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

1 Purpose of resubmission

1.1 The resubmission requested a Section 100 listing for ocrelizumab for the treatment of early, active primary progressive multiple sclerosis (PPMS).

1.2 Listing was requested on the basis of a cost-utility analysis versus best supportive care (BSC). Key components of the clinical issue addressed by the resubmission are presented in Table 1. Underlined text refers to changes compared with the previous submission.

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

Component	Description
Population	Adult patients with primary progressive multiple sclerosis (PPMS) diagnosed in the previous 5 years and with active* inflammatory disease in the previous 12 months[a]
Intervention	Ocrelizumab (600mg IV infusion every 6 months)
Comparator	Best Supportive Care (BSC).
Outcomes	Reduction in disability progression • Time to onset of confirmed disability progression, using EDSS scores; • Change in walking speed, using timed 25-Foot Walk (T25FTW); and • Upper limb-dysfunction, using 9-hole peg test (9HPT). Brain MRI • Change in T2 lesion volume; and • Change in total brain volume. Quality of life • Utility of disability state, using EDSS scores; and • SF-36 scores.
Clinical claim	In adults with PPMS, ocrelizumab is more effective than best supportive care in delaying the accumulation of physical disability[a]

Source: Table 1.2, p4 of the resubmission.
EDSS = expanded disability status scale

* The restriction defined active disease as: ≥1 Gd-enhancing T1 lesions; OR Evidence for dissemination in space (DIS) based on ≥1 new or enlarging T2 lesions relative to the previous scan

[a] In comparison to the previous submission, the resubmission has limited the restriction to adults with PPMS diagnosed in the previous 5 years and with active inflammatory disease in the previous 12 months. The resubmission has removed a safety claim and described the efficacy claim in terms of delaying accumulation of physical disability.

2 Background

Registration status

2.1 Ocrelizumab was approved by the TGA on July 13, 2017 for:

- The treatment of patients with primary progressive multiple sclerosis (PPMS) to delay the progression of physical disability.
- 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.

2.2 This resubmission was based on efficacy data from a *post-hoc* analysis of a subgroup of patients in the ORATORIO trial who had 'Magnetic Resonance Imaging (MRI) Activity' and were ≤50 years of age. The resubmission stated that the subgroup was aligned with the proposed restriction and the European Medicines Agency (EMA) label.

Previous PBAC consideration

2.3 Ocrelizumab was previously considered by the PBAC for PPMS in November 2017. A summary of key matters of concerns in presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Restriction	The ORATORIO trial included a narrower population than the likely Australian PPMS population, in terms of age, EDSS, functional systems scale score, disease duration from onset of MS symptoms (paragraph 6.7, Ocrelizumab, Public Summary Document (PSD), November 2017 PBAC Meeting). 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" (pre-PBAC response). 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 (paragraph 7.3)	Not adequately addressed. The resubmission narrowed the requested restriction to patients with active disease who have been diagnosed with PPMS in the past 5 years and are ambulatory at initiation. This would address some of the issues, but the applicability of the trial population to the requested restriction remains a potential issue, as does the use of time since diagnosis as a proxy for age. Additionally, the requested restriction allows for continuation of ocrelizumab treatment indefinitely, beyond a disability level for which there is no evidence of benefit.
Clinical effectiveness	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 (paragraph 7.3). 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 (paragraph 7.3). The PBAC considered that the overall evidence base for the effectiveness of ocrelizumab in PPMS was not robust (paragraph 7.5). 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.	Not addressed: The resubmission based the clinical claim on post-hoc subgroup analysis of trial evidence which the evaluation considered was not robust.

Component	Matter of concern	How the resubmission addresses it
Safety	The claim of an acceptable safety profile that is comparable with placebo was not adequately supported. 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.	Not adequately addressed. The resubmission did not present additional comparative safety data. The resubmission updated extended harms data which indicated no new safety signals. The resubmission's modification of the restriction would restrict some older patients at initiation given the criteria of diagnosis within the past 5 years, but it was unclear to what extent this criteria was a proxy for age.
Economic analysis	There was a high and uncertain ICER associated with ocrelizumab for PPMS, particularly in the context of concerns regarding the marginal clinical benefit demonstrated in the overall ORATORIO population and the potentially negligible treatment effect in some patient subgroups (paragraph 7.8).	The resubmission addressed this issue by narrowing the requested restriction to patients more likely to benefit, but also revised the HR for clinical effect (CDP24 from 0.7 to 0.53) by selecting a subpopulation that does not align with the proposed restriction. The model remains highly sensitive to estimates of effect, and the base case estimate of effect remains optimistic.
	Treatment effect was assumed to be constant over the model duration (56 years) (paragraph 7.9).	Addressed, but only in sensitivity analyses. The model now includes functionality for waning treatment effect. The model is sensitive to these estimates.
	The model population was younger than the expected treatment population (paragraph 7.9).	This is partially addressed by narrowing the restriction. However, the restriction is not restricted by age, and the economic evaluation also further decreased the starting age from 44 to 40 (ITT population mean was 44).
	The survival benefit generated by the model as a result of applying EDSS-specific mortality multipliers was not supported by the data from ORATORIO (paragraph 7.9).	These have been retained. However, revision of health state costs led to the ICER decreasing with the removal of the multipliers.
	There is potential for double counting with the addition of disutility associated with upper limb dysfunction (paragraph 7.9).	Addressed. These have been removed.
Financial estimates	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 (paragraph 7.11).	The resubmission still adds incident and prevalent patients, but the requested restriction is defined by patients diagnosed within the previous 5 years, and the prevalent population is estimated in a manner consistent with this.
	The model was sensitive to the estimates of uptake and eligibility in the prevalent population, which were based on expert opinion and likely underestimated.	Uptake has not been changed. Eligibility is based on ORATORIO data, which was considered to have applicability issues.
	The broad restriction wording would translate to higher uptake of ocrelizumab in subgroups of patients for whom there is little evidence of benefit. (paragraph 7.11)	The restriction was narrowed in the resubmission.

Source: Ocrelizumab, PSD, November 2017 PBAC Meeting and pp1-99 of the resubmission.
CDP = confirmed disability progression; EDSS = expanded disability status scale; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; PPMS = primary progressive multiple sclerosis.

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

3 Requested listing

3.1 The listing requested in the submission is presented below. Underlined text indicates changes or additions made in relation to the previous submission. The condition was specified as multiple sclerosis in the previous submission versus primary progressive multiple sclerosis in the resubmission. A further change is that the previous submission requested a 'Streamlined Public hospital Authority Required' and 'Private hospital Authority Required' compared with 'Authority Required – In Writing' in the resubmission. Unlike the previous submission, the resubmission requested a grandfather restriction.

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Ocrelizumab Concentrate solution for infusion, 300 mg in 10mL, 1 vial (public)	2	0	$17,533.00 published $[redacted] effective	Ocrevus®, Roche Products Pty Ltd
Concentrate solution for infusion, 300 mg in 10mL, 1 vial (private)	2	0	$17,580.39 published $[redacted] effective	

Category / Program:	Section 100 – Highly Specialised Drugs Program
Condition:	Primary Progressive Multiple Sclerosis
Treatment phase:	Initial
Restriction:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required – Telephone, Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	The condition must be diagnosed as clinically definite primary progressive multiple sclerosis, defined as having one year of disability progression (retrospective or prospectively determined) independent of clinical relapse; AND 2 of the following 3 criteria: ≥1 T2-hyperintense lesion(s) characteristic of MS in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial; OR ≥2 T2-hyperintense lesions in the spinal cord; OR Presence of CSF-specific oligoclonal bands AND Patient must have been diagnosed with the condition within the previous 5 years; AND Patient must have evidence of active disease within the previous 12 months defined by the presence of: ≥1 Gd-enhancing T1 lesions; OR Evidence for DIS based on ≥1 new or enlarging T2 lesions relative to the previous scan, AND Patient must be ambulatory (without assistance or support).
Definitions	MS, multiple sclerosis; CSF, cerebrospinal fluid
Prescriber Instructions:	Where applicable, the date of the diagnosis, magnetic resonance imaging scans and treatment initiation date must be recorded in the patient's medical records.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Category / Program:	Section 100 – Highly Specialised Drugs Program
Condition:	Primary Progressive Multiple Sclerosis
Treatment phase:	Continuing
Restriction:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required – Telephone, Electronic ☐ Streamlined
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.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Category / Program:	Section 100 – Highly Specialised Drugs Program
Condition:	Primary Progressive Multiple Sclerosis
Treatment phase:	Grandfathering
Restriction:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required – Telephone, Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	Patient must have received treatment with this drug for this condition prior to the [PBS listing date]; AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Source: Tables 1.9 and 1.10, p16 of the resubmission.

3.2 The requested effective ex-manufacturer price (AEMP) decreased from $[redacted] in the November 2017 submission to $[redacted] in the resubmission. The requested effective price for PPMS is equal to that of the current effective price for ocrelizumab in the relapsing-remitting setting.

3.3 The PBAC previously noted that ocrelizumab was associated with a modest treatment effect in the broader ORATORIO trial population and considered that 'ocrelizumab should be used in the population of PPMS patients for which there is evidence of clinical benefit' (November 2017 PSD, paragraph 7.3). Thus, the resubmission presented results from a post-hoc analysis of the pivotal ORATORIO trial to support a claim of superior efficacy in the patient subgroup most likely to benefit from treatment: patients aged 50 years or less with active inflammatory disease.

3.4 The resubmission considered that the age cut-off defined the patient population who would derive the most benefit, but that it may unfairly exclude some older patients from access given PPMS may still present in patients above 50 years of age. Consequently, in place of specific age eligibility criterion, the resubmission suggested a diagnosis of PPMS within 5 years was a suitable proxy for patients 50 years or younger.

3.5 Evidence for the suitability of time since diagnosis as a proxy for age was not presented. The commentary noted that there was a mismatch between the ORATORIO subgroup and the requested listing, with baseline characteristics of the ORATORIO trial indicating that some patients in the ORATORIO subgroup would be excluded with the requested restriction. The ESC and PBAC considered the rationale for using diagnosis within the last five years as a proxy for patient age of 50 years or less was not adequately justified.

3.6 The resubmission included an initiation criterion that patients must be ambulatory without support, but this was not included in the continuation criteria. The ORATORIO trial excluded patients who were not ambulatory at baseline, and there was no evidence presented specifically demonstrating the effect of ocrelizumab in non-ambulatory patients. Though the ORATORIO trial did not suspend or discontinue ocrelizumab treatment due to progression, because no non-ambulatory patients were included at baseline, and because the main outcome was time to confirmed disability progression, there was only a limited evidence base for patients who have progressed to non-ambulatory disability. Ambulatory patients reliant on support (EDSS 6.0 and 6.5) were included in the ORATORIO trial. However, it would be expected that this portion of the trial population would be less likely to achieve clinical benefit from treatment, and thus the resubmission's addition of this criterion (ambulation status) may be reasonable.

3.7 The Pre-Sub-Committee Response (PSCR) argued that PPMS patients who progress to a non-ambulant state may still be benefiting from treatment, such as through preserved upper limb function and therefore it was not reasonable to exclude non-ambulatory patients from continuing treatment. The ESC noted no evidence was presented to support this claim. The ESC considered that as ocrelizumab has been considered to be of inferior safety to best supportive care (Paragraph 7.7, November 2017 Ocrelizumab PSD), it would be appropriate to include clinical criteria for continuation/discontinuation ('stopping rule') as otherwise ocrelizumab could be used indefinitely in patients with little or no clinical benefit who may also suffer from adverse events.

3.8 The pre-PBAC response reiterated that patients who are non-ambulatory may still be experiencing benefit, such as through prolonged or improved upper limb function as observed in the 9-hole peg test outcomes in the ORATORIO trial. The pre-PBAC response stated that, based on advice from neurologists, a stopping rule could be based on sustained loss of upper limb function. The 9-hole peg test outcomes from the ORATORIO trial that were presented in the resubmission were for the outcome of a 20% increase in the 9-hole peg test sustained for 12 weeks, and thus the PBAC considered these results may not adequately indicate the long-term effect of ocrelizumab at preserving limb function in non-ambulatory patients. The PBAC considered that the pre-PBAC response's proposed stopping rule could potentially allow use in patients with EDSS up to 8.5, while evidence had not been presented that clearly demonstrated the efficacy of ocrelizumab in patients with EDSS above 6.5

(patients with EDSS of up to 8.5 may experience sustained upper limb function noting that the EDSS scale, with which clinical evidence aligns, does not adequately capture upper limb function). Overall, the PBAC considered that the magnitude of the clinical benefit with ocrelizumab was unclear once a patient's disease progresses above EDSS 6.5.

3.9 The ESC considered it may be appropriate for the initiation criteria to specify no prior use of PBS-reimbursed DMT for RRMS. The pre-PBAC response agreed with this suggestion.

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

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 relapsing-remitting multiple sclerosis (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 primary progressing MS (PPMS). PPMS is characterised by a more rapid course of progression than RRMS and an accumulation of disability from the onset of symptoms independent of relapses or remissions. Some PPMS patients have relapses or develop new lesions. A longitudinal MRI study (Ingle 2005)[1] concluded that enhancement is present in some cases of early PPMS and is associated with greater disease impact in terms of both clinical and MRI measures. PPMS (as opposed to RRMS) can be diagnosed from one year of disease progression (retrospectively or prospectively determined), and two of the following three criteria: (1) At least one T2 lesion in at least one area characteristic of MS (periventricular, Juxtacortical, infratentorial); (2) At least two T2 lesions in the spinal cord; isoelectric focusing evidence of oligoclonal bands and/or (3) elevated IgG index (Tur 2015).[2]

4.2 Data from the pivotal ORATORIO trial indicate that some patients with PPMS may be more likely to benefit from ocrelizumab treatment than others. In response to concerns from the PBAC in regard to the November 2017 submission, the resubmission has narrowed the target population to patients with early, active PPMS.

4.3 The ESC noted that recommendations from clinical experts in the NICE guidance, suggested early disease is most appropriately defined as being within 5-years of

[1]Ingle GT, Sastre-Garriga J, Miller DH, Thompson AJ. Is inflammation important in early PPMS? A longitudinal MRI study. Journal of Neurology, Neurosurgery and Psychiatry; 2005 76(9):1255–8.

[2] Tur C, Thompson AJ. Early accurate diagnosis crucial in multiple sclerosis. Practitioner; 2015: 259(1785):21–27.

symptom onset. However, in the MSBase analysis presented in this submission, the mean time since diagnosis was 12.6 years but the mean time since onset of symptoms was longer, 17 years. Further, the ORATORIO trial included patients on the basis of disease duration from onset of symptoms. The ESC therefore considered it was possible that using time since diagnosis is likely to include people with more advanced disease.

4.4 Should ocrelizumab receive a positive recommendation, ocrelizumab would be the only PBS therapy specifically listed for PPMS.

4.5 Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20- expressing B-cells.

5 Comparator

5.1 As in the previous submission, the resubmission nominated best supportive care (BSC) as the main comparator. BSC was previously accepted as the appropriate main comparator by the PBAC (paragraph 7.4, ocrelizumab, PSD, November 2017 PBAC Meeting). The main arguments provided in support of this nomination were that despite the range of effective options available for RRMS, no other treatment has previously shown efficacy in PPMS.

5.2 The resubmission stated that although there is no clear definition of BSC, the term is used broadly to describe the treatments directed at symptoms of multiple sclerosis, alongside physical rehabilitation strategies.

5.3 The ESC noted PBS listed medicines for the treatment of RRMS are possibly being used in the treatment of PPMS and that the extent of use may be informed by an analysis of the MSBase database. The use of medicines in the treatment of PPMS would impact on the cost-effectiveness and the financial estimates in terms of the offsets.

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 (9), health care professionals (6) and organisations (3) via the Consumer Comments facility on the PBS website. The comments outlined the clinical need for effective treatments for PPMS and described the benefits patients have realised through private or compassionate access to ocrelizumab, such as stopping or slowing the progression of disability and the lack of side effects experienced on treatment.

6.3 The PBAC noted the advice received from MS Australia and MS Research Australia

which highlighted the clinical significance of the results of the ORATORIO trial in PPMS and outlined the importance of delayed disability progression in PPMS to patients through retaining quality of life for longer and savings to other parts of the health system such as residential care and the National Disability Insurance Scheme. The PBAC also noted the advice received from the Australian and New Zealand Association of Neurologists which outlined that the greatest gains with ocrelizumab treatment were likely to be realised in patients with earlier, MRI-active disease and supported the listing of ocrelizumab for this cohort of PPMS patients.

Clinical trial

6.4 The November 2017 submission was based on the ORATORIO trial comparing ocrelizumab to placebo (ITT: n=732).

6.5 This resubmission was based on efficacy data from a *post-hoc* analysis of a subgroup of patients in the ORATORIO trial who had 'Magnetic Resonance Imaging (MRI) Activity' and were ≤50 years of age (n=230).

6.6 Details of the ORATORIO trial are presented in the resubmission are provided in Table 3.

Table 3: Trial and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
ORATORIO	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.	2016 *NEJM* 2017; 376 (3) 209-220

Source: Table 2.3, p27 of the resubmission.

6.7 The key features of the ORATORIO trial and the *post-hoc* subgroup analysis are summarised in Table 4.

Table 4: Key features of the included evidence

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	CPD 12; CDP 24	Yes (sensitivity analyses)
ORATORIO open-label extension		R, OL, 144 weeks*	Low	PPMS	CDP 12; CDP 24	Yes (sensitivity analysis)
ORATORIO MRI active, ≤50 years	230**	Post-hoc subgroup analysis	High	Active PPMS in patients ≤50 years	CDP 12; CDP 24	Yes (sensitivity analysis
ORATORIO MRI active, ≤50 years extended control period			High		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; MRI = magnetic resonance imaging; OL=open-label; OS=overall survival; PFS=progression-free survival; R=randomised.

Source: pp24-46 of the resubmission

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

** Based on Figure 2.4, p37of the resubmission.

6.8 As a post-hoc subgroup analysis, selecting for multiple patient characteristics (age, MRI activity), these estimates have a high risk of bias.

6.9 The submission included minimal baseline characteristics of the ORATORIO 50 years or younger and MRI active subgroup, which only included baseline age and sex.

Comparative effectiveness

6.10 The resubmission acknowledged that no tests for interaction in any of the ORATORIO pre-defined subgroup analyses were statistically significant, and observed differences were potentially due to expected variation. Relevant subgroups for which there was no statistically significant interaction included age (45 or younger versus over 45 years) and presence of gadolinium-enhancing T1 lesions.

6.11 The resubmission presented results from the *post-hoc* analyses of a subgroup of patients with disease activity defined by magnetic resonance imaging (MRI) and the subgroup of patients aged 50 or younger with MRI activity. The November 2017 submission was primarily based on the ITT analysis of the ORATORIO trial. The resubmission presented hazard ratios but not the proportion of patients with events, nor median time to confirmed disability progression for any of the outcomes.

6.12 Key efficacy results are presented in Table 5.

Table 5: key results from the ITT analysis and post-hoc subgroup analyses of ORATORIO

Population	Placebo (N = 244) n (%)	Ocrelizumab (N = 487) n (%)	HR (95% CI)	*Test for interaction p*-value
CDP 12				
ITT	244 (100)	487 (100)	0.76 (0.59–0.98)	-
'MRI activity' subgroup	104 (42.6)	189 (38.8)	0.68 (0.46–0.99)	0.03631
Complement subgroup	140 (57.4)	298 (61.2)	0.84 (0.60–1.18)	-
'MRI active ≤50 Years' subgroup	79 (32.4)	151 (31.0)	0.55 (0.36–0.85)	0.0654
Complement subgroup	165 (67.6)	336 (69.0)	0.91 (0.66–1.24)	-
CDP-24				
ITT	244 (100)	487 (100)	0.75 (0.58–0.98)	-
'MRI activity' subgroup	104 (42.6)	189 (38.8)	0.71 (0.47–1.06)	0.5839
Complement subgroup	140 (57.4)	298 (61.2)	0.79 (0.55–1.13)	--
'MRI active ≤50 Years' subgroup	79 (32.4)	151 (31.0)	0.54 (0.35–0.85)	0.0677
Complement subgroup	165 (67.6)	336 (69.0)	0.91 (0.65–1.27)	

Source: Table 2.11, p38, Table 2.8, p38, Table 2.9, p38 and Table 2.12, p39 of the resubmission.
CDP=confirmed disability progression; CI=confidence interval; HR=hazard ratio; MRI=magnetic resonance imaging;
Note: 'MRI activity' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline.
Note: the "n" in these analyses does not refer to number of events, but rather the number of patients analysed in the relevant subgroup. Number of events was not presented.

6.13 Key efficacy results from the ITT analysis and subgroup analyses of the open-label extended control period are presented in Table 6. The MRI active, 50 years or younger subgroup results of the open-label extension (HR = 0.53; shaded cells) was applied in the economic evaluation, despite the test for interaction not indicating that these baseline characteristics are a treatment effect modifier for ocrelizumab.

Table 6: Subgroup analysis in extended control period – CDP-12 and CDP-24

Population	Placebo N=243; n (%)	Ocrelizumab N=486; n (%)	HR (95% CI)	Interaction test (p-value)
CDP-12				
ITT	243 (100%)	486 (100%)	0.75 (0.59, 0.96)	-
'MRI activity' subgroup	104 (42.8%)	189 (38.9%)	0.69 (0.47, 1.00)	0.4101
Complement subgroup	139 (57.2%)	297 (61.1%)	0.81 (0.59, 1.10)	
'MRI active ≤50 Years' subgroup	79 (32.5%)	151 (31.1%)	0.56 (0.37, 0.85)	0.0793
Complement subgroup	164 (67.5%)	335 (68.9%)	0.88 (0.65, 1.18)	
CDP-24				
ITT	243 (100%)	486 (100%)	0.70 (0.55, 0.90)	-
'MRI activity' subgroup	104 (42.8%)	189 (38.9%)	0.68 (0.46, 0.99)	0.6880
Complement subgroup	139 (57.2%)	297 (61.1%)	0.72 (0.52, 1.00)	
'MRI active ≤50 Years' subgroup	79 (32.5%)	151 (31.1%)	0.53 (0.35, 0.81)	0.1097
Complement subgroup	164 (67.5%)	335 (68.9%)	0.81 (0.60, 1.10)	

Source: Table 2.14, p41; Table 2.15, p41 of the resubmission.
CDP=confirmed disability progression; CI=confidence interval; HR=hazard ratio; MRI=magnetic resonance imaging;
'MRI activity' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline.
Note: the "n" in these analyses does not refer to number of events, but rather the number of patients analysed in the relevant subgroup. Number of events was not presented.

6.14 The difference between the CDP hazard ratios for the MRI active, 50 years or younger subgroup, the MRI active subgroup and the ITT subgroup indicate that age or an unknown variable associated with age could be the more important treatment effect modifier, which would have implications in the designation of years since diagnosis as a proxy for age. Relative differences between the hazard ratios could be a result of

expected heterogeneity and thus these differences should be interpreted with caution.

6.15 The ESC noted there was no clear evidence presented to establish time since diagnosis as a proxy for patients aged 50 or less and therefore considered there was substantial uncertainty in the clinical effectiveness as the presented analyses were not likely to be representative of the requested population. The ESC considered it would be appropriate for the Sponsor to present an analysis of time since diagnosis by age from the ORATORIO dataset to provide further clarity on the exchangeability of these variables. The pre-PBAC response argued such an analysis would likely be assessing efficacy in younger patients, consistent with the subgroup analyses included in the resubmission. The pre-PBAC response also argued that younger patients benefited most from treatment in ORATORIO, which was 'likely related to the underlying pathology and disease course of PPMS; the optimal treatment window is in patients with early disease in terms of disease duration, level of disability, and active inflammation'. The pre-PBAC response noted that including an age restriction in the listing may introduce equity concerns. The PBAC agreed with the ESC that the submission had not adequately justified that time since diagnosis was a reasonable proxy for age and therefore considered the subgroup analyses may not reliably represent the requested PBS population. However, the PBAC also agreed with the pre-PBAC response that defining a PBS population around patient age may be inequitable. The PBAC acknowledged the pre-PBAC response's claims that age may be associated with the underlying pathology and disease course of PPMS which supported use in early disease, but also considered that age itself as a treatment effect modifier was of questionable biological plausibility and that other factors related to age were possible drivers of the potential treatment effect modification identified in the patient age ≤50 years old subgroup.

Comparative harms

6.16 The PBAC previously accepted the claim of inferior comparative safety of ocrelizumab over BSC. However, the PBAC considered that the previous submission's 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 (Paragraph 7.7, ocrelizumab PSD, November 2017 PBAC Meeting). The pre-PBAC response argued that as the narrower population requested in the resubmission was likely to be younger than the original submission that the PBAC's previous view regarding risks for older patients were less relevant in the resubmission, and reiterated that ocrelizumab maintains a positive risk/benefit ratio in the requested population.

6.17 The resubmission did not present comparative harms data. A summary of adverse events from the ORATORIO ITT population is reproduced from the November 2017 submission in Table 7.

Table 7: Summary of key adverse events in ORATORIO (ITT)

AE	Ocrelizumab n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)
Patients with at least one AE	462/486 (95.1)	215/239 (90.0)	**1.06 (1.01, 1.11)**	**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)**	**0.05 (0.01, 0.09)**
Infusion related reaction	194/486 (39.9)	61 /239 (25.5)	**1.56 (1.23, 1.99)**	**0.14 (0.07, 0.21)**
Upper respiratory tract infection	53/486 (10.9)	14/239 (5.9)	**1.86 (1.05, 3.29)**	**0.05 (0.01, 0.09)**
Nasopharyngitis	110/486 (22.6)	65/239 (27.2)	0.83 (0.64, 1.08)	-0.05 (-0.12, 0.02)
AEs included in the economic evaluation.				
Serious infusion related reaction	5/486 (1.0)	0/239	-	0.01 (0.00,0.02)
Serious pneumonia	6/486 (1.2)	2/239 (0.8)	1.46 (0.30, 7.25)	0.02 (-0.02, 0.02)
Serious urinary tract infection	5/486 (1.0)	2/ 239(0.8)	1.23 (0.24, 6.30)	0.00 (-0.01,0.01)
Urosepsis	2/486 (0.4)	3/239 (1.3)	0.33 (0.06, 1.95)	-0.01 (-0.03, 0.01)

Source: Tables 2.5.11 and 2.5.12, pp66-67 of the November 2017 submission.
AE = adverse event; CI = confidence interval; RD = risk difference; RR = risk ratio

Benefits/harms

6.18 The results of the efficacy subgroup analysis, which did not include number of patients with events, prevented a comparison of benefits, and the lack of comparative safety evidence presented for the subgroup in question meant it was not possible to update comparative harms for the subgroup discussed in the resubmission. Given the high risk of bias in the post-hoc analyses, an estimate of the comparative benefits from the subgroup analyses would be expected to be better than in the ITT population, but the accuracy of such an estimate may be difficult to assess.

6.19 The PBAC considered in November 2017 (Paragraph 6.21, Ocrelizumab, PSD, November 2017 PBAC Meeting) that on the basis of the ORATORIO trial [ITT analysis]:

- 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.

Clinical claim

6.20 The resubmission stated that for adult PPMS patients with early and active inflammatory disease (based on MRI imaging):

- Ocrelizumab is superior in terms of effectiveness compared with placebo.
- Ocrelizumab is inferior in terms of safety compared with placebo, but the adverse event profile is established and manageable with minimal impact on quality of life, and a positive risk/benefit ratio is maintained.

6.21 The PBAC previously noted that the treatment effect of ocrelizumab in the ITT population was "modest" and that in certain subgroups, the treatment effect was negligible, and that given the small absolute differences in efficacy demonstrated by ocrelizumab over placebo, the clinical significance of trial outcomes was uncertain (paragraph 7.6 ocrelizumab, PSD, November 2017 PBAC Meeting).

6.22 The resubmission attempted to address these issues by restricting the population to a subpopulation most likely to derive benefit. Given that the PBAC assessed that there was a modest treatment effect in the ITT population, after excluding subpopulations where the effect may be negligible, it can reasonably be inferred that the treatment effect in remaining patients would at least be maintained if not improved. However, the post-hoc subgroup analyses are susceptible to bias, and the resulting hazard ratio of estimate CDP-24, on which the economic analysis is based (despite the test for interaction not indicating that these baseline characteristics were a treatment effect modifier), was likely to substantially overestimate the treatment effect:

- The analyses should be considered exploratory - hypothesis-generating and not confirmatory;
- The subgroup of interest (those with MRI activity and aged ≤50 years at baseline) represented approximately a third of the ORATORIO trial population (possibility that the analyses were underpowered cannot be excluded); and
- There was no indication that any statistical analyses were adjusted for multiple looks at the data.

6.23 Furthermore, the post-hoc analysis was not consistent with the requested restriction, which instead of restricting by age (50 or younger), restricted by time since diagnosis (the past 5 years). The ESC considered the applicability of the results for this subgroup to the requested listing was not adequately justified. It is possible that the requested restriction may encompass a population that is more consistent with the MRI-active subgroup of the ORATORIO trial, which the subgroups analyses indicated was associated with a lesser treatment effect than the 'MRI-active plus age 50 years or younger' subgroup (HR for CDP-24 in the extended control period of 0.68 versus 0.53, respectively).

6.24 The PBAC previously considered that the claim that ocrelizumab has an acceptable safety profile that is comparable with placebo in the previous submission 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 (paragraph 7.7, November 2017 ocrelizumab PSD).

6.25 With the exception of updated extended harms data, and limiting use to patients with active disease who have been diagnosed within 5 years, the resubmission did not present any new discussion of safety. The ESC considered it would have been informative to present the safety data for the proposed PBS population.

6.26 The PBAC considered that the claim of superior comparative effectiveness in the early and MRI-active population was adequately supported, but that subgroup results relied on in the economic model likely overestimated the magnitude of the benefit in the requested PBS population (due to limitations of the subgroup data and the potential lack of applicability of the subgroup results to the requested listing, as outlined above).

6.27 The PBAC noted no new data on clinical safety were presented and considered the clinical claim of inferior comparative safety to placebo was reasonable, consistent with its view expressed in its November 2017 consideration of ocrelizumab.

Economic analysis

6.28 As in the November 2017 submission, the resubmission presented a cost-utility analysis.

6.29 Table 8 presents a summary of the key components of the economic evaluation.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost utility analysis
Outcomes	Life-years gained, quality-adjusted life years gained
Time horizon	Lifetime in the model base case (60 years) versus 3 years in ORATORIO trial
Methods used to generate results	Markov model
Health states	EDSS 0-9
Cycle length	1 year
Transition probabilities	EDSS transition matrix based on natural history of PPMS matching restriction criteria, treatment effect hazard ratio from ORATORIO subgroup matching restriction criteria applied to ocrelizumab arm
Software package	Excel 2016

Source: Table 3.3, p48 of the resubmission
EDSS = expanded disability status scale; PPMS = primary progressive multiple sclerosis.

6.30 Table 9 presents the key revisions to the November 2017 economic evaluation made in the resubmission.

Table 9: Key revisions from the November 2017 economic evaluation

Component	Revision	Comment
Start age	Adjusted to average start age of ORATORIO subgroup (40 years, down from 44 years in the ITT population)	May not be aligned with requested restriction
EDSS baseline distribution	Adjusted to EDSS baseline distribution of ORATORIO subgroup	Reasonable
Natural history EDSS transition matrix	Adjusted to EDSS transition matrix of MSBase population matching proposed restriction criteria	Reasonable
Hazard ratio for CDP	CDP 24 for ORATORIO ECP subgroup (HR = 0.53) compared to 0.7 of the ITT ECP previous submission.	Favoured ocrelizumab substantially. Unlikely to reflect treatment effect in target population.
HRQoL utilities	Updated to published Australian utilities obtained from ORATORIO (Diagi 2017). Disutility associated with upper limb dysfunction excluded from base case analysis	This did not have a large effect on the ICER.
Mortality	Background mortality updated to reflect latest ABS Life Tables (version released 30 Oct 2019). Mortality effect multipliers applied by EDSS state	The use of mortality multipliers was previously not considered appropriate by the PBAC.
Treatment efficacy waning	Structural model change to allow sensitivity analyses of waning treatment effect	The model was sensitive to assumptions on treatment efficacy waning.
Cost of health care resources utilised	Updated to current cost values, included residential care cost	The ESC considered the included health care resource costs associated with residential care were highly uncertain and the updated health state costs favoured ocrelizumab unreasonably.

Source: Table 3.1, p47 of the resubmission.
ABS = Australian Bureau of Statistics CDP = confirmed disability progression; ECP = extended control period; EDSS = expanded disability status scale; HRQoL = Health related quality of life; ITT = intention to treat; Oct = October; SPA = special pricing arrangement; RSA = Risk sharing arrangement

6.31 Table 10 presents a summary of key drivers of the model. The model results were most sensitive to the selected ORATORIO population (ITT, active disease subgroup, or active disease and 50 years or younger subgroup); the inclusion or exclusion of nursing home costs, and the specification of waning treatment effect.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Treatment effect	The hazard ratio (for 24-month CDP) between ocrelizumab and placebo was for the post-hoc subgroup of MRI activity and age 50 years or younger was selected (HR = 0.53). The ESC and PBAC noted the subgroup does not align with the requested restriction and was not satisfied time since diagnosis was a suitable proxy for the population used in the model.	High, favours ocrelizumab
Health state costs	The resubmission included high costs associated with nursing home care in EDSS health states 7, 8 and 9. The ESC also noted the ORATORIO trial did not include any patients in the EDSS 7-9 range at baseline, and therefore considered the clinical effectiveness in this population was highly uncertain.	High, favours ocrelizumab
Waning treatment effect	The base case did not include any treatment effect waning.	High, favours ocrelizumab.

Source: Tables 3.22 – 3.28, pp71 – 76 of the resubmission.
CDP = confirmed disability progression; EDSS = expanded disability status scale.

6.32 The estimate of treatment effect had a substantial impact on QALYs accrued as well as health state costs. Hence the result was sensitive to the high treatment effect estimate applied in the base case, which was based on the *post-hoc* subgroup of MRI activity and age 50 years or younger (CDP-24 HR = 0.53). Given the impact of the active disease subgroup on the ICER (see sensitivity analyses below), the age subgroup may be a driver of the ICER but this subgroup result was only reported combined with the MRI activity subgroup and therefore could not be analysed.

6.33 The PSCR stated that subsidy for the combined subgroup was sought in the resubmission to address the PBAC's previous request (in its consideration of the initial submission) to demonstrate a greater absolute benefit in CDP for PPMS in a resubmission and that greater absolute benefit in delaying disease progression cannot be addressed by a subgroup analysis for MRI activity alone. The ESC considered the hazard ratio used in the economic model to be uncertain and reiterated its concerns that there was insufficient evidence presented to consider time since diagnosis to be a reasonable proxy for age, and that the modelled population was therefore likely not reflective of the requested listing.

6.34 The model applied the same hazard ratio to high EDSS states (7, 8, 9), as it did to lower EDSS states. Though the application of a hazard ratio to these high disability states was consistent with the resubmission's rationale that ocrelizumab would delay disability progression, there was no evidence that ocrelizumab would delay progression in higher states to the same extent as in the lower states included in the pivotal evidence. As noted previously by the PBAC, there was no evidence of clinical benefit at EDSS above 6.5 (paragraph 7.3, Ocrelizumab PSD, November 2017 PBAC Meeting). The approach also led to large differences in time spent at high EDSS states between ocrelizumab and BSC, which favoured ocrelizumab. A summary of the utility values and costs by EDSS health state and the model outputs for mean time spent in each EDSS state are presented in Table 11.

6.35 The pre-PBAC response argued that, while the same HR was applied to transitions across all EDSS health states, the large differences in time spent in high EDSS states were mainly due to delayed disability progression in lower EDSS health states. The pre-PBAC response noted that most patients in the ocrelizumab arm of the model had ceased treatment in the higher EDSS states, with 77%, 85% and 93% of the mean time spent in EDSS 7, 8 and 9 (respectively) being accrued in patients who were off-treatment. The pre-PBAC response also argued the impact of the HR applied to transitions from higher EDSS health states could be examined by removing the HR (treatment effect modifier) for all transitions from EDSS 7 and above, which increased the ICER from $45,000 to < $55,000 per QALY (base case) to $55,000 to < $75,000 per QALY.

Table 11: Key elements of model outputs in EDSS states

EDSS state	0	1	2	3	4	5	6	7	8	9	Total
Mean utility value	0.837	0.766	0.78	0.73	0.68	0.68	0.63	0.48	-0.082	-0.228	
Direct medical resource costs per year in each state	$8,455				$8,766			$49,954			
Mean time in EDSS health state (years)											
Ocrelizumab on treatment	0.080	0.159	0.724	1.428	2.571	1.785	3.882	1.401	0.623	0.147	12.800
Ocrelizumab off treatment	0.042	0.092	0.430	0.698	1.772	1.765	6.091	4.660	3.950	1.936	21.437
Ocrelizumab (total)	0.122	0.251	1.154	2.126	4.343	3.55	9.973	6.061	4.573	2.083	34.237
BSC	0.038	0.096	0.536	1.265	2.987	2.841	9.325	6.871	6.001	3.235	33.196
Increment	**0.084**	**0.155**	**0.618**	**0.861**	**1.356**	**0.709**	**0.648**	**-0.81**	**-1.428**	**-1.152**	**1.041**

Source: 'Ocrelizumab' and 'comparator' sheets of 'Economic Evaluation PPMS Resub.xls'
BSC = best supportive care; EDSS = Expanded Disability Status Scale.

6.36 The resubmission estimated costs in a manner mostly consistent with the previous submission. The resubmission additionally updated the cost of ocrelizumab, administration costs, costs of clinician visits and monitoring, costs of adverse events, and direct costs per year associated with EDSS level (the resubmission also updated indirect costs which were not included in the base case).

6.37 Of the revised costs inputs, the only revisions that had a noticeable impact on the ICER were the direct medical resource costs by EDSS level; the resubmission updated costing data for the EDSS states from Palmer (2011) in the previous submission to Ahmad (2018) in the resubmission. The resubmission noted that in contrast to Palmer (2011), the Ahmad (2018) costing study reported the cost of residential care per severity level and thus allowed inclusion of nursing home and equivalent costs in the economic evaluation. The inclusion of substantial nursing home costs associated with EDSS 7-9 health states favoured ocrelizumab. The direct costs of EDSS states 7, 8 and 9 increased from $7,958 in the previous submission to $49,954 in the resubmission, primarily due to an inclusion of nursing home costs of $35,175 per year.

6.38 The model is sensitive to EDSS costs, specifically in EDSS states of 7-9 where the nursing home costs are applied, because the model estimated a large difference in mean time in high EDSS states (Table 11). These differences in mean time spent in high EDSS states are mainly due to the application of a low CDP-24 hazard ratio across all CDP EDSS states. Consequently, BSC patients were estimated to accrue substantially more time in high EDSS health states than ocrelizumab.

6.39 The PSCR argued that a reduction in the accrual of residential care costs due to delays in treatment progression associated with ocrelizumab treatment was reasonable, as a treatment which delays disease progression can only result in a shift in absolute time spent in different health states, including those where the model accumulates nursing home costs. Over [redacted]% of the ocrelizumab drug cost ($[redacted]) were offset by reduced medical resource use ($69,880). The ESC noted the offsets in medical resource use

were largely driven by differences in nursing home costs between the ocrelizumab and BSC arms, which were introduced in the resubmission.

6.40 The ESC considered that while including relevant residential care costs (such as nursing home costs) were reasonable in-principle, the costs included in the economic model were highly uncertain as:

- The submission did not include clinical evidence that treatment with ocrelizumab delays patients requiring residential/nursing home care; and
- Ahmad 2018 reported the results of an Australian longitudinal MS study which was sponsored by MS Australia and not subject to peer review. The reported costs were informed by 15% (488/3163) of the study participants completing a cost diary over a period of 6 months. However, as only 2 of the participants resided in a nursing home, the nursing home costs were estimated indirectly using a variety of sources:
    - The Australian Bureau of Statistics Survey of Disability, Aging and Carers 2009 (4430.0) in which it was estimated that 5.66% of people with MS reside in a nursing home. The ESC noted more recent reports for this survey dated 2012, 2015 and 2018 are available.
    - The Australian Institute of Health and Welfare (AIHW) estimate of accommodation support which was $109,715 per person for 2015-16. This cost was inflated to 2017 levels. The ESC considered the AIHW estimate was unlikely to accurately reflect nursing home costs for MS patients as it is the mean amount paid under the NDIS for all people on the NDIS (not just those with MS) for 'accommodation support' (not just nursing home care; accommodation support is defined as services that provide accommodation to people with disability, and services that provide support to enable a person with disability to remain in their existing accommodation or to move to more suitable or appropriate accommodation).
    - Based on the above, an estimated mean annual nursing home cost of $6,343 (= 0.0566 x 109,715 x 1.0215) was calculated. This cost was applied to the 18% (88/488) of the participants completing the cost diary classified as having 'severe disability' (defined as an EDSS score of 7 or more) to estimate an average nursing home cost of $35,175 ($6,343/0.18). The ESC noted applying the cost to the proportion with an EDSS ≥ 7 who responded to cost diary introduced further uncertainty.

- Overall the ESC considered the estimated nursing home cost of $35,175 to be unreliable and not suitable for use in the economic model due to high uncertainty of the reliability of this estimate. The ESC further noted that excluding this cost increased the ICER from $45,000 to < $55,000 per QALY to $95,000 to < $115,000 per QALY. The ESC considered, in the absence of a reliable estimate of the nursing home cost or the reduction in the extent of nursing home care, the ICER excluding nursing home costs was more reliable.

6.41 The pre-PBAC response acknowledged the uncertainty regarding the true cost of residential care for patients with PPMS, however argued an assumption of no costs related to residential care, especially in EDSS 8.0 and above health states disregards the severity of disability patients face at later stages of their disease. The PBAC agreed in principle, however agreed with the ESC that the estimate in Ahmad 2018 was unreliable and further, considered the model assumption that all patients accrued these costs from EDSS 7.0 onwards in the model was unrealistic given many patients who are wheelchair-bound may be able to and would prefer to remain in the home setting.

6.42 Removing the mortality effect multipliers, as preferred by the PBAC previously, decreased the ICER. This was largely driven by the high incremental costs accrued in the later EDSS health states for which the mortality effect multipliers are the highest, as well the use of negative utility values at high EDSS health states (i.e. patients in the comparator arm die sooner due to the mortality multiplier and hence spend less time in the higher EDSS states with a lower utility value and higher cost).

6.43 While informative, the added functionality for treatment effect waning was applied as sudden reductions of treatment effect (the hazard ratio was multiplied by the waning percentage) starting at 10 years. This approach consequently underestimated the ICER for each scenario applying no efficacy decrement until the end of the waning effect period.

6.44 Table 12 presents the results of the stepped economic analysis.

6.45 The results of key sensitivity analyses are summarised in Table 13.

Table 12: Results of the stepped economic evaluation

Step and component	Ocrelizumab	BSC	Increment
Step 1: trial-based costs and outcomes			
Costs	$[redacted]	$0	$[redacted]
LY	2.850	2.850	0.000
QALY	1.907	1.866	0.042
Incremental cost/QALY gained			**$[redacted]**
Step 2: extrapolation over lifetime horizon			
Costs	$[redacted]	$0	$[redacted]
LY	16.260	16.014	0.245
QALY	8.749	7.453	1.296
Incremental cost/QALY gained			**$[redacted]**
Step 3: incorporation of medical resource utilisation costs			
Costs	$[redacted]	$399,632	$[redacted]
LY	16.260	16.014	0.245
QALY	8.749	7.453	1.296
Incremental cost/QALY gained			**$[redacted]**
Step 4: incorporation of AE costs			
Costs	$[redacted]	$399,632	$[redacted]
LY	16.260	16.014	0.245
QALY	8.749	7.453	1.296
Incremental cost/QALY gained			**$[redacted]**
Step 5: application of utility values (included in all previous and subsequent steps)			
Step 6: incorporation of SPA			
Costs	$[redacted]	$399,632	$[redacted]
LY	16.260	16.014	0.245
QALY	8.749	7.453	1.296
Incremental cost/QALY gained			**$[redacted]**

Source: Tables 3.16-3.10, pp68-70 of the resubmission.

BSC = best supportive care; AE = adverse events; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SPA = special pricing arrangement.

The redacted table shows the base case ICER in the range of $45,000 to < $55,000 per QALY.

6.46 As the nursing home costs included in the model based on Ahmad 2018 were unreliable, the ESC considered it reasonable to test the sensitivity of the model to excluding these costs. The ICERs with nursing home costs set to $0 for both the base case population and the ORATORIO ITT and MRI active subgroups have been added to the table below.

Table 13: Sensitivity analyses

Analyses		Incremental costs	Incremental QALYs	ICER
Base case (HR = 0.53)		$[redacted]	1.296	$[redacted]
Univariate				
Nursing home costs	Excluded	$[redacted]	1.296	$[redacted]
ORATORIO ITT population (Base case: subgroup with active disease and restricted to younger patients[a])	ORATORIO ITT population [a] (HR = 0.70)	$[redacted]	0.702	$[redacted]
	ORATORIO subgroup with active disease [a] (HR = 0.68)	$[redacted]	0.768	$[redacted]
Multivariate				
ORATORIO population with nursing home costs set to $0	ORATORIO ITT [a] (HR = 0.70)	$[redacted]	0.702	$[redacted]
	ORATORIO subgroup with active disease [a] (HR = 0.68)	$[redacted]	0.768	$[redacted]
Waning treatment effect (base case: excluded)	75% remaining after 10 years	$[redacted]	1.197	$[redacted]
	50% remaining after 10 years	$[redacted]	1.101	$[redacted]
	75% after 7 years	$[redacted]	1.144	$[redacted]
	50% remaining after 7 years	$[redacted]	0.998	$[redacted]
	25% remaining after 7 years	$[redacted]	0.857	$[redacted]
	0% after 7 years	$[redacted]	0.723	$[redacted]

Source: Tables 3.22 – 3.28, pp71 – 76 of the resubmission *and conducted during preparation of the ESC Advice*.

BSC = best supportive care; CDP = confirmed disability progression; ECP = extended control period; EDSS = expanded disability status scale; HR = hazard ratio

[a] The resubmission altered the start age (and consequently the time horizon of the economic evaluation), the EDSS distribution at treatment initiation, the applicable natural history transition matrix and the CDP HR according to the corresponding variables from ORATORIO

Note: These analyses were conducted by changing cell D16 of the General Model inputs sheet from "6" to "4" and "5," respectively, as well as changing F22 of the Health state costs sheet from $35,175 to $0.

The redacted table shows ICERs in the range of $45,000 to < $55,000 per QALY, to $155,000 to < $255,000 per QALY.

Drug cost/patient/year

6.47 Table 14 shows the drug cost per patient for ocrelizumab and placebo/BSC.

Table 14: Drug cost per patient for ocrelizumab and placebo/ BSC

	Ocrelizumab Trial dose and duration	Ocrelizumab Model	Ocrelizumab Financial estimates	Placebo Trial dose and duration	BSC Model	BSC Financial estimates
Mean dose	600mg every six months	600mg every six months	600mg every six months	**NA**	**NA**	**NA**
Mean duration	3.0 years	Life-time	6 years	2.8 years	Life-time	NA
Discontinuation rate	NR	6.94% per year	7% per year	NR	NA	NA
Cost/patient/month	$[redacted]	$[redacted]	$[redacted]	$0	$0	$0
Cost/patient/year	$[redacted]	$[redacted]	$[redacted]	$0	$0	$0

Source: p68 of the resubmission. Mg = milligram; NA = not applicable

6.48 Though PPMS may be considered to be a lifelong condition, and the economic model has modelled it as such, the resubmission did not present data on the duration of active disease, for which listing is sought.

6.49 The resubmission stated that the annual drug acquisition cost is $[redacted] (compared to or $[redacted] in the November 2017 submission) based on a weighted DPMQ of $[redacted] and 2 administrations per year.

Estimated PBS usage & financial implications

6.50 This resubmission was considered by DUSC. As in the November 2017 submission, the resubmission took an epidemiological approach to estimating use and financial implications.

6.51 Key inputs of the financial estimates are presented in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value and source	Comment
Proportion of MS patients with PPMS	10%; Miller 2007	DUSC commented that 6% of respondents to the Australian MS Longitudinal Study reported to have PPMS. DUSC considered that the proportion of MS patients with PPMS may be lower than 10% and that this assumption may overestimate the number of eligible patients.
Annual incidence of MS	6.7 per 100,000 persons; Ribbons (2017)	This estimate was revised from 2.4 per 100,000 in the November 2017 submission. DUSC considered this may overestimate the incidence of MS in Australia, but the linear increase in incidence reported in Ribbons was not accounted for.
Prevalent population	Estimated as sum of incident populations for the five years prior to listing.	The November 2017 submission added the number of incident and prevalent patients to estimate use, which resulted in an overestimate of the projected number of treated patients. The resubmission continued to add the two populations. However, the resubmission's prevalent population aligned with the requested restriction of patients diagnosed in the previous 5 years.
Treatment uptake of ocrelizumab in incident and prevalent PPMS patients (90%)	Assumption/ expert opinion	Although no DMT alternatives are listed specifically for PPMS, it is unclear whether some patients may use RRMS listed DMTs. DUSC considered there are likely to already be PPMS patients being treated with DMTs listed for RRMS, including ocrelizumab.
Eligibility	Assumption that 44% of PPMS patients aged ≤50 years in ORATORIO have MRI activity.	As previously noted, since the time since diagnosis has not been adequately justified as a proxy for age, this is likely not an appropriate estimate. Additionally, the proportion of patients meeting these criteria in the ORATORIO trial may not be reflective of the proportion of patients meeting these criteria in the Australian population.
Discontinuation	7% per year , consistent with input from economic model, based on extrapolation of ORATORIO data	This was consistent with the economic evaluation, but based on ITT continuation data rather than data relevant to the subgroup. Though the requested restriction does not include any continuation criteria that would restrict continuation beyond intolerance to therapy and compliance to treatment, the commentary and DUSC considered that it remained unclear whether this estimate was accurate.
MBS items	Item 14245: cost / IV administration ($99.50); Item 105: clinician attendance ($44.35); Item 63125: MRI ($492.80); Item 65070: blood count ($16.95); Item 66512: liver function test ($17.70)	As in the November 2017 submission, administration costs were underestimated. This was not likely to substantially affect financial estimates.

Source: Table 4.2, p82-83 of the resubmission.

MBS = Medicare benefits Schedule; MRI = magnetic resonance imaging; MS = Multiple Sclerosis; PBS = Pharmaceutical Benefits Scheme; PPMS = primary progressive multiple sclerosis; RPBS = Repatriation Pharmaceutical Benefits Scheme

6.52 Table 16 presents the estimated use and financial implications in the resubmission.

Table 16: 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of ocrelizumab						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for BSC						
Cost to PBS/RPBS less copayments	None					
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Previous submission - November 2017						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4.9, p87, Table 4.10, p88 and Table 4.22, p96 of the resubmission; Table 4.2.4, pp140-141 of the November 2017 submission

[a] Assuming 2 per year as estimated by the resubmission.

The redacted table shows that at Year 6, the estimated number of patients was 500 < 5,000 and the net cost to the PBS would be $10 million to < $20 million. The net cost to the PBS in the previous submission was estimated to be $40 million < $50 million.

6.53 The DUSC considered the estimates in the resubmission were likely to be overestimated and identified the following main issues:

- The reliability of the estimates depends on the acceptance of the proposed PBS restriction of patients diagnosed in the last five years as a proxy for patients who are aged 50 years or younger.
- The incidence data (based on Ribbons 2017) reflects an area (Newcastle region) of Australia with historically higher reported incidence of MS than other parts of Australia which may overestimate the incidence in Australia, however the linear increase in incidence has not been accounted for. The pre-PBAC response stated that the incidence rate applied (6.7/100,000) was based on previous DUSC advice. DUSC had previously stated that the incidence rate applied in November 2017 (2.4/100,000) was a possible underestimate and that there was 'more recent data available from Ribbons 2017 based on the Newcastle population which had a much higher prevalence estimate'. The PBAC considered that the estimated applied in the resubmission was likely an overestimate.
- The resubmission's estimate of patient eligibility (44%) was based on the proportion of people less than 50 years in the ORATORIO trial with active disease. DUSC considered that this was unlikely to be an accurate estimate of eligibility for several reasons: (i) the differences between the requested restriction and the ORATORIO

subgroup population, (ii) the PBAC's previous concerns that the ORATORIO trial (ITT population) did not reflect the Australian treatment setting in PPMS, and (iii) the fact that the proportion from an international trial with stringent inclusion criteria, would not be expected to have a distribution of patient characteristics comparable to the Australian population.

- The estimated continuation rate has been appropriately accounted for, however DUSC considered it was inappropriate for the restriction to allow continuation of ocrelizumab treatment indefinitely. DUSC considered that a higher discontinuation rate should be applied if continuation criteria are included in the proposed PBS restriction.

6.54 The submission stated that, as of September 2019, < 500 patients with PPMS were receiving treatment with ocrelizumab through a compassionate use program. The resubmission added the grandfather patients to the prevalent and incident populations. The DUSC considered that some of the grandfather patients would overlap the prevalent population.

Quality Use of Medicines

6.55 No Quality Use of Medicines information was presented.

Financial Management – Risk Sharing Arrangements

6.56 The resubmission proposed an RSA in the form of annual expenditure caps for ocrelizumab in PPMS with a [redacted] rebate for any expenditure above the caps. The expenditure caps were proposed to be set at the forecast annual net cost to PBS/RPBS. The ESC noted net cost to the PBS will be overestimated (due to the offsets being underestimated) if patients with PPMS are accessing PBS listed treatment for RRMS.

6.57 At the PPMS Stakeholder meeting (December 2018), it was considered that MS is now widely recognised as a single disease rather than as RRMS, PPMS and secondary progressive MS (SPMS), with these terms having been developed prior to the availability of MRI. As such, there may be some overlap between patients currently being treated with PBS-subsidised therapies for RRMS (such as ocrelizumab) and the new PPMS population proposed for ocrelizumab. Given the degree of overlap, it may not be appropriate for ocrelizumab to have separate subsidy caps for the RRMS and PPMS indications.

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

7 PBAC Outcome

7.1 The PBAC did not recommend extending the Section 100 (Highly Specialised Drugs Program – Public and Private Hospitals) listing of ocrelizumab to include the treatment of patients with early (diagnosed within the past five years), MRI-active primary progressive multiple sclerosis (PPMS). The PBAC considered that the key subgroup analysis that was relied on in the submission was inconsistent with the requested PBS

population which led to difficulties in assessing the cost-effectiveness of ocrelizumab. The PBAC considered that the economic model had likely underestimated the ICER as the likely treatment effect and nursing home care costs had been overestimated.

7.2 The PBAC considered there is a high clinical need for effective therapies for PPMS. The PBAC acknowledged the comments from consumers, health professionals and organisations. The comments from patients outlined the benefits that slowing the progression of disability can have on quality of life. The PBAC also noted the advice received from the Australian and New Zealand Association of Neurologists which outlined that the greatest gains with ocrelizumab treatment were likely to be in patients with earlier, MRI-active disease and supported the listing of ocrelizumab for this cohort of PPMS patients.

7.3 The PBAC considered the requested restriction for patients with active PPMS within the past 12 months and a PPMS diagnosis in the past 5 years to be appropriate and consistent with the advice of stakeholders. The PBAC agreed with the submission that it was more appropriate to define the patient population on the basis of time since diagnosis as restricting access to ocrelizumab on the basis of age would be inequitable.

7.4 The proposed continuing restriction did not include criteria for measuring response or assessing appropriateness for continuing therapy ('stopping rule') despite the PPMS Stakeholder meeting (December 2018) stating that 'it may be appropriate to consider treatment discontinuation for patients who continue to decline on treatment, although given the variable disease course, the decline may need to be assessed over a 12-24 month period' and 'could possibly be based on the EDSS (e.g. a change of 0.5-1 over a relatively short period), or, deterioration in upper limb function, or, deterioration in cognition'. The pre-PBAC response proposed a stopping rule based on sustained loss of upper limb function and the PBAC recalled that clinical stakeholders had highlighted the importance of upper limb function for patient quality of life at the PPMS Stakeholder meeting (December 2018). The PBAC considered that, while sustained loss of upper limb function may be an appropriate basis for a stopping rule, the magnitude of the clinical benefit with ocrelizumab was unclear once a patient's disease progresses above EDSS 6.5. The PBAC advised that input from stakeholders could be used to better define the stopping rule.

7.5 The PBAC reaffirmed its view expressed in November 2017 that the best supportive care, as nominated in the original submission and current resubmission, was the appropriate comparator.

7.6 Compared with the previous submission, no new clinical trials were presented. The resubmission relied on a new *post-hoc* subgroup analysis of the ORATORIO trial, based on the 'MRI-active plus age ≤ 50 years' subgroup. The PBAC noted that this subgroup was not consistent with the population defined by the requested restriction (patients with active PPMS within the past 12 months and a PPMS diagnosis in the past 5 years).

7.7 The PBAC noted that the subgroup used was consistent with the patient characteristics it had identified as being likely treatment effect modifiers (age or MRI-

active disease) in November 2017. Further, the PPMS Stakeholder meeting (December 2018) found that patients generally benefit most from treatment in the active inflammatory disease phase of PPMS which generally occurs early in the disease course. However, the PBAC considered that the resubmission had not adequately established a relationship between patient age and early disease/time since diagnosis with regards to treatment effect. The PBAC noted that time since symptom onset was a pre-specified subgroup analysis in the ORATORIO trial and considered that the submission had not adequately justified use of clinical data based on age rather than time since symptom onset. The PBAC acknowledged the pre-PBAC response's claims that age may be associated with the underlying pathology and disease course of PPMS which supported use in early disease, but considered that other factors related to age were possible drivers of the potential treatment effect modification in the patient age ≤ 50 years subgroup. The PBAC noted that age was associated with a substantial reduction in the hazard ratio compared to MRI-activity alone.

7.8 The PBAC noted the mean and median age of patients at PPMS diagnosis in Australia is about 46 years (based on the MS Base registry, 2020), which indicates the proposed PBS population will include a high proportion of patients aged over 50 years. As such, it is possible that the requested restriction may encompass a population that is more consistent with the MRI-active subgroup of the ORATORIO trial, which the subgroup analyses indicated was associated with: (a) a lesser treatment effect than the 'MRI-active plus age ≤ 50 years' subgroup (the HR for CDP-24 in the extended control period was 0.68 versus 0.53, for the MRI-active and the 'MRI-active plus age ≤ 50 years' subgroups respectively); and (b) a similar treatment effect to the ITT population, which the PBAC previously considered to be modest (HR of 0.68 versus 0.70 in the ITT population).

7.9 Overall, the PBAC considered that the applicability of the results for the identified subgroup to the requested listing was not adequately justified and agreed with the ESC that the result for the subgroup was likely to substantially overestimate the treatment effect as:

- the subgroup analyses were not pre-specified;
- the subgroup of interest (those with MRI activity and aged ≤50 years at baseline) represented approximately one-third of the ORATORIO trial population (possibility that the observed differences were due to expected variation);
- the test for interaction did not indicate that these baseline characteristics were treatment effect modifiers; and
- there was no indication that any statistical analyses were adjusted for multiple looks at the data.

7.10 The PBAC also noted that MRI active disease appeared to have been defined differently in the ORATORIO trial *post-hoc* subgroup than in the requested PBS listing. Activity between screening and baseline (4 week) appeared to have been used in the

post-hoc subgroup while activity within the last 12 months was proposed in the requested listing.

7.11 The PBAC considered that the claim of superior comparative effectiveness in the early and MRI-active population was adequately supported, but that subgroup results applied in the economic model likely overestimated the magnitude of the benefit in the requested PBS population.

7.12 The PBAC noted no new data on comparative harms were presented and reaffirmed its view, based on the safety analyses previously presented in November 2017, that ocrelizumab is of inferior comparative safety to placebo.

7.13 The PBAC considered that the ocrelizumab treatment effect included in the economic model (HR of 0.53 based on the 'MRI-active plus age ≤ 50 years' subgroup) was likely overestimated for the reasons outlined above, and also because the model assumed that the treatment effect would not wane over the duration of treatment. The PBAC considered that a more conservative HR should have been applied in the model, and noted that using only the HR from the MRI-active disease subgroup (0.68) increased the ICER to $115,000 to < $135,000 per QALY, and the using the HR from the ITT population (0.70) increased the ICER to $135,000 to < $155,000 per QALY. The PBAC considered that it would also be informative to include the impact of an appropriate stopping rule in the economic model.

7.14 The PBAC noted the model was highly sensitive to assumptions around the costs of nursing home care and how these were accrued in the model, and agreed with the ESC that the annual cost estimate of $35,175 in the Ahmad 2018 report was highly uncertain (due to the methods used in Ahmad 2018 to estimate these costs) and likely overestimated. The PBAC considered the assumption that all patients at EDSS 7.0 and higher would accrue these costs was implausible, as many patients who require a wheelchair will not enter residential care or accrue these costs until their condition has further progressed. The PBAC noted that no clinical evidence was provided to support that treatment with ocrelizumab reduces nursing home care.

7.15 The PBAC agreed with DUSC that the financial estimates were likely to have been overestimated particularly as the incidence data reflects an area of Australia with historically higher reported incidence of MS than other parts of Australia. The PBAC also reiterated its view from November 2017 that the population in the ORATORIO trial was unlikely to reflect PPMS treatment in the Australian setting and thus the resubmission's estimate of patient eligibility (44%) was unlikely to be accurate.

7.16 The resubmission proposed an RSA in the form of annual expenditure caps for ocrelizumab in PPMS with a [redacted] rebate for any expenditure above the caps. The PBAC considered this was appropriate but agreed with the ESC that the net cost to the PBS will be overestimated (due to the offsets being underestimated) if patients with PPMS are accessing PBS listed treatment for RRMS.

7.17 The PBAC considered that any resubmission would need to be a major resubmission and would need to address the following issues:

- Clarify the most appropriate discontinuation criteria, noting that further input from clinical experts in this area may be required;
- Update the economic model based on any discontinuation criteria, and using more conservative inputs given the issues raised; and
- Update the financial estimates based on any discontinuation criteria, and to address the likely overestimated population.

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

9 Sponsor's Comment

Roche is disappointed with the outcome given the genuine unmet need for an effective treatment option for patients with PPMS. Roche will continue to support the MS community in Australia whilst we evaluate the options available within the parameters of the existing data to find a suitable path forward. Roche would like to take this opportunity to thank the many healthcare professionals, and broader members of the MS community, who supported the resubmission.