will continue over the longer term. The PSCR (p4) stated that the more recent listings resulted in an unavoidable use of limited data, but that the forecast was updated in the revised model provided with the PSCR, which utilised the latest available PBS data (up to March 2017). The updated forecast has not been evaluated.

- The estimated uptake rates for ocrelizumab were based on expert advice from the Sponsor's advisory panel. No documentation of the expert advice was provided with the submission. The PSCR (p4) stated that the sponsor's Multiple Sclerosis Advisory Board meeting convened on 4th April 2016. Attendees were invited based on neurologists' recommendations of Australian MS thought leaders. In total, 12 clinicians were invited and 11 attended including three from VIC, four from NSW, two from WA, and one each from QLD and NZ. The estimated uptake rates used in the submission were based on consensus from the advisors.
- The submission claimed that there would be no substitution of older interferon therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b) in clinical practice. It was unclear whether this claim was reasonable. The PSCR (p4) stated that there is a downward trend in the number of prescriptions for the older interferon therapies as there is a shift in the RRMS treatment paradigm due to the availability of newer, more efficacious and convenient therapies. The PSCR (p4) argued that therefore these older therapies are unlikely to be prescribed into the future. The ESC considered given the superior efficacy and similar overall incidence of adverse events with ocrelizumab compared with SC interferon beta-1a, and convenience in administration (twice a year), it is likely that ocrelizumab will substitute older therapies in addition to the newer, higher efficacy treatments.

6.49 The submission did not consider substitution of daclizumab (recently PBS-listed for multiple sclerosis) or rituximab (identified as a possible off-label therapy in treatment guidelines) in the utilisation estimates. The PSCR (p4) argued that ocrelizumab is unlikely to significantly displace the use of daclizumab as daclizumab is comparable to that of older, less efficacious agents (e.g. dimethyl fumarate) and it is therefore not considered a comparator. The PSCR (p4) stated that rituximab (which is not PBS listed for the treatment of RRMS) was not considered a therapy ocrelizumab would substitute and that it is not possible to estimate off-label use of rituximab for RRMS.

6.50 The PBAC considered that the estimated financial impact was highly uncertain due to the rapidly changing market for multiple sclerosis medicines. The PBAC noted that the financial estimates would also need to be recalculated based on its recommendation that ocrelizumab be cost-minimised to fingolimod, and taking into account that ocrelizumab is anticipated to substitute for all currently PBS listed medicines for RRMS.

Quality Use of Medicines

6.51 The submission stated that the availability of ocrelizumab for the treatment of patients with RRMS addresses an unmet clinical need where despite the availability of current treatments, patients continue to experience disease progression and suffer relapses.

Financial Management – Risk Sharing Arrangements

6.52 [redacted] However, the sponsor proposed [redacted] consistent with the cost-minimisation analysis.

6.53 The submission stated that the sponsor is willing to enter into negotiations regarding a risk-sharing agreement (annual expenditure caps).

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of ocrelizumab for the treatment of relapsing-remitting multiple sclerosis on a cost-minimisation basis with fingolimod. The PBAC recommended ocrelizumab on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program – public and private hospital).

7.2 The PBAC noted that ocrelizumab is a first-in-class medicine among currently PBS-subsidised treatments for multiple sclerosis. The PBAC noted the input from consumer comments and the consumer hearing that additional treatment options for multiple sclerosis are valued by patients and clinicians.

7.3 The PBAC accepted cost-minimisation on the basis that the annual treatment costs of ocrelizumab and fingolimod should be the same, at equi-effective doses of ocrelizumab 600 mg once every 24 weeks and fingolimod 500 micrograms daily and taking into account the cost of infusions for ocrelizumab.

7.4 The PBAC agreed that the nominated comparators of fingolimod, natalizumab and alemtuzumab were appropriate clinical comparators; however, considered that in practice, ocrelizumab would substitute for all PBS subsidised medicines for RRMS.

7.5 Based on the results of the direct, randomised head-to-head trials (OPERA-I, OPERA-II) of ocrelizumab and subcutaneous interferon beta-1a, the PBAC was satisfied that ocrelizumab is superior in comparative efficacy to interferon beta-1a. Based on the results of the pivotal trials and the network meta-analysis presented, the PBAC was satisfied that ocrelizumab has superior comparative efficacy to interferon beta-1b,

peginterferon beta-1a, glatiramer acetate, teriflunomide and dimethyl fumarate, for the purposes of Section 101(3B) of the *National Health Act 1953* (the Act).

7.6 The PBAC considered that based on the evidence presented, the clinical claim that ocrelizumab has non-inferior comparative efficacy to fingolimod was adequately supported. However, the PBAC considered there were transitivity issues with the trials used in the multi-step indirect comparison, and that there was substantial uncertainty with the multi-step indirect comparisons presented. The PBAC also noted the upper limits of the confidence intervals versus natalizumab and alemtuzumab in the network meta-analysis exceeded the specified non-inferiority margin (1.23) for annualised relapse rate. Based on the evidence presented, the Committee concluded the clinical claim of non-inferior comparative efficacy to natalizumab and alemtuzumab was not adequately supported.

7.7 The PBAC noted that the series of naïve indirect comparisons of adverse events associated with ocrelizumab, fingolimod, alemtuzumab and natalizumab did not account for between trial differences and considered that the evidence was insufficient to adequately inform the comparative safety of ocrelizumab and its nominated comparators.

7.8 The PBAC recommended the alignment of the listing of ocrelizumab with current listings for RRMS therapies, and that the restriction be based on existing restrictions for other infusible therapies for RRMS (alemtuzumab and natalizumab).

7.9 The PBAC considered that the estimated PBS usage and financial implications presented in the submission and revised in the PSCR and pre-PBAC response were highly uncertain due to:

- The submission assumed no overall growth in the multiple sclerosis market, which may not be reasonable as improvements in MRI technology allow earlier diagnosis of multiple sclerosis;
- The rapidly changing market for multiple sclerosis and uncertainty regarding the extent to which ocrelizumab may substitute for currently PBS listed medicines for RRMS;
- The potential that there may be leakage of use for primary progressive and secondary progressive multiple sclerosis.

7.10 The PBAC noted that the financial estimates would need to be revised to take into account the basis on which ocrelizumab was recommended for listing.

7.11 The PBAC advised that a Risk Share Arrangement with annual expenditure caps was appropriate to mitigate the uncertainty in the utilisation and financial estimates.

7.12 The PBAC advised that ocrelizumab is not suitable for prescribing by nurse practitioners, similar to other therapies listed on the PBS for RRMS.

7.13 The PBAC recommended that the Early Supply Rule should not apply.

7.14 The PBAC advised the ocrelizumab should not be treated as interchangeable on an individual patient basis with any other drugs for the purposes of section 101 (3BA) of the Act.

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OCRELIZUMAB Solution concentrate for I.V. infusion 300 mg in 10 mL	2	0	Ocrevus®	Roche Products Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program – Public and Private Hospitals
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Multiple sclerosis
PBS Indication:	Multiple sclerosis
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required – Telephone (Private Hospital) ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined (Public Hospital)
Treatment phase:	Initial treatment
Treatment criteria:	Must be treated by a neurologist.

Clinical criteria:	The treatment must be a sole PBS-subsidised therapy for this condition. AND Patient must be ambulatory (without assistance or support), 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, AND 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.
Prescriber Instructions	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Category / Program	Section 100 – Highly Specialised Drugs Program – Public and Private Hospitals
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Multiple sclerosis
PBS Indication:	Multiple sclerosis
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required – Telephone (Private Hospital) ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined (Public Hospital)
Treatment criteria:	Must be treated by a neurologist.

Clinical criteria:	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 not show continuing progression of disability while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.