

6.10 OCRELIZUMAB, Solution concentrate for I.V. infusion 300 mg in 10 mL, Ocrevus[®], Roche Products Pty Ltd

1 Purpose of application

- 1.1 Section 100 listing for ocrelizumab for treatment of primary progressive multiple sclerosis (PPMS). This was the first ocrelizumab submission for PPMS.
- 1.2 The basis for listing was a cost-utility model of ocrelizumab in comparison to best supportive care.
- 1.3 The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Patients with primary progressive multiple sclerosis
Intervention	Ocrelizumab (600mg IV infusion every 6 months)
Comparator	Best supportive care (BSC)
Outcomes	Delay in disease progression
Clinical claim	Ocrelizumab is superior to BSC in terms of efficacy and is inferior to BSC in terms of safety with an acceptable safety profile, comparable to placebo.

Source: Table 1.1.3, p7 of the submission.

IV = intravenous; HrQoL = health-related quality of life

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity-Published (Effective)	Proprietary name and manufacturer
OCRELIZUMAB 300mg/10 mL injection, 1 x 10mL vial	2	600mg	0	\$ [REDACTED] (\$ [REDACTED]) ¹ \$ [REDACTED] (\$ [REDACTED]) ²	Ocrevus®, Roche
Category / Program	Section 100 (Highly Specialised Drugs program)				
Condition:	Multiple sclerosis				
Treatment phase:	Initial				
Restriction:	Public hospital Authority Required (Streamlined) Private hospital Authority Required				
Treatment criteria:	Must be treated by a neurologist.				
Clinical criteria:	The condition must be diagnosed as clinically definite primary progressive multiple sclerosis by one year of disease progression (retrospectively or prospectively determined) AND; 2 of the following 3 criteria (if a subject has brainstem or spinal cord syndrome all symptomatic lesions are excluded from the criteria): Evidence of DIS in the brain based on ≥ 1 T2 lesion in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial); OR Evidence of DIS in the spinal cord based on ≥ 2 T2 lesions in the cord; OR Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) Note: in T2 lesions, Gadolinium enhancement of lesions is not required.				
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)				
Condition:	Multiple sclerosis				
Treatment phase:	Continuation				
Restriction:	Public hospital Authority Required (Streamlined) Private hospital Authority Required				
Treatment criteria:	Must be treated by a neurologist.				
Clinical criteria:	Patient must have previously received treatment with this drug for primary progressive multiple sclerosis; AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy				

Source: Table 1.4.3, p22-24 of the submission.

- 2.1 The submission proposed a Special Pricing Arrangement (SPA) in the form of a [REDACTED] % rebate on the published ex-manufacturer's price of ocrelizumab.
- 2.2 Ocrelizumab is anticipated to be used as a chronic treatment. The ORATORIO trial differed in its treatment regimen to that of the TGA approved Product Information (PI) and the requested restriction. In the ORATORIO trial, ocrelizumab 600 mg I.V. was administered at 24 week intervals, given as two infusions of 300mg given 14 days apart. The PI recommended a dosing interval of every 6 months, with the initial dose administered as one 300mg infusion, followed by a second 300mg infusion two weeks later, and specified a minimum interval of 5 months between each dose.

¹ Public hospital price

² Private hospital price

- 2.2 The proposed restriction is consistent with the TGA indication, but was much broader than the inclusion and exclusion criteria of the ORATORIO trial, as the restriction allows use among patients aged older than 55 years and does not specify an EDSS requirement (unlike the ORATORIO trial). The Pre-Sub-Committee Response (PSCR) (p3-4) stated that broad PBS listing criteria was proposed based on advice from three advisory board meetings, interactions with health care professionals and in the absence of a defined patient subgroup in whom clearly superior clinical benefit was derived in the ORATORIO trial.
- 2.3 The pre-PBAC response (p1) claimed that results from ORATORIO showed a consistent treatment effect across subgroups via various patient-relevant measures and therefore, the efficacy and safety outcomes observed in the ITT population of ORATORIO is expected to be realized in the PBS population. The pre-PBAC response (p2) asserted that the TGA deemed a broad indication for PPMS appropriate stating the age limitation in the trial program as a precaution only. The PBAC noted the TGA indication, however, considered that regulatory approval of ocrelizumab for PPMS does not translate to acceptable cost effectiveness of ocrelizumab. The PBAC also noted comments from the TGA Delegate indicating that ocrelizumab is likely to be more beneficial in certain patient subgroups and may confer minimal benefit in other subgroups for PPMS (refer to paragraphs 6.12 and 6.13).
- 2.4 The PBAC noted the DUSC's advice that the requested restriction allows for older patients with higher EDSS scores than the ORATORIO trial, and that there is no evidence of treatment effectiveness in patients over the age of 55 years or with a baseline EDSS of over 6.5. The DUSC noted that, unlike the PBS restrictions for alemtuzumab and natalizumab in relapsing remitting multiple sclerosis (RRMS), the requested restriction for ocrelizumab in PPMS does not require that the patient is ambulant. The DUSC advised that the restriction should include criteria based on disease severity for initial therapy and criteria based on prior treatment effectiveness for continuing therapy.

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

3 Background

Registration status

- 3.1 TGA status: – Ocrelizumab was TGA registered on 13 July 2017 for:
- The treatment of patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and to reduce the frequency of relapse.
 - The treatment of patients with primary progressive multiple sclerosis (PPMS) to delay the progression of physical disability.

Ocrelizumab was considered and recommended for listing at the July 2017 PBAC meeting for relapsing remitting multiple sclerosis (RRMS).

4 Population and disease

- 4.1 Multiple sclerosis (MS) 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. Most patients are initially diagnosed with RRMS, characterised by acute clinical attacks (relapses) followed by partial/full recovery and periods of clinical stability (remissions). Approximately 10% of MS patients are diagnosed with PPMS, which is characterised by a more rapid course of progression than RRMS and an accumulation of disability from the onset of symptoms without relapses or remissions.
- 4.2 Ocrelizumab, if listed, would be the only PBS-listed treatment for PPMS.

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

5 Comparator

The submission nominated best supportive care (BSC) as the main comparator. Given that there are no other PBS-listed treatments for PPMS, this was reasonable.

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 (63), a health care professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments supported the PBS listing of ocrelizumab for PPMS and emphasised the need for treatments that may slow the progression of disease, preserve physical functioning and maintain quality of life. The comments described ocrelizumab as the first therapy to have shown evidence of efficacy in patients with PPMS. They also highlighted the benefit of a twice-yearly treatment option over more frequent injections such as with interferons. The comments argued that it was inequitable for ocrelizumab to be available only to patients with RRMS.
- 6.3 The PBAC noted the advice received from MS Australia and MS Research Australia strongly supporting the PBS listing of ocrelizumab for PPMS. The organisations described the gradual progression of the disease and the resulting long term disability for patients with PPMS. They emphasised the unmet clinical need for patients with PPMS and that given ocrelizumab was the first and only treatment option available, even a modest delay in disability can provide benefit to individuals and their families and the broader community.

Clinical trials

6.4 The submission was based on one randomised, double blind placebo control trial comparing ocrelizumab 600mg every 24 weeks, administered as two infusions of 300mg given 14 days apart, to placebo (ORATORIO: N=732).

6.5 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trial		
ORATORIO	Clinical Study Report. Clinical Study Report. A Phase III, Multicentre, Randomized, Parallel-group, Double-blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults With Primary Progressive Multiple Sclerosis. Montalban. Ocrelizumab versus placebo in primary progressive multiple sclerosis.	March 2016 New England Journal of Medicine. 2017; 376(3):209-20.

Source: Table 2.2.1, p 36 of the submission.

6.6 The key features of the ORATORIO trial are summarised in Table 3.

Table 3: Key features of the included evidence, ocrelizumab versus placebo

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ORATORIO	732	R, DB, 120 weeks	Low	PPMS	CDP 12; CDP 24	Yes (sensitivity analyses)
ORATORIO open label extension		R, OL, 144 weeks*	Low	PPMS	CDP 12; CDP 24	Yes (base case)

CDP=confirmed disability progression, defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit ≥ 12 weeks (or ≥ 24 weeks) after the initial disability progression (i.e., that observed increase in disability was sustained for a period of 12 or 24 weeks); DB=double blind; MC=multi-centre; OL=open label; R=randomised.

Source: compiled during the evaluation

* The submission stated that after the primary cut-off of 120 weeks, the open label study remained blinded and random controlled until 144 weeks.

6.7 The ORATORIO trial included a narrower population than the likely Australian PPMS population, with the following inclusion criteria:

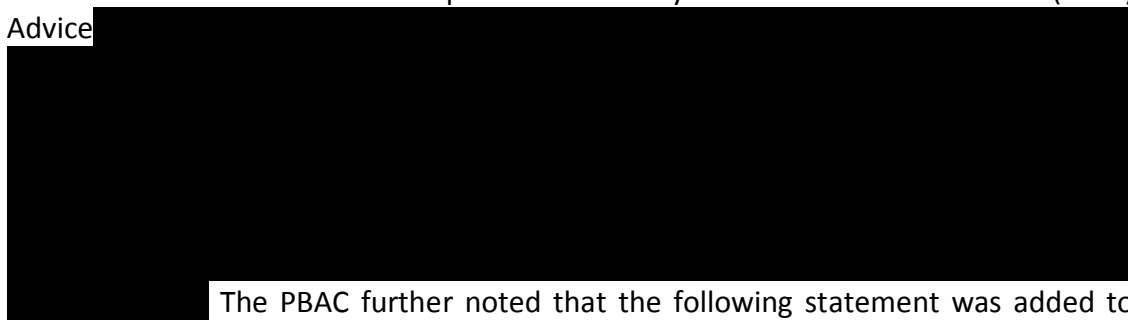
- Patients aged 18-55 years;
- Patients with EDSS at screening from 3.0 to 6.5 points;
- A score of ≥ 2.0 on the functional systems scale;
- A disease duration from onset of MS symptoms of less than 15 years for patients with an EDSS at screening of >5.0 ; and 10 years in patients with an EDSS at screening of ≤ 5.0 .

6.8 Characteristics of Australian PPMS patients from the MSBase registry indicated that the current Australian population is older (mean of 58 years), have been diagnosed with PPMS for longer (12 years versus approximately 3 years), have a higher EDSS score, includes a greater proportion of females and a greater proportion of patients have had prior disease modifying therapies compared with those enrolled in ORATORIO.

6.9 The pre-PBAC response (p1) stated that a survey of 154 clinicians in Germany, France, Italy, Spain and the UK conducted in September 2017 summarised the ideal PPMS

patient for ocrelizumab as one who is “fast progressing with EDSS <6.5, and underlying inflammation; progression needs to urgently be slowed to save as much neurological function as possible”. One clinician noted ‘though the unmet need for EDSS >6.5 patients is high, they are too far progressed to benefit from OCR’. The pre-PBAC response stated that results of this survey were consistent with advice from Australian MS experts consulted for the preparation of the submission, who stated that they have a higher likelihood of treating ambulatory patients with shorter disease duration and/or with gadolinium positive (Gd+) T1 lesions; representing approximately 50% of the prevalent PPMS population. The pre-PBAC response argued that the cohort of PPMS patients currently captured in the MSBase Registry does not accurately reflect the population expected to be treated with ocrelizumab. The PBAC noted that the requested restriction did not limit use of ocrelizumab to patients as described by the pre-PBAC response.

- 6.10 The PBAC noted that in the Request for Advisory Committee on Medicines (ACM) Advice



The PBAC further noted that the following statement was added to the ocrelizumab TGA Product Information (p9): “A post-hoc analysis suggested that patients who are 50 years of age or below, or patients who have inflammation determined by MRI (Gd enhancing or T2 lesion) may receive a greater treatment benefit than patients who are over 50 years of age or patients who do not have inflammation by MRI.”

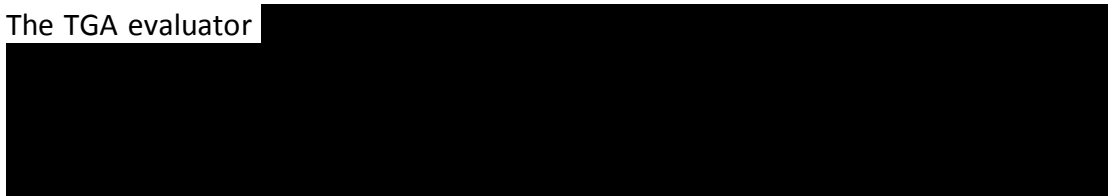
- 6.11 The PBAC was concerned about the applicability of the trial results to the potential PBS population, given the anticipated differences in patient baseline characteristics. The PBAC was concerned that the requested PBS restriction, which is broader than the trial eligibility criteria, and which does not restrict access to PPMS patients most likely to respond to ocrelizumab, may result in use of ocrelizumab that was less efficacious (or not efficacious) and therefore not cost effective. The PBAC advised this was an important consideration in the context of the modest clinical effect observed in the trial.

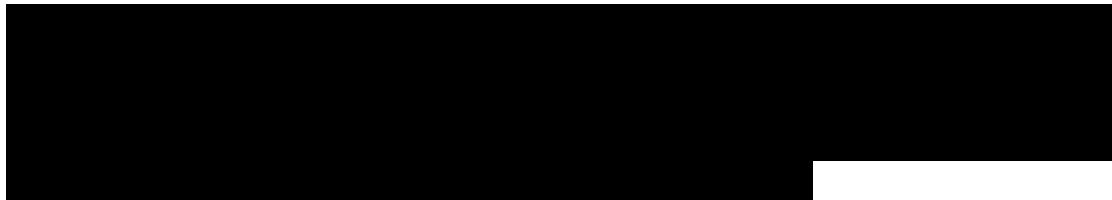
- 6.12 The TGA evaluator (Clinical Evaluation Report [CER])



In the context of PPMS, all other Phase III trials have failed to demonstrate efficacy of treatment over placebo, including rituximab (which is also a CD20 antagonist).

- 6.13 The TGA evaluator





Comparative effectiveness

6.14 The results of key outcomes in the ORATORIO trial are presented in Table 4.

Table 4: Results of key outcomes in ORATORIO

Outcome	Ocrelizumab n/N (%)	Placebo n/N (%)	Difference in time to CDP for 30%*	P value (log rank test)	Hazard ratio (95% CI)
12 week CDP (primary)	160/487 (32.9)	96/244 (39.3)	19.9 weeks	0.0321	0.76 (0.59, 0.98)
12 week CDP (Extended period)***	██████████	106/244 (43.4)	NA	0.0151	0.74 ██████████
24 week CDP (primary)	144/487 (29.6)	87/244 (35.7)	26.3 weeks	0.0365	0.75 (0.58, 0.98)
24 week CDP (Extended period)	██████████	93/244** (38.20)	NA	0.0056	0.70 ██████████

Source: Tables 2.5.1-2.5.4, pp57-61 of the submission; Tables 115 & 116, pp171-172 of the TGA CER

CDP = confirmed disability progression; CI = confidence interval; ITT = intention to treat; n = number of participants reporting data; N = total participants in group; NA = not applicable

* in neither arm of the trial did 50% of patients achieve confirmed progression, and so difference in median time to confirmed progression was unavailable, the difference in time to onset of CDP 12 for 30% of patients is presented instead

** back calculated from percentages during the evaluation.

*** the sponsor's response to EMA Questions 'ORATORIO EMA120 2017.pdf'(Table 7) indicated different proportions for the extended 12 week CDP results: 40.99% for Placebo and 34.18% for ocrelizumab. No explanation of this discrepancy was provided.

6.15 There were statistically significant improvements across all confirmed disability progression outcomes (CDP; first disability progression, which is confirmed at the next regularly scheduled visit ≥ 12 weeks (or ≥ 24 weeks) after the initial disability progression).

6.16 The TGA CER ██████████
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6.17 The CER ██████████
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6.18 Pre-defined subgroup analyses presented by the submission indicated that gender, age and T1 gadolinium (Gd) status of lesions may be treatment effect modifiers. The submission noted that the analyses were not powered to demonstrate efficacy differences between the subgroups.

Comparative harms

6.19 In the ORATORIO trial, ocrelizumab was associated with higher rates of at least one adverse event, adverse events leading to dose modification or interruption, infusion related reactions and upper respiratory tract infections compared to placebo. It would be expected that the increased risk of infusion related reactions associated with ocrelizumab would be greater compared with BSC in practice than observed compared with placebo (sham injections) in the ORATORIO trial. The ESC considered that there may be a higher incidence of adverse events in an older and frailer PBS population. The PBAC agreed with the ESC's views.

Benefits and harms

6.20 A summary of the comparative benefits and harms for ocrelizumab versus placebo is presented in Table 5.

Table 5: Summary of comparative benefits and harms for ocrelizumab and placebo

Benefits						
Time-to-event Outcome (120 Weeks follow-up in primary analysis; 144 weeks follow-up after extended period)						
Event	Ocrelizumab n/N (%)	Placebo n/N (%)	RR*	RD*	NNT*	HR (95% CI)
12 week CDP (primary)	160/487 (32.9)	96/244 (39.3)	0.87 (0.71, 1.07)	-0.05 (-0.12, 0.02)	20	0.76 (0.59, 0.98)
12 week CDP (Extended period)	177/487 (36.3)	██████████	0.84 (0.7, 1.01)	-0.07 (-0.15, 0.01)	14	0.74 ██████████
24 week CDP (primary)	144/487 (29.6)	87/244 (35.7)	0.83 (0.67, 1.03)	-0.06 (-0.13, 0.01)	17	0.75 (0.58, 0.98)
24 week CDP (Extended period)	151/487** (31.1)	██████████	0.81 (0.66, 1.00)	-0.07 (-0.14, 0.00)	14	0.70 ██████████
Harms						
	Ocrelizumab	Placebo	RR (95% CI)	Events/100 patients*		RD (95% CI)
				Ocrelizumab	Placebo	
At least one AE	462/486 (95.1)	215/239 (90.0)	1.06 (1.01, 1.11)	95	90	0.05 (0.01, 0.09)
AEs leading to dose modification or interruption	47/486 (9.7)	12/239 (5.0)	1.93 (1.04, 3.56)	10	5	0.05 (0.01, 0.09)
Infusion related reaction	194/486 (39.9)	61/239 (25.5)	1.56 (1.23, 1.99)	40	26	0.14 (0.07, 0.21)
Upper respiratory tract infection	53/486 (10.9)	14/239 (5.9)	1.86 (1.05, 3.29)	11	6	0.05 (0.01, 0.09)
Nasopharyngitis	110/486 (22.6)	65/239 (27.2)	0.83 (0.64, 1.08)	23	27	-0.05 (-0.12, 0.02)

* Calculations of RR, RD and NNT by the TGA varied because they were based on rates of events at 120 weeks rather than proportions of patients with events. As calculated during the evaluation.

** Back calculated from percentages during the evaluation.

*** The sponsor's response to EMA Questions 'ORATORIO EMA120 2017.pdf' (Table 7) indicated different proportions for the extended 12 week CDP results: 40.99% for Placebo and 34.18% for ocrelizumab. No explanation of this discrepancy was provided.

Abbreviations: AE = adverse event; CDP = confirmed disability progression; CI = confidence interval; NNT = number needed to treat; RD = risk difference; RR = risk ratio

Source: Compiled during the evaluation/

6.21 On the basis of the ORATORIO trial presented by the submission:

- For every 100 patients treated with ocrelizumab approximately five fewer patients would progress over a duration of 120 weeks.

- For every 100 patients treated with ocrelizumab, approximately 40 patients would have an infusion related reaction compared to best supportive care (as there would be no placebo sham injections in practice); and
- For every 100 patients treated with ocrelizumab, approximately five additional patients would suffer a respiratory tract infection compared to placebo.

Interpretation of clinical evidence

- 6.22 The submission stated that ocrelizumab is superior in terms of effectiveness compared with BSC and is inferior in terms of safety compared with BSC, but has an acceptable safety profile that is comparable with placebo.
- 6.23 The evaluation considered that there were concerns regarding the reproducibility of the modest treatment effect of ocrelizumab, given the existence of only one trial. The evaluation noted that further analyses, although post-hoc, did not demonstrate superiority in older subgroups of patients and subgroups of patients with absence of Gd lesions. Therefore, the evaluation considered that given the median age in the MSBase database was over 58 years old, a substantial portion of Australian PPMS patients may not benefit significantly from ocrelizumab treatment.
- 6.24 The PSCR (p2) argued that since no study has previously demonstrated a delay in disability progression, there is no established standard, on a cohort level, for what is a clinically relevant reduction of risk of disability progression. The PSCR claimed that >95% of multiple sclerosis neurologists practising in the European Union (n=60) considered the disability progression outcomes of ORATORIO to be clinically relevant (based on anonymised feedback sought by the sponsor). The PSCR argued that in addition to the endpoints highlighted in the commentary, ocrelizumab also showed clinically and statistically significant improvements in the patient relevant exploratory outcomes of upper limb function and decrease in fatigue.
- 6.25 The ESC agreed with the evaluation that the treatment effect for ocrelizumab appeared modest. The ESC was of the view that if baseline differences between the anticipated PBS population and the trial population were accounted for (refer to paragraphs 6.7 -6.8), the effect size of ocrelizumab may be further reduced. The ESC was concerned that there may be a higher incidence of adverse events in a potentially older PBS population with more severe disease. The ESC noted however, that the CDP result was sustained at the 12 and 24 week time points.
- 6.26 The PBAC considered that the claim of superior comparative effectiveness was reasonable, however, the Committee considered the clinical benefit of ocrelizumab was modest.
- 6.27 The PBAC considered that the claim of inferior comparative safety was reasonable. However, the PBAC considered that the claim that ocrelizumab has an acceptable safety profile that is comparable with placebo was not adequately supported. The PBAC noted ocrelizumab was associated with a greater rate of infusion related reactions and upper respiratory tract infections than placebo in the ORATORIO trial. Additionally, the older Australian population would be expected to have a higher risk of infections.

Economic analysis

6.28 Table 6 presents a summary of the economic model presented in the submission.

Table 6: Summary of model structure and rationale

Component	Description
Type of analysis	Cost utility analysis
Outcomes	Life years gained and QALYs gained
Time horizon	Life time (56 years), versus 3 years in the key trial data.
Methods used to generate results	Markov model
Health states	EDSS 0 to 9 (untreated and treated) and death
Cycle length	1 year
Transition probability	EDSS transition based on natural history of PPMS, treatment hazard ratio applied in ocrelizumab arm.
Software package	Excel 2010

Source: Table 3.1.1, p 82 of the submission. QALY = quality-adjusted life year.

- 6.29 The model population was based on that in the ORATORIO trial and hence reflective of a younger and likely healthier population than what would be expected in the Australian population. Though the model could adjust starting age, it was not specified to test various assumptions regarding variation in treatment effect by age or presence of Gd lesions.
- 6.30 Utility values were based on ORATORIO EQ-5D responses for EDSS health states 2 to 7 and on a utility model from Orme (2007), a UK MS survey, for health states zero to 1 and 8 to 9. Negative utility values reflecting states worse than death were used in EDSS health states 8 and 9. Since the utility values were not based on trial data, setting those values to zero would be more conservative.
- 6.31 The PSCR (p4) argued that setting the utility values to zero for the EDSS 8 and 9 health states would trivialise the severity of the advanced disease stages of PPMS. The PSCR claimed that these health states have been described as worse than death in various MS quality of life studies, which confirms the results found by Orme (2007). The PSCR stated that the valuation of HRQoL using EQ-5D methodology allows health states to appropriately be perceived as worse than death. The PSCR argued that in order to allow a fair comparison of results of cost-utility analyses across disease areas it is crucial that negative utilities are accounted for when appropriate. The ESC noted that sensitivity analyses with negative utilities set to zero increased the incremental cost-effectiveness ratio (ICER), from the base case of more than \$200,000 to more than \$200,000 per quality adjusted life years (QALY) gained.
- 6.32 The submission applied additional disutilities associated with upper limb dysfunction. The disutilities were generated from a linear EQ-5D utility model using ORATORIO data on changes in the 9 peg-hole test. Details of the model specifications were not made available. The ESC considered that this overall approach was not adequately justified and might have favoured ocrelizumab due to “double-counting” of disutility already captured in the EQ-5D values.
- 6.33 The PSCR (p5) stated that the EDSS model presented in the submission excluded patients with a sustained 20% increase in the 9 peg-hole test. The PSCR argued

therefore, including the additional disutility estimated for upper limb dysfunction does not represent double counting of the effect of upper limb dysfunction on HRQoL. The ESC noted that sensitivity analyses with the disutility of upper limb dysfunction excluded increased the ICER, from the base case of more than \$200,000, to more than \$200,000 per QALY gained.

Table 7: Key drivers of the model

Description	Method/Value	Impact
Estimate of treatment effect	The hazard ratio of CDP 24 between ocrelizumab and placebo in the open label extension	High, favours ocrelizumab
Broad assumption of applicability of trial population to Australian population	Starting age in model of 44 years. There were indications that the Australian population was likely to be older than those enrolled in the ORATORIO trial, and also indications that the treatment effect may be less in older patients.	Likely high, favours ocrelizumab. Although the model could adjust starting age, it was not specified to test various assumptions regarding variation in treatment effect by age (or presence of Gd lesions)
Utility/disutility values	Modelled based on ORATORIO utility values, and Orme values, negative utility states, and disutility associated with upper limb dysfunction	Moderate, favours ocrelizumab
Assumption of a survival benefit	Model applies mortality multipliers to each EDSS health state	Moderate, favours ocrelizumab ^a

Source: compiled during the evaluation

^a when negative utility values are also set to one

6.34 The PSCR (p4) maintained that a lifetime time horizon was appropriate and claimed that there was no evidence of a diminishing treatment effect in patients remaining on treatment in the ORATORIO trial. The PSCR argued given that all-cause discontinuations have been included in the economic evaluation, it was appropriate, based on the results from ORATORIO, to assume that patients remaining on treatment would continuously benefit from ocrelizumab. The ESC noted that there was no evidence that ocrelizumab’s treatment effect, based on 144 weeks from the trial, would be maintained over 56 years. The pre-PBAC response (p2-3) stated that all-cause treatment discontinuation was included in the economic evaluation, resulting in an average treatment duration of [REDACTED] over a 56 year time horizon. The pre-PBAC response (p3) claimed that results of the open label extension period presented in the submission confirmed or exceeded the results observed during the duration of the initial pivotal trial, and that there is no evidence of treatment effect waning. The PBAC noted that the primary analysis was based on 120 weeks of follow up, and that the extended period was based on 144 weeks of follow up. The PBAC agreed with the ESC that there was no evidence that ocrelizumab’s treatment effect would be maintained over 56 years, particularly given the marginal absolute differences in treatment effect between ocrelizumab and placebo.

6.35 The PSCR (p5) stated that EDSS-specific mortality multipliers were applied to the background mortality estimates because MS patients have a greater risk of mortality than the general population. The PSCR argued that the survival benefit modelled in the economic evaluation is a direct result of the applied increased mortality risk associated with increased disability. The PSCR argued given that treatment with ocrelizumab delays disability progression, treated patients remain longer in lower EDSS health states which results in a slightly decreased mortality risk compared to

untreated patients. The ESC noted that the EDSS-specific mortality multipliers were sourced from a long-term observational study in Denmark published in 1997 (Pokorski). The ESC noted that there were a number of translation issues associated with using this study, including, historical data, regional difference, inclusion of all types of MS patients, and unclear methods relying on broad classifications such as ‘definite’, ‘probable’ and ‘possible’ MS, and ‘mild’, ‘moderate’ and ‘severe’ disease. The ESC considered that the incorporation of survival gain in the model through using this approach, which was not demonstrated in the pivotal trial, was not adequately justified.

6.36 The pre-PBAC response (p2) acknowledged that the available evidence from ORATORIO was insufficient to directly claim a survival benefit for ocrelizumab. However, the pre-PBAC response argued that as mortality relative to the general population has been shown in the literature (unrelated to ORATORIO) to increase with greater disability, a treatment effectively delaying disability progression must also therefore improve survival. The pre-PBAC response also argued that the small survival benefit modelled (██████ life years) is plausible as a consequence of the treatment effect of ocrelizumab on disability progression, and that this small survival benefit would not be detectable in a short term clinical trial with limited patient numbers.

6.37 Table 8 presents results of the stepped economic evaluation.

Table 8: Results of the stepped economic evaluation based on the proposed effective price of ocrelizumab

Step and component	Ocrelizumab	BSC	Increment
Step 1: Trial-based costs and outcomes			
Costs	\$██████	0	\$██████
LY	██████	██████	██████
QALY	██████	██████	██████
Incremental cost/QALY gained			\$██████
Step 2: Extrapolation over lifetime horizon			
Costs	\$██████	0	\$██████
LY	██████	██████	██████
QALY	██████	██████	██████
Incremental cost/QALY gained			\$██████
Step 3: Inclusion of resource costs			
Costs	\$██████	\$██████	\$██████
LY	██████	██████	██████
QALY	██████	██████	██████
Incremental cost/QALY gained			\$██████
Step 4: Inclusion of AE costs			
Costs	\$██████	\$██████	\$██████
LY	██████	██████	██████
QALY	██████	██████	██████
Incremental cost/QALY gained			\$██████

Source: Table s 3.8.1-3.8.5, pp 118-121 of the submission. BSC = best supportive care; AE = adverse events; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SPA = special pricing arrangement.

6.38 The submission stated that the sponsor recognised ‘the ICER for ocrelizumab in PPMS does not fall within the range of traditionally accepted values’ (p122 of the submission). The submission made a number of arguments for why the model results alone were not sufficient to assess the holistic value for money of ocrelizumab. These arguments are summarised in Table 9.

Table 9: The submission’s arguments for unmeasured value in current model

Submission’s argument	Comment
‘...The economic evaluation is likely a conservative reflection of ocrelizumab’s cost-effectiveness given that an expected attributable survival benefit as well as quality of life benefits could not be comprehensively accounted for’ (p122 of the submission)	The ESC noted there was no evidence for survival benefit of ocrelizumab in PPMS, and considered the current survival benefit modelled was likely an overestimate.
‘Standard discount rates pose significant challenges for a treatment where upfront treatment is used to delay accumulation of disability over time.’ (p122 of the submission)	The model was fairly sensitive to reductions in discount rates, however, given that the model assumed a sustained treatment effect for patients remaining on ocrelizumab throughout the life time model, which was not supported by the trial’s duration of follow-up of 144 weeks, a discount rate less than 5% would increase this estimate of sustained effect. The ESC considered that the assumption of a lifetime treatment effect was not adequately justified based on the available clinical data, and any change in the discount rate could be tested in sensitivity analyses rather than applied in the base case scenario.
‘Fatigue, cognition and upper limb function are patient relevant outcomes that may not be adequately reflected in the CDP results from ORATORIO’	This was conceivable and the analysis commissioned regarding utility of fatigue could be informative should it be made available. Nevertheless the submission had adjusted for upper limb dysfunction, and the methodology was not adequately described.
‘The high burden of disability in PPMS means that the retaining critical functions can have flow-on benefits to carers (especially partners and parents), improved productivity and workforce participation and reduced dependence on disability benefits and support.’	This was acknowledged, but even if assessment of indirect costs were recommended in the PBAC guidelines, the submission’s sensitivity analysis indicated that the resulting ICER would still not be close to a traditionally accepted estimate of cost-effectiveness.

Source: pp 122-123 of the evaluation. CDP = confirmed disability progression; ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Scheme; PPMS = primary progressive multiple sclerosis

6.39 The ESC noted the arguments for “unmeasured value” and the emphasis on equity considerations regarding PPMS relative to relapsing remitting MS, in the submission and PSCR. The ESC considered that these were matters for consideration by the PBAC. The PBAC noted the submission’s arguments for “unmeasured value” and considered that these did not justify the low and unacceptable cost-effectiveness of ocrelizumab in PPMS.

6.40 Results of the univariate sensitivity analyses presented by the submission and additional analyses conducted during the evaluation are summarised in the table below.

Table 10: Results of univariate sensitivity analyses

Univariate analyses		Incremental costs	Incremental QALYs	ICER
Base case		████████	██████	████████
Discount rate (BC = 5%)	3.5%	████████	██████	████████
	0%	████████	██████	████████
CDP HR (BC = 0.70)	0.76	████████	██████	████████
	0.59 (LCI of primary endpoint)	████████	██████	████████
	0.98 (UCI of primary endpoint)	████████	██████	████████
Mortality effect Pokorski (1997)	Removed	████████	██████	████████
Indirect costs (BC: excluded)	Included	████████	██████	████████
Natural history EDSS (BC: PPMS + PRMS)	PPMS only	████████	██████	████████
Model start age (BC = 44)	52 (As per MSBase)	████████	██████	████████
Utilities (BC: trial based; disutility of upper limb dysfunction included)	Orme (2007) utilities	████████	██████	████████
	Trial based with negative utilities set to 0	████████	██████	████████
	Disutility of upper limb dysfunction excluded	████████	██████	████████
Implications of stopping rules				
Stop treatment at EDSS 7		████████	██████	████████
Stop treatment at age 55		████████	██████	████████
Stop treatment at EDSS 7 or Age 55		████████	██████	████████
Multivariate sensitivity analyses				
Mortality multiplier removed & negative utilities set to 0		████████	██████	████████

Source: Table 3.9.6, p128 of the submission, and calculated during the evaluation

The redacted table shows ICERs in the range of \$105,000/QALY to more than \$200,000/QALY.

- 6.41 Overall, the model was most sensitive to estimates of treatment effect. In the base case analysis, the submission utilised CDP24 from the open label extension period to estimate the treatment effect (HR = 0.70). Alternatively, relying on the primary endpoint of the ORATORIO trial (HR=0.76) led to an increase in the ICER (more than \$200,000/QALY gained).
- 6.42 The PSCR (p4) stated that the CDP24 result based on the longest available study follow-up was applied in the economic evaluation because it is deemed most representative of the treatment effect achievable in clinical practice. The PSCR noted the sensitivity analyses conducted by the evaluation, using the lower and upper 95% confidence interval of the CDP12 outcome, and stated that the likelihood of the treatment effect being at either of the upper and lower confidence interval limits is low at 2.5%.
- 6.43 The ESC noted that differences in the hazard ratio applied in the sensitivity analyses, including use of the CDP12 outcome, and lower and upper confidence limits,

resulted in substantial changes in the ICER which demonstrated some of the economic uncertainty associated with ocrelizumab. The ESC considered that the economic model reflects the trial population, which was younger and likely healthier than the expected PBS population. Given previously noted concerns regarding the estimates of effect size, sensitivity analyses were performed during the evaluation using the upper and lower 95% confidence intervals of the primary endpoint (CDP12) in ORATORIO (0.59, 0.98). The ICER decreased to \$105,000/QALY - \$200,000/QALY gained when relying on the lower bound of CDP12, and increased to \$105,000/QALY - \$200,000/QALY when relying on the upper bound. The sensitivity analysis showed that even in the most optimistic of efficacy scenarios, the ICER was well above what is traditionally considered cost-effective. The PSCR (p4) presented a similar calculation using CDP24 (HR=█, 95% CI: █), which resulted in the ICER interval of (\$105,000 - \$200,000; more than \$200,000) per QALY gained.

6.44 The ESC considered that in the context of the:

- Modest clinical improvements across CDP12 and CDP24 outcomes;
- Translation issues of the ORATORIO trial to the potential PBS population;
- Large impact of the hazard ratio used in the economic model on the ICER;
- Constant treatment effect over 56 years extrapolated from 144 weeks; and
- Assumed survival benefit incorporated into the economic model;

the cost/QALY gained for ocrelizumab in the PBS setting could potentially be much higher than the base case presented in the submission. The PBAC agreed with the ESC's views.

6.45 The PBAC considered the estimates of mean treatment effect appeared to be optimistic estimates considering that the Australian prevalent pool of patients is on average over 50 years old, and ocrelizumab has not established effect in PPMS in patients over 55 (p19 of TGA PI).

Drug cost/patient/year: \$█

6.46 The undiscounted annual drug acquisition cost of ocrelizumab based on two 600mg infusions per year was estimated to be \$█ (or \$█ when applying the effective price proposed) per patient, taking into account fees and mark-ups applicable to S100 HSD listing, and a private/public setting split of 20%/80%, respectively.

6.47 Ocrelizumab was recommended in July 2017 for listing in relapsing remitting MS (RRMS). Consequently, its effective price will be negotiated in post-PBAC discussions with the sponsor. The PSCR (p5) stated █

Estimated PBS usage & financial implications

6.48 This submission was considered by DUSC. The submission took an epidemiological approach to estimate use and financial implications. The submission relied on

epidemiological data from Miller (2007), Barnett (2003), Multiple Sclerosis Research Australia (MSRA 2010) and expert opinion from an advisory board to calculate these estimates.

6.49 Table 11 presents the estimated use and financial implications associated with listing ocrelizumab.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	████	████	████	████	████	████
Number of scripts dispensed ^a	████	████	████	████	████	████
Estimated financial implications of ocrelizumab (effective price)						
Cost to PBS/RPBS	████████	████████	████████	████████	████████	████████
Copayments	████	████	████	████	████	████
Cost to PBS/RPBS less copayments	████████	████████	████████	████████	████████	████████
Net financial implications						
Net cost to PBS/RPBS	████████	████████	████████	████████	████████	████████
Net cost to MBS*	████	████	████	████	████	████
Overall net cost to Government	████████	████████	████████	████████	████████	████████

a Assuming 2 scripts per year as estimated by the submission.

Source: Table 4.2.1, p139 of the submission, Table 4.2.3, p140 of the submission, Table 4.2.4, pp140-141 of the submission., Table 4.5.2 p143 of the submission, Table 4.5.4, p144 of the submission, and 'utilisation and cost model.xlsx'.

* Based on figures from the September 2017 DUSC Advice, updated from the sponsor's pre-sub-committee response.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$30 - \$60 million per year.

6.50 At year 1, the estimated number of patients was less than 10,000 per year and the net cost to the Government would be \$20 - \$30 million per year.

6.51 At year 6, the estimated number of patients was less than 10,000 per year and the net cost to the Government would be \$30 - \$60 million per year.

6.52 The DUSC considered the estimates presented in the submission to be underestimated and highly uncertain. The main issues were identified as follows.

- The number of incident patients was added to the number of prevalent patients to estimate use, resulting in an overestimate of the projected number of treated patients.
- The financial estimates were sensitive to inputs based on expert opinion of uptake and eligibility in the prevalent population. Both estimates risked being underestimates in the base case, leading to underestimates of use and cost to

government. A risk share arrangement is necessary to reduce uncertainty in the costs to government.

- The requested restriction was broadly worded and allowed for access to a broader PPMS population than the population included in the ORATORIO clinical trial. DUSC advised that the restriction should include criteria based on disease severity for initial therapy, and criteria based on prior treatment effectiveness in the request for continuing therapy.
- The submission did not account for two separate administrations in the initial treatment of ocrelizumab (300mg administered two weeks apart). This underestimated administration costs.

6.53 The pre-PBAC response (p3) stated that the sponsor is willing to present a revised utilisation and cost model.

Quality use of medicines

6.54 The submission stated that there are no planned quality use of medicine programs specifically to support the listing of ocrelizumab for PPMS.

6.55 The submission noted that two global ocrelizumab non-interventional, observational studies will be commencing in 2017 to assess the long term safety and efficacy of ocrelizumab in patients with MS. These studies are:

- MSBase PASS-Ocrelizumab safety sub-study long term safety study of ocrelizumab treated patients with multiple sclerosis; and
- MSCORE-P- Prospective assessment of real world long-term natural history and ocrelizumab effectiveness in progressive MS Disease.

6.56 The DUSC advised that ocrelizumab would benefit from a quality use of medicines (QUM) program to monitor long term safety and adverse events. The DUSC noted that the older Australian population with more severe disease likely to be treated compared to individuals eligible for the ORATORIO trial would have a higher risk of infection, and considered that patients would benefit from ongoing support to manage these events. The PBAC agreed with the DUSC that ocrelizumab would benefit from a quality use of medicines program.

6.57 The pre-PBAC response (p3) stated that the sponsor has developed 'the Conductor Program' to support patients in the management of ocrelizumab. The program consists of: (1) a secure web portal that can be accessed by doctors and nurses to enrol patients and manage infusion dates, times and location. (2) nurse-support for patients to elect to receive 6-monthly phone calls from a MS nurse; and (3) an ocrelizumab patient app providing information about MS and ocrelizumab, synchronising with the patient portal to auto-populate information regarding the patient's healthcare team and infusion schedule.

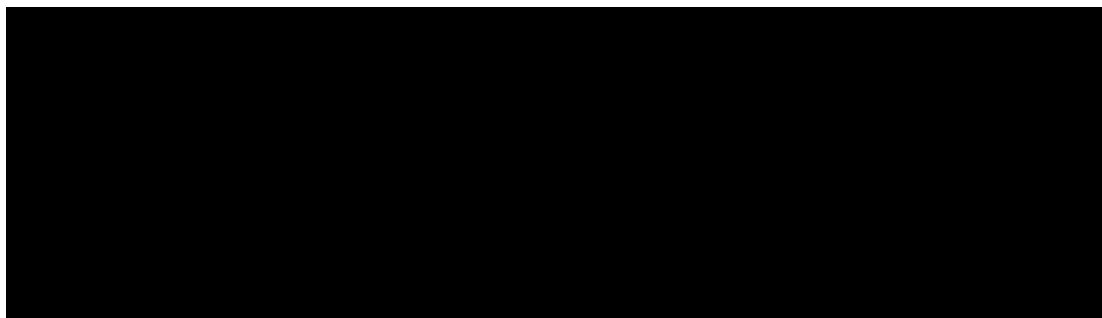
Financial management – risk sharing arrangements

6.58 The submission stated that the sponsor is willing to undertake a risk sharing arrangement. No further details were provided.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of ocrelizumab for the treatment of patients with primary progressive multiple sclerosis (PPMS), on the basis of modest clinical benefit and the resulting high and uncertain incremental cost-effectiveness ratio (ICER). The PBAC was concerned about the applicability of trial results to the potential PBS population, and that the base case ICER presented by the submission may be underestimated as ocrelizumab is likely to be less effective in the PBS population than observed in the ORATORIO trial. The PBAC was also concerned about the uncertainty with the utilisation estimates due to issues with defining the target PBS population, and the high and likely underestimated financial impact.
- 7.2 The PBAC noted the consumer comments received in support of a PBS listing for ocrelizumab, and considered that these reflected the high, unmet clinical need for treatment options for patients with PPMS.
- 7.3 The PBAC noted that the requested PBS restriction was broader than the trial eligibility criteria. The PBAC noted the sponsor's assertion that a broad PBS restriction was proposed "in good faith, seeking to ensure equity of access and to facilitate clinical judgement" (p1, pre-PBAC response). The PBAC considered however, that a PBS restriction consistent with the trial inclusion and exclusion criteria was important in identifying the appropriate PBS population, particularly in the context of the modest clinical benefit demonstrated in the ORATORIO trial. The PBAC noted that there was no evidence of clinical benefit of ocrelizumab in patients older than 55 years or with an EDSS >6.5 points. The PBAC was therefore concerned that the applicability of the treatment effect observed in the ORATORIO trial to the requested PBS population was uncertain. The PBAC further noted that pre-specified and post hoc subgroup analyses indicated that patient characteristics such as age and inflammation determined by MRI may be treatment effect modifiers. Given the modest treatment effect observed in the trial, the PBAC was concerned that the treatment effect of ocrelizumab may be less, and/or there may be a higher incidence of adverse events in an older and frailer PBS population. The PBAC therefore advised that ocrelizumab be used in the subgroup of PPMS patients for which there is evidence of clinical benefit.
- 7.4 The PBAC accepted best supportive care (BSC) as the appropriate main comparator.
- 7.5 The PBAC noted that the submission was based on a single head-to-head trial comparing ocrelizumab to placebo. The PBAC noted that ocrelizumab is the first disease modifying therapy to demonstrate effectiveness in delaying disability progression in PPMS, and that other therapies (glatiramer acetate, rituximab and fingolimod) trialled for PPMS had failed. The PBAC further noted that the TGA Clinical Evaluation Report (CER [REDACTED])



In noting the above issues, the PBAC considered that the overall evidence base for the effectiveness of ocrelizumab in PPMS was not robust.

- 7.6 The PBAC noted that the ORATORIO trial demonstrated statistically significant improvements across all confirmed disability progression outcomes for ocrelizumab over placebo (CDP; defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit ≥ 12 weeks [or ≥ 24 weeks] after the initial disability progression). However, the PBAC considered that the treatment effect for ocrelizumab was modest, with the difference in time to onset of CDP12 being only approximately 20 weeks for 30% of patients. The PBAC was concerned that a large number of patients would be required to receive treatment for one person to gain benefit (number needed to treat = 20; for the primary outcome of 12 week CDP), and that in certain subgroups, the treatment effect of ocrelizumab may be negligible. Given the small absolute differences in efficacy demonstrated by ocrelizumab over placebo, the PBAC considered that the clinical significance of the trial outcomes was uncertain.
- 7.7 The PBAC accepted the claim of inferior comparative safety of ocrelizumab over BSC. However, the PBAC considered that the claim that ocrelizumab has an acceptable safety profile that is comparable with placebo was not adequately supported. The PBAC noted ocrelizumab was associated with a greater rate of infusion related reactions and upper respiratory tract infections than placebo in the ORATORIO trial. Additionally, the potentially older PBS population with more severe disease may experience a higher risk of infections and/or other adverse events.
- 7.8 The PBAC noted that the treatment effect in the base case economic analysis was based on the CDP24 outcome from the ORATORIO extension period (HR=0.70), rather than on the primary endpoint of the trial (CDP12; HR=0.76). Using the CDP12 estimate increased the ICER to more than \$200,000 per QALY gained (base case = more than \$200,000). The PBAC further noted that the estimate of treatment effect was a major driver in the economic model. Sensitivity analyses indicated that the ICER scales up quickly when the treatment effect is less favourable than the base case point estimate applied in the economic model, while decreasing only moderately with a more favourable point estimate. Applying the 95% confidence interval of the primary endpoint (CDP12 95% CI: 0.59, 0.98) in the economic model resulted in the ICER ranging from \$105,000/QALY - \$200,000/QALY to more than \$200,000/QALY. The PBAC considered that this reflected the high and highly uncertain ICER associated with ocrelizumab for PPMS, particularly in the context of the Committee's concerns regarding the marginal clinical benefit demonstrated in

the overall ORATORIO population and the potentially negligible treatment effect in some patient subgroups.

- 7.9 The PBAC agreed with the concerns raised by the ESC that:
- The treatment effect was assumed to be constant over the model duration (56 years) which did not take into account potential treatment effect modifiers such as time, health state and patient characteristics.
 - The model population was younger than the expected treatment population. Pre-defined and post hoc subgroup analyses indicated that age was a potential treatment effect modifier, however no adjustments were made in the model to capture these differences.
 - The survival benefit generated by the model as a result of applying EDSS-specific mortality multipliers was not supported by the data from ORATORIO.
 - There is potential for double counting with the addition of disutility associated with upper limb dysfunction.
- 7.10 The PBAC noted the submission's arguments for "unmeasured value" and considered that this did not justify the high ICER of ocrelizumab in PPMS. The PBAC noted that even when the most favourable treatment effect, at the lower end of the 95% CI for the CDP12 outcome (HR = 0.59), was applied in the economic model, the resulting ICER/QALY of \$105,000 - \$200,000 was still significantly above what the Committee considers to be within a cost-effective range.
- 7.11 The PBAC noted that the submission's estimated net cost of ocrelizumab to the PBS/RPBS was approximately more than \$100 million over six years based on the effective price proposed by the sponsor. The PBAC agreed with the DUSC that the estimated financial impact to the PBS of listing ocrelizumab was underestimated. The PBAC noted that the submission added the number of incident and prevalent patients to estimate use, which resulted in an overestimate of the projected number of treated patients. However, the financial estimates were sensitive to the estimates of uptake and eligibility in the prevalent population, which were based on expert opinion and likely underestimated. The PBAC considered that given the high clinical need in PPMS and that there are currently no other PBS subsidised treatments available, the uptake rate is anticipated to be higher than that proposed by the submission. The PBAC was concerned that the broad restriction wording would further translate to higher uptake of ocrelizumab, and in subgroups of patients for whom there is little evidence of benefit. The PBAC also noted that administration costs were underestimated, as the submission did not account for two separate administrations in the initial treatment of ocrelizumab (300mg administered two weeks apart).
- 7.12 The PBAC noted that the sponsor proposed a Risk Share Agreement (RSA), however no details for the RSA were proposed. The PBAC considered that a RSA alone was insufficient to address the Committee's concerns regarding the uncertainty associated with ocrelizumab's treatment effect, potential PBS population and cost effectiveness.

7.13 The PBAC considered that any resubmission for ocrelizumab for PPMS would require a major submission addressing the issues raised by the PBAC and its subcommittees (ESC and DUSC). The PBAC considered that demonstration of more robust evidence and a greater absolute benefit in delaying disease progression for PPMS, and/or a substantial price reduction would be required to achieve a cost-effective listing for ocrelizumab for PPMS.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Roche is committed to continue working with all stakeholders to enable reimbursement of ocrelizumab for Australians with PPMS.