5.07 UBLITUXIMAB, Solution concentrate for I.V. infusion 150 mg in 6 mL (25 mg per mL), Briumvi®, Kirchmann Enterprises Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested Section 100, Highly Specialised Drugs Program (Public and Private Hospitals) listing for ublituximab for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS).

1.2 Listing was requested on the basis of a cost-minimisation approach and cost comparison analysis versus three comparators: ocrelizumab, ofatumumab and fingolimod.

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

Component	Description
Population	Adult patients with relapsing-remitting multiple sclerosis (RRMS)
Intervention	Ublituximab 150mg/6mL vial for intravenous infusion 150mg initial infusion, followed by 450mg infusion at 2 weeks, then 450mg infusion every 24 weeks.
Comparator	Ocrelizumab infusion 600m given every 6 months. Ofatumumab subcutaneous injection 20mg at weeks 0, 1 and 2 then 20mg /month. Fingolimod oral 0.5mg daily.
Outcomes	Annualised Relapse Rates (ARR), Confirmed Disability Progression at 3 and 6 months (CDP), Adverse Events
Clinical claim	Ublituximab is non-inferior in terms of efficacy and safety compared to ocrelizumab and ofatumumab for the treatment of RRMS. Ublituximab is superior to fingolimod in terms of efficacy and non-inferior in terms of safety.

Source: Tables 1.1, p2 and 1.6, p29 of the submission.

2 Background

Registration status

2.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, a positive TGA Delegate's Overview has been received. The Product Information is currently being finalised between the TGA and the sponsor.

2.2 Ublituximab was approved in the USA in 2022, for the indication "treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults".

2.3 Ublituximab was approved by the European Medicines Agency (EMA) in 2023, for the narrower indication "treatment of adult patients with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features".

2.4 The proposed TGA approved indication is the same as the EMA wording: "Treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features".

Previous PBAC consideration

2.5 The PBAC has not previously considered ublituximab.

2.6 The most recent PBAC consideration for relapsing-remitting multiple sclerosis (RRMS) was in March 2024 in relation to ofatumumab. In March 2021, the PBAC recommended the listing of ofatumumab on the basis of a claim of non-inferiority to fingolimod, and the March 2024 submission sought to substitute a claim of superiority of ofatumumab to fingolimod.

2.7 The PBAC did not support the ofatumumab March 2024 proposal, because "the clinical evidence presented did not adequately support the submission's underlying claim that ofatumumab (proposed as a high-efficacy tier DMT[1]) has superior comparative effectiveness versus fingolimod (as a proxy for the proposed mid-efficacy tier DMTs)" (paragraph 7.1, ofatumumab Public Summary Document (PSD), March 2024 PBAC Meeting).

2.8 At present, treatments for multiple sclerosis (MS) are divided by the PBAC into two tiers: a high-efficacy tier (fingolimod, cladribine, ozanimod, natalizumab, alemtuzumab, ocrelizumab, ofatumumab[2]) and low-efficacy tier (interferons, dimethyl fumarate, diroximel fumarate, glatiramer acetate and teriflunomide). The ofatumumab March 2024 submission proposed, on the basis of the claim of superiority of ofatumumab to fingolimod, that the high-efficacy tier be sub-divided, with natalizumab, alemtuzumab, ocrelizumab and ofatumumab remaining high-efficacy and fingolimod, cladribine and ozanimod being re-classified as mid-efficacy.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
UBLITUXIMAB					
ublituximab 150 mg in 6 mL solution for injection, 1 vial	NEW S100 Public (HB)	4	4	0	Briumvi
ublituximab 150 mg in 6 mL solution for injection, 1 vial	NEW S100 Private (HS)	4	4	0	Briumvi

[1] DMT = disease-modifying therapy.

[2] Siponimod is also PBS listed and can be used in RRMS or secondary progressive MS (SPMS), however the criteria for use differ from other RRMS DMTs.

Restriction Summary [new variation of 9523] / Treatment of Concept: [new variation of 9523]
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (Streamlined) [NEW]
Authority type: ☒ Non-complex Authority Required (non-CAR)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Multiple sclerosis
Treatment phase: Initial treatment
Clinical criteria:
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; **OR**
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition
AND
Clinical criteria:
Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition
AND
Clinical criteria:
Patient must be ambulatory *(without assistance or support)*
AND
Treatment criteria
Must be treated by a neurologist
Prescribing instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
UBLITUXIMAB					
ublituximab 150 mg in 6 mL solution for injection, 1 vial	NEW S100 Public (HB)	3	3	0	Briumvi
ublituximab 150 mg in 6 mL solution for injection, 1 vial	NEW S100 Private (HS)	3	3	0	Briumvi

Restriction Summary [new variation of 9635] / Treatment of Concept: [new variation of 9635]
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (Streamlined) [NEW]
Authority type: ☒ Non-complex Authority Required (non-CAR)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

Administrative Advice: Special Pricing Arrangements apply.
Indication: Multiple sclerosis
Treatment phase: Continuation treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not show continuing progression of disability while on treatment with this drug
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition
AND
Clinical criteria:
Patient must have demonstrated compliance with, and an ability to tolerate this therapy
AND
Treatment criteria
Must be treated by a neurologist

3.2 The submission proposed an initial and a continuing restriction. Both were modelled on the current restrictions for other DMTs for RRMS. The requirement for "at least 2 documented attacks of neurological dysfunction [...] in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy [emphasis added] is interpreted to mean that this requirement applies only to the first use of a DMT, after which patients can switch to another therapy without meeting the requirement for recent acute attacks - because of adverse events, or needing to cease treatment with the current DMT due to continuing progression of disease, for example.

3.3 The submission requested a Special Pricing Arrangement but did not propose an effective price.

3.4 The Pre-Sub-Committee Response (PSCR) noted the requirement in the draft Product Information for co-administration with a H1 receptor antagonist such as diphenhydramine, however requested the PBAC consider whether a broader restriction that is not restricted by the class of antihistamine may be acceptable, as no H1 receptor antagonists are currently listed on the PBS and would have to be accessed privately.

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

4 Population and disease

4.1 MS is a disorder of the central nervous system (CNS), in which immune-mediated inflammation, demyelination and neuronal destruction lead to functional deficits and disability. Most patients are young adults at onset and in about 85% of patients the disease follows a course of repeated acute episodes with at least partial resolution (relapsing or relapsing-remitting multiple sclerosis, RMS or RRMS). Resolution of relapses is commonly incomplete, and accumulating deficits may lead to long-term

disability. A reduced frequency of relapses is, therefore, expected to reduce accumulated disability. However, of the five major health problems associated with RRMS (motor control, fatigue, other neurological symptoms, continence problems and neuropsychological symptoms) some, notably fatigue and depression, are not straightforwardly related to incomplete resolution of acute relapses.

4.2 The submission did not propose that listing of ublituximab would change the treatment algorithm for RRMS.

4.3 Ublituximab is a monoclonal antibody to the B cell antigen CD20, as are ocrelizumab and ofatumumab. When antibody is bound to the CD20 antigen, natural killer (NK) cells bind to the antibody's Fc segment and destroy the B cells (antibody dependent cellular cytolysis, ADCC). Ublituximab differs from ocrelizumab and ofatumumab primarily by the sugar content of its Fc segment being lower (referred to as "glycoengineering"), which increases the affinity of the Fc segment for the NK cell receptor.

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

5 Comparator

5.1 The submission nominated as comparators ocrelizumab, ofatumumab and fingolimod. Ocrelizumab and ofatumumab have very similar mechanisms of action, and in the case of ocrelizumab the same route and frequency of administration as ublituximab. The submission proposed fingolimod as a comparator "as it is the most frequently used oral treatment" but noted that fingolimod was most often used for patients with less severe disease who did not wish to have injected treatment, so it was unlikely to be replaced by ublituximab.

5.2 The proposed comparators were appropriate, however additional therapies were also listed on a cost minimisation basis with one or more of the nominated comparators (see paragraph 5.4).

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.4 The PBAC has advised that fingolimod, cladribine, ozanimod, natalizumab, alemtuzumab, ocrelizumab, and ofatumumab should be considered alternative therapies to one another and are superior to the lower tier therapies in RRMS (paragraph 7.3-7.4, ofatumumab PSD, March 2021 PBAC Meeting).

5.5 The ESC recalled a submission was made for ofatumumab to the March 2024 PBAC meeting, and noted the PBAC did not recommend the formation of three efficacy tiers

at that time, as the clinical evidence did not adequately support the submission's underlying claim that ofatumumab has superior comparative effectiveness to fingolimod (paragraph 7.1, ofatumumab PSD, March 2024 PBAC meeting). The ESC therefore advised that all therapies described in paragraph 5.4 could reasonably be considered alternative therapies to ublituximab.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented a history of treating MS patients focusing on the evolution of clinical diagnosis led by lesion load and nature of relapse, where high effectiveness therapies are often preferred as early intervention, and discussed longer-term real-world data for relapse and 'no evidence of disease activity' supports the anti-CD20 class of therapies as being highly effective.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual (1), and a consumer organisation (1) via the Consumer Comments facility on the PBS website. The comments described disease burden, including the inability to return to work and the challenges of continuing disability impacting daily life.

6.3 The PBAC welcomed the input from MS Australia supporting the listing of ublituximab, and noted the input stressed the importance of having more treatment options available for patients as due to the varied nature of the disease, no one treatment suited all. It also discussed the mechanism of action of ublituximab, the positive results of the clinical trials and the results of a systematic review that indicated it offers comparable efficacy to other high-efficacy monoclonal antibody therapies.

Clinical trials

6.4 No head-to-head trials of ublituximab versus any of the comparators were identified. The submission relied on indirect treatment comparisons (ITC), using:

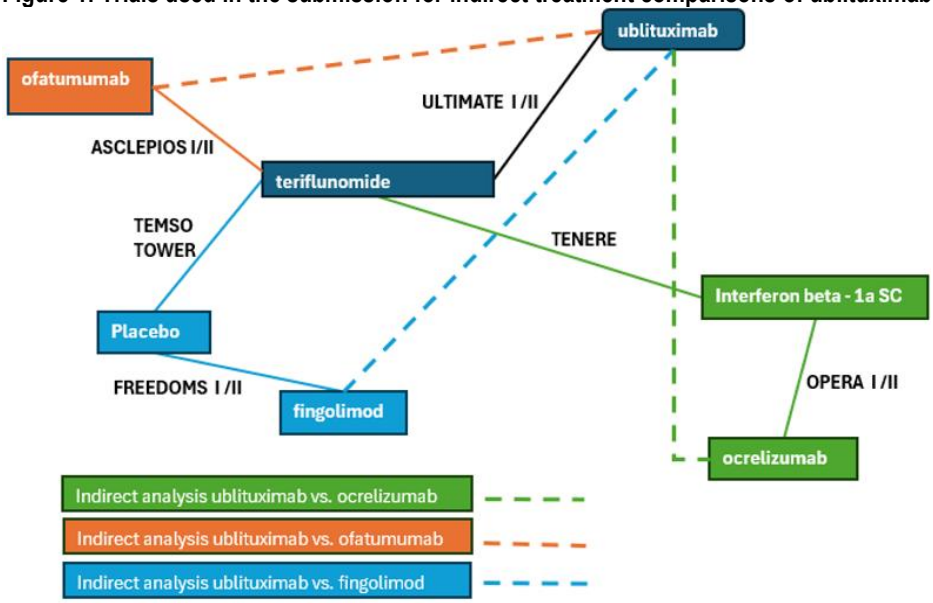
6.5 two randomised controlled trials (RCTs) of ublituximab vs teriflunomide (ULTIMATE I/II);

- two RCTs of ofatumumab vs teriflunomide (ASCLEPIOS I/II);
- two RCTs of ocrelizumab vs interferon beta (OPERA I/II);
- two RCTs of fingolimod vs placebo (FREEDOMS I/II);
- one RCT of ocrelizumab vs interferon beta; and to link these,

6.6 two RCTs of teriflunomide vs placebo (TEMSO and TOWER), and one RCT of teriflunomide vs interferon beta (TENERE).

6.7 This is shown diagrammatically in Figure 1.

Figure 1: Trials used in the submission for indirect treatment comparisons of ublituximab vs comparators.



Source: Figure ES.3, p.v of the submission.

6.8 The published reports for the trials used and their key features are shown in Table 2 and Table 3.

Table 2: Trials and associated reports presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
Ublituximab		
ULTIMATE I NCT03277261	TG Therapeutics Inc. (2021). TG1101-RMS301 Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY). Steinman L, et al. Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis.	2017 N Engl J Med 2022, 387:704-714.
ULTIMATE II NCT03277248	TG Therapeutics Inc. (2021). TG1101-RMS302 Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY). Steinman L, et al. Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis.	2017 N Engl J Med 2022, 387:704-714.
Ocrelizumab		
OPERA I/II	Hauser S, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis.	N Engl J Med 2017; 376:221-234.
Ofatumumab		
ASCLEPIOSI/II	COMB157G2301. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS I). COMB157G2302. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS II) COMB157G2301: A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS I/II) Hauser, S. L., et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis.	December 2019 December 2019 NR N Engl J Med. 2020; 383(6): 546-557
Fingolimod		
FREEDOMS I	FTY720D2301. A 24-month double-blind, randomized, multicenter, placebo controlled, parallel-group study comparing the efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis. Kappos, L., et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis.	NR N Engl J Med. 2010; 362(5): 387-401
FREEDOMS II	FTY720D2309. A 24-month double-blind, randomized, multicenter, placebo controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis. Calabresi, P. A., et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial.	13 January 2012 Lancet Neurology. 2014; 13(6): 545-556.
Teriflunomide		
TEMSO	O'Connor, P., et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis.	N Engl J Med. 2011; 365(14): 1293-1303.
TOWER	Confavreux, C., et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial.	Lancet Neurology. 2014; 13(3): 247-256
TENERE NCT00883337	Vermersch, P., et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial.	Multiple sclerosis (Houndmills, Basingstoke, England) 2014; 20(6): 705-716.

Source: Table 2-5, pp49-52 of the submission. NR = not reported. Blue shaded trials have been considered recently by the PBAC (March 2024).

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)
Ublituximab vs teriflunomide					
ULTIMATE I	545	R, DB, 96 weeks	Low	RRMS or SPMS; 98% RRMS	ARR, CDP for 3 and 6 months
ULTIMATE II	544	R, DB, 96 weeks			
Ocrelizumab vs interferon beta					
OPERA I	821	R, DB, 96 weeks	Low	RMS; % with RRMS not stated.	ARR, CDP for 3 and 6 months, % relapse free
OPERA II	835	R, DB, 96 weeks			
Ofatumumab vs teriflunomide					
ASCLEPIOS I	927	R, DB, 30 months	Low	RRMS or SPMS; 94% RRMS	ARR, CDP for 3 and 6 months, % relapse free
ASCLEPIOS II	955	R, DB, 30 months		RRMS, SPMS, or PRMS; 97% RRMS	
Fingolimod vs placebo					
FREEDOMS I	1272	R, DB, 24 months	Low	RRMS	ARR, CDP for 3 and 6 months, % relapse free
FREEDOMS II	1083	R, DB, 24 months		RRMS	
Teriflunomide vs interferon beta					
TENERE	324[1]	R, OL, 48-115 weeks	High	RRMS, SPMS, or PRMS; 99% RRMS	Time to failure (relapse or treatment discontinuation from any cause); ARR secondary.
Teriflunomide vs placebo					
TEMSO	1088	R, DB, 96 weeks	High	RRMS, SPMS, or PRMS; 91% RRMS	ARR, % relapse free
TOWER	1169	R DB, 48+ weeks	High	RRMS, SPMS, or PRMS; 97% RRMS	

Source: Table 2-8, pp59-60 of the submission.; Table 3, paragraph 6.8, ofatumumab PSD, March 2024 PBAC Meeting; trials recently reviewed by PBAC are highlighted in light blue.

[1] Patients were randomised 1:1:1 to IFN or teriflunomide 7 mg or 14 mg daily; the figure of 215 given in the submission (Table 2-8, p60) is the number allocated to IFN or teriflunomide 14 mg, the dose used in the ULTIMATE I/II and ASCLEPIOS I/II trials.

ARR = annualised relapse rate; CDP = confirmed disability progression; DB = double blind; IFN = interferon beta; PPMS = primary progressive multiple sclerosis; PRMS = progressive-relapsing multiple sclerosis; R = randomised; RMS= relapsing multiple sclerosis (i.e., RRMS, PRMS and SPMS included; PPMS excluded); RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

6.9 The previous submissions to the PBAC for the listing of ocrelizumab (July 2020) and ofatumumab (March 2021), and the March 2024 ofatumumab submission, all relied on indirect treatment comparisons against fingolimod using the same data as the present submission.

6.10 The present submission also presented a network meta-analysis (NMA). PBAC noted in March 2024 that only one NMA was presented by the submission then under consideration, although eight published NMAs had been identified (paragraph 6.37, ofatumumab PSD, March 2024 PBAC Meeting). The present submission also presented only one NMA (ICER, 2023); this NMA was among those not presented in March 2024 but briefly considered by PBAC (paragraph 6.52, 6.53, ofatumumab PSD, March 2024 PBAC Meeting).

6.11 The trials of teriflunomide versus placebo (TOWER and TEMSO) and the trial of teriflunomide versus interferon beta (TENERE) are central to indirect treatment comparisons of ocrelizumab, ofatumumab and ublituximab with fingolimod. At its March 2021 and March 2024 meetings the PBAC determined that TOWER and TEMSO

had a high overall risk of bias, and that for this reason indirect treatment comparisons depending on those trials were difficult to interpret (paragraph 6.9, ofatumumab PSD, March 2024 PBAC Meeting).

6.12 The present submission took issue with PBAC's assessment of TEMSO and TOWER as having a high overall risk of bias. These issues are summarised and discussed below.

6.13 The PBAC assessed TEMSO as having a high risk of detection bias, "as relapse outcomes identified by a blinded assessor had to be confirmed by an unblinded treating neurologist, meaning that the assessment was effectively unblinded" (paragraph 6.15, ofatumumab PSD, March 2021 PBAC Meeting; paragraph 6.9, ofatumumab PSD, March 2024 PBAC Meeting). The present submission correctly noted that the study protocol does not state that the treating neurologist was unblinded to treatment allocation and suggested that for this reason PBAC's reference to effective unblinding and its assessment of the risk of detection bias in TEMSO as high was erroneous. However, blinding of treatment allocation was not the issue: as noted in a Cochrane review of teriflunomide for multiple sclerosis[3], a high risk of detection bias was considered to arise because the treating neurologist, who decided whether a relapse had occurred, was not blinded to the patient's history of adverse events and concomitant medications, including steroid treatment for relapses. The examining neurologist (the "blinded assessor") was blinded to those results (O'Connor, 2011), but this was assessed as inadequate blinding of outcome assessment, since the blinded assessor did not make the relevant decision. In the case of the TENERE study of teriflunomide, which was open label, the treating neurologist who made the decision as to whether a relapse occurred was not blinded to treatment allocation.

6.14 In OPERA I/II, ASCLEPIUS I/II and ULTIMATE I/II a similar system of blinded examining neurologists was used, but protocol-defined relapses were adjudicated centrally, rather than by treating neurologists, which effectively eliminated the risk of detection bias considered to arise in TEMSO and TOWER.

6.15 The risk of attrition bias was rated as high in TOWER because the dropout rate was very high (29.8%), and as unclear in TEMSO because, although the dropout rate was lower (20.1%) the reasons for dropouts were, in the PBAC's judgement, not adequately described. The submission disputed the PBAC's assessment on the ground that dropout rates were similar in all study arms but discrepancies between the arms were not the reason for the risk of attrition bias being rated high or unclear.

6.16 There was a noteworthy difference in discontinuation rates for teriflunomide across trials where it was the intervention or active comparator. In the pivotal ublituximab trials (ULTIMATE I/II), discontinuation of teriflunomide was 8.4% and 12.5%,

[3] He D, Zhang C, Zhao X, et al. Teriflunomide for multiple sclerosis. Cochrane Database of Systematic Reviews, https://doi.org/10.1002/14651858.CD009882.pub3

respectively. This was lower than that observed in other trials, with overall teriflunomide discontinuation rates of 17.5% and 17.7% in ASCLEPIOS I/II (ofatumumab trials) and discontinuation rates in the teriflunomide vs placebo trials of 26.5% in TEMSO, 33.9% in TOWER, and 19.8% in TENERE.

6.17 The ESC considered the risk of bias issues for the teriflunomide bridging studies (TEMSO, TOWER and TENERE) introduced significant uncertainty to the multi-step indirect treatment comparisons of ublituximab to fingolimod and ocrelizumab, which compounded the inherent uncertainty of such multi-step comparisons. Given these issues, the ESC was concerned the comparisons to ocrelizumab and fingolimod may not be robust, particularly in the case of fingolimod given the comparisons were relied upon for a claim of superior comparative effectiveness. However, the ESC also noted the indirect comparison with ofatumumab was based on a single-step indirect comparison with teriflunomide as the common comparator, and the ULTIMATE I/II (ublituximab) and ASCLEPIOS I/II (ofatumumab) trials appeared to be of high quality, with a low risk of bias.

6.18 The Pre-PBAC Response argued the risk of bias impact due to potential unblinding in TOWER was overstated and should not invalidate the complete indirect treatment comparison results, including the claim of superiority of ublituximab over fingolimod made in the submission.

6.19 ULTIMATE I/II had a lower mean age and fewer female patients than other trials, especially compared to FREEDOMS I/II, which also had a significantly longer time between symptom onset and the trial but despite this a lower mean baseline EDSS (paragraph 6.11, ofatumumab PSD, March 2024 PBAC Meeting). Patients in TENERE had lower mean baseline EDSS than patients in other trials, including FREEDOMS I/II, despite similar duration of disease.

6.20 The proportion of patients with prior use of disease-modifying therapies was lower in ULTIMATE I/II (≈40%) than in ASCLEPIOS I/II (≈60%) and FREEDOMS II (74%), but higher than in OPERA I/II (<30%), TEMSO, TOWER and TENERE. It is notable that in TENERE the proportion with prior use of disease-modifying therapies was clearly lower among patients allocated to teriflunomide (11.7%) than among patients allocated to interferon (24%).

6.21 These baseline differences are similar to those previously determined by PBAC to raise transitivity issues with indirect treatment comparisons using this data set (paragraph 6.15, ofatumumab PSD, March 2024 PBAC Meeting). The evaluation considered prior use of DMTs may be particularly important as a transitivity issue.

Comparative effectiveness

6.22 Efficacy results for ULTIMATE I and II are shown in Table 4.

6.23 Data for confirmed disability progression for 12 and 24 weeks were presented in the CSRs only for the pooled trials and are shown separately in Table 5. Disability progression was defined as an increase in EDSS score of at least 1.0 from the week 12

assessment or the previous observation, and sustained progression was defined as the increase in EDSS being confirmed at scheduled visits at least 12 and 24 weeks after the increase had been reported (Steinman, 2022, Protocol Supplement, p13/378).

6.24 There were fewer relapses among patients randomised to ublituximab. The annualised rate of relapse (ARR) was about twice as high in patients allocated to teriflunomide, and the difference in ARR was statistically significant.

6.25 Relapses requiring hospitalisation were less frequent in ublituximab-treated patients, but most patients in both treatment groups did not require hospitalisation for a relapse during the study.

6.26 The proportion of patients who were relapse free was high in both treatment groups, but higher in the ublituximab-treated group at all time periods. The difference was in the range usually considered to be clinically meaningful, with one extra patient relapse free for every 27 patients treated for 24 weeks, for every 12 patients treated for 48 weeks, and for every seven patients treated for 96 weeks.

Table 4: Efficacy outcomes in ULTIMATE I and II

	ULTIMATE I		ULTIMATE II	
	Ublituximab N = 271	**Teriflunomide N = 274**	**Ublituximab N = 272**	**Teriflunomide N = 272**
Relapses to 96 weeks, n	44	111	53	102
Relapses per patient to 96 weeks Mean (SD) Median (IQR) Range	 0.2 (0.5) 0.0 (0, 0) 0 - 3	 0.4 (0.8) 0.0 (0, 0) 0 - 4	 0.2 (0.6) 0.0 (0, 0) 0 - 4	 0.38 (0.7) 0.0 (0, 1) 0 - 5
Number of patients with at least 1 relapse, n (%)	36 (13.3%)	68 (24.8%)	34 (12.5%)	72 (26.5%)
ARR, LS mean (95% CI)	0.08 (0.04, 0.14)	0.19 (0.12, 0.28)	0.09 (0.05, 0.17)	0.18 (0.11, 0.29)
Difference in ARR, UBLI-TER (95% CI)	**-0.11 (-0.17, -0.06)**		**-0.09 (-0.15, -0.03)**	
Rate ratio (95% CI)	**0.41 (0.27, 0.62)**		**0.51 (0.33, 0.78)**	
Proportion free of relapse, % (95% CI) 24 weeks 48 weeks 96 weeks	 96.2 (93.1, 98.0) 92.4 (88.4, 95.0) 86.0 (81.2, 89.7)	 90.8 (86.6, 93.7) 83.6 (78.6, 87.5) 74.4 (68.7, 79.2)	 92.6 (88.8, 95.2) 90.0 (85.8, 93.1) 87.4 (82.8, 90.8)	 90.7 (86.5, 93.6) 82.2 (77.0, 86.3) 72.1 (66.2, 77.2)
EDSS change from baseline to 96 weeks Mean (SD) Median (IQR) Range	 -0.2 (0.6) 0.0 (-0.5, 0.0) -2.0 - 2.5	 0.0 (0.7) 0.0 (0.0, 0.0) -2.5, 3.5	 -0.1 (0.6) 0.0 (0, 0) -3.0, 1.5	 -0.0 (0.6) 0.0 (0, 0) -3.0, 3.0
Gd-enhancing MRI lesions at 96 weeks Mean (SD) Median (IQR) Range	 0.0 (0.1) 0 (0, 0) 0 - 1	 0.7 (1.6) 0 (0, 1) 0 - 8	 0 (0) 0 (0,0) 0 - 1	 0.7 (1.8) 0 (0, 1) 0 - 13

Source: ULTIMATE I CSR, Table 20, p74; Table 22, pp79-80; Table 24, pp84-85; Table 27, pp91-93; Table 36, pp115-119; Table 40, p132, pp120-121. ULTIMATE II CSR, Table 20, p75; Table 24, pp85-86; Table 27, pp92-94; Table 36, pp117-120; Table 40, p133, pp121-122.
ARR = annualised relapse rate; CI = confidence interval; EDSS = expanded disability status scale, scored from 0 to 10, with higher scores indicating greater disability; Gd = gadolinium; IQR = inter-quartile range; LS = least squares; MRI = magnetic resonance imaging; SD = standard deviation.

Table 5: Confirmed disability progression for 12 and 24 weeks in pooled ULTIMATE I/II

	Ublituximab N = 543	**Teriflunomide N = 546**
Patients with CDP for 12 weeks, n (%)	28 (5.2%)	32 (5.9%)
Hazard ratio (95% CI)	0.86 (0.52, 1.44)	
Patients with CDP for 24 weeks, n (%)	18 (3.3%)	26 (4.8%)
Hazard ratio (95% CI)	0.68 (0.37, 1.24)	

Source: ULTIMATE I CSR, Table 26, p89, Table 33, p110.
CDP = confirmed disability progression; CI = confidence interval.

6.27 In the pooled analysis, there was no statistically significant difference in the proportion of patients with confirmed disability progression lasting 12 or 24 weeks. Extended disability status scale (EDSS) scores did not change meaningfully in either treatment group. Time to confirmed disability progression lasting at least 12 weeks was not different between groups. The PSCR argued 3-month and 6-month CDP was

numerically greater for teriflunomide compared to ublituximab, and that while not statistically significant, based on an exploratory endpoint, nearly double the number of patients in the ublituximab arm reported lessening of disability at both 3 and 6 months.

QoL and MRI outcomes in ITT population

6.28 SF-36 mental and physical component summary scores in a reference population have a mean of 50 and a standard deviation of 10; higher scores indicate improvement, and the minimum clinically important difference is about 5 points. In ULTIMATE I/II mean score was within the normal range at baseline and did not change meaningfully during treatment.

6.29 Average cumulative lost time at work over 96 weeks was 2-3 weeks, with no difference between ublituximab-treated and teriflunomide-treated patients.

6.30 Imaging indicators of disease activity improved in both treatment groups. Most patients in both groups had none or very few unresolved gadolinium-enhancing lesions or new T2-hyperintense lesions on MRI, but fewer patients in the ublituximab-treated group had large numbers of unresolved or new lesions.

6.31 The PSCR reiterated the observed ARR ratio of 0.453 for ublituximab over teriflunomide in the pooled ULTIMATE trial dataset and argued that result is both statistically and clinically significant, and that clear benefits were also seen for MRI and quality of life outcomes. The PSCR also argued the results for the SF-36 physical component summary (PCS) from baseline to week 96 statistically significantly favoured ublituximab (PCS score difference 1.12, 95% CI 0.26, 1.98, p=0.01) and was comparable to that observed in a pooled analysis of the ocrelizumab (OPERA I/II) trials, which reported a PCS score difference (versus interferon beta-1a) of 0.92 (95% CI 0.14, 1.70, p=0.02)[4]. The PSCR also argued mean SF-36 scores at baseline for the ublituximab trials were consistent with the overall RRMS population.

Subgroup analyses for annualised relapse rate

6.32 In both trials, the superiority of ublituximab relative to teriflunomide was less and not statistically significant in patients with EDSS scores greater than 3.5 at baseline. However, mean baseline EDSS was between 2.8 and 3.0 for all ublituximab and teriflunomide arms across the ULTIMATE I/II trials. The size of the EDSS >3.5 subgroups to inform this subgroup comparison is unknown and may be small.

6.33 There was no consistent difference in the effect of ublituximab in patients who had or had not received a disease-modifying therapy (DMT) before enrolment. The submission asserts that this should counter concerns that differences among trials in rates of prior DMT and the DMTs used raise transitivity issues for the indirect

[4] Hauser, S, Bar-Or A, Comi G, et al. (2017). "Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis." N Engl J Med 376(3): 221-234. Data from Table 2/Supplement Table S9.

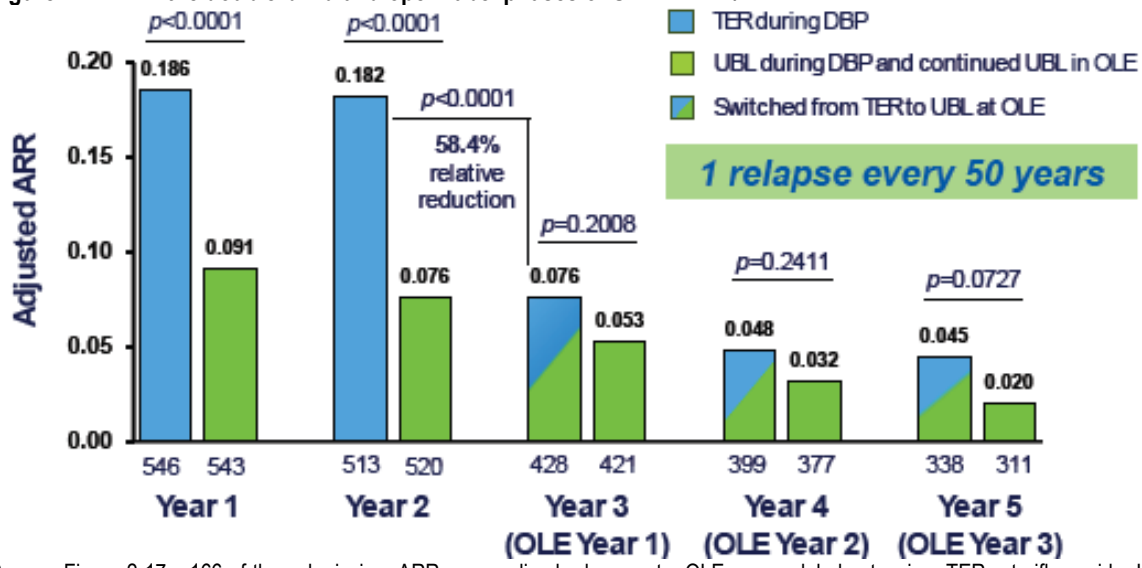
treatment comparisons . However, the results of the open-label extension of ULTIMATE I/II reinforce the transitivity concerns arising from prior DMT. The PSCR argued that as there was no consistent difference in the effect of ublituximab in patients who had or had not received a prior DMT, the validity of the indirect treatment comparison was not adversely impacted by differences in prior use of DMTs observed across trials.

Open Label Extension of ULTIMATE I/II

6.34 Patients completing the double-blind phase of ULTIMATE I/II were eligible to continue open-label ublituximab. Of 494 patients allocated to ublituximab who completed the double-blind phase, 422 (85.4%) entered the open-label phase, and 297 (70.4% of those entering the open-label phase) had completed three years open-label treatment at the data cut-off of 1 January 2024. Of 491 patients allocated to teriflunomide who completed the double-blind phase 429 (87.4%) entered the open-label phase and 327 (76.2%) had completed three years open-label treatment at the data cut-off of 1 January 2024.

6.35 Annualised relapse rate fell over the treatment period, and after three years of open-label treatment was about one-third of the rate in the second year of the double-blind phase. Patients switching from teriflunomide to ublituximab had lower annualised relapse rates than during the double-blind phase, but never achieved the same rate as those allocated to ublituximab in the double-blind phase. This is shown in Figure 2.

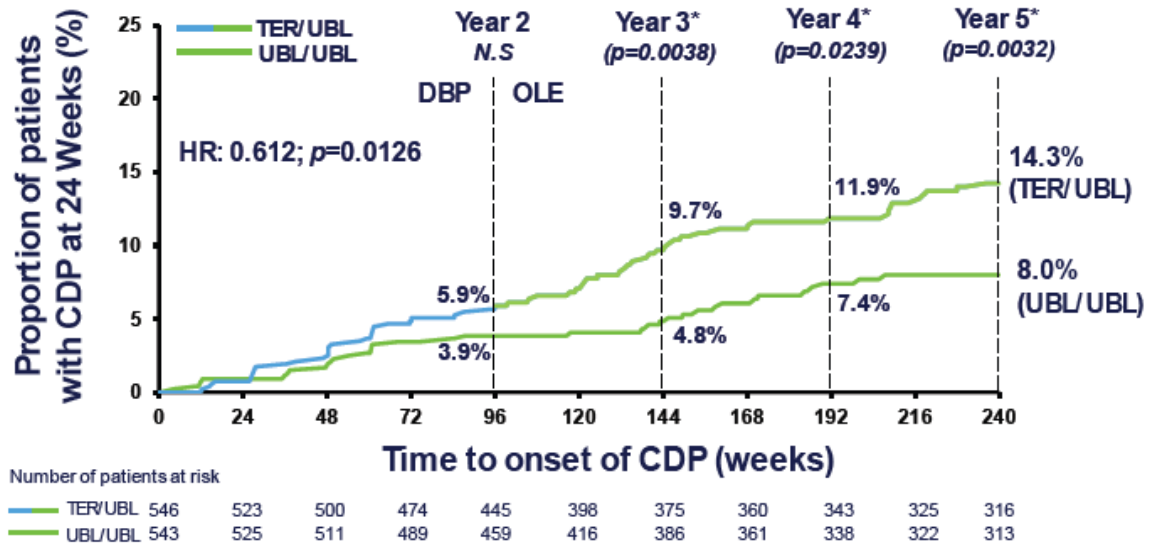
Figure 2: ARR in the double-blind and open-label phases of ULTIMATE I/II



Source: Figure 2-17, p166 of the submission. ARR = annualised relapse rate; OLE = open-label extension; TER = teriflunomide; UBL = ublituximab.

6.36 Time to confirmed disability progression lasting 24 weeks or longer (not "at 24 weeks") during the open-label phase is shown in Figure 3. Consistent with the results for annualised relapse rate, more patients allocated to teriflunomide in the double-blind phase had long-lasting confirmed disability progression during the open label phase (14.3% - 5.9% = 8.4% vs 8.0% - 3.9% = 4.1%).

Figure 3: Time to CDP lasting 24 weeks or longer in the double-blind and open-label phases of ULTIMATE I/II



Source: Figure 2-18, p157 of the submission. CDP = confirmed disability progression; TER = teriflunomide; UBL = ublituximab.

6.37 The evaluation considered these results suggest that prior teriflunomide treatment had a clinically relevant effect on the efficacy of ublituximab. If this were to apply to other DMTs, the differences in the proportions of patients with prior DMT use in the trials used in the ITCs would be a major transitivity issue.

6.38 The PSCR argued that outcomes in the open label extension do not negate the lack of impact of use vs. no use of prior DMTs on the effectiveness ublituximab versus teriflunomide, and further argued that in high risk patients, earlier and more aggressive DMT treatment leads to a reduced risk of relapse and disability accumulation over the longer term. The ESC considered clinical preference would ultimately depend on lesion load and the nature of the relapse. In cases of mild tingling with very low lesion load, therapies considered to have lower efficacy may be preferred for some patients, as opposed to cases with high lesion load and significant motor weakness, where early treatment with high efficacy therapies would be considered. The Pre-PBAC Response acknowledged this and argued that it was reasonable to re-consider the established relativities in RRMS, in recognition of emerging evidence of an evolution in the classification of RRMS treatments and the shift towards early use of high efficacy therapies.

Efficacy Summary for Ublituximab vs Teriflunomide

6.39 Ublituximab reduced the number of relapses and increased the number of patients free of relapse over 96 weeks compared to teriflunomide. The evaluation considered there was no clear difference in patients' level of disability, chance of experiencing significant worsening of disability, quality of life, or missed work time.

Indirect Treatment Comparisons

6.40 Three indirect treatment comparisons (ITCs) were undertaken in the submission: ublituximab versus ofatumumab using teriflunomide as common comparator; ublituximab versus ocrelizumab, using teriflunomide and interferon beta as intermediate comparators; and ublituximab versus fingolimod using teriflunomide and placebo as intermediate comparators.

6.41 These indirect treatment comparisons are compromised by the weaknesses of the trials of teriflunomide vs placebo (TEMSO and TOWER) and teriflunomide vs interferon beta (TENERE) previously noted by the PBAC as compromising comparisons of ofatumumab with fingolimod.

6.42 Results for ublituximab versus ofatumumab for annualised relapse rate and confirmed disability progression at 12 and 24 weeks are shown in Table 6.

Table 6: ITC ublituximab vs ofatumumab

	ARR (95% CI)	ARR ratio (95% CI)	CDP 12 weeks, Hazard Ratio (95% CI)	CDP 24 weeks, Hazard Ratio (95% CI)
ULTIMATE I				
Ublituximab N = 271	0.08 (0.04, 0.14)	**0.41 (0.27, 0.62)**	NR	NR
Teriflunomide N = 274	0.19 (0.12, 0.28)			
ULTIMATE II				
Ublituximab N = 272	0.09 (0.05, 0.17)	**0.51 (0.33, 0.78)**	NR	NR
Teriflunomide N = 272	0.18 (0.11, 0.29)			
ASCLEPIOS I				
Ofatumumab N = 454	0.11 (0.09, 0.14)	**0.50 (0.37, 0.65)**	**0.65 (0.45, 0.81)**	**0.61 (0.40, 0.93)**
Teriflunomide N = 452	0.22 (0.18, 0.26)			
ASCLEPIOS II				
Ofatumumab N = 469	0.11 (0.08, 0.13)	**0.42 (0.31, 0.56)**	**0.66 (0.45, 0.97)**	0.76 (0.49, 1.17)
Teriflunomide N = 469	0.25 (0.21, 0.30)			
Pooled ULTIMATE I/II	-	**0.45 (0.34, 0.61)**	0.84 (0.50, 1.41)	0.66 (0.36, 1.20)
Pooled ASCLEPIOS I/II	-	**0.46 (0.38, 0.57)**	**0.66 (0.50, 0.86)**	**0.68 (0.50, 0.92)**
ITC Ubli/Ofa		0.98 (0.68, 1.40)	1.29 (0.72, 2.30)	0.97 (0.49, 1.92)

Source: Tables 2-27, pp115-116; 2-29, pp118-119; 2-30, pp119-120; 2-37, p133 of the submission. ARR = annualised relapse rate; CDP = confirmed disability progression; CI = confidence interval; Ofa = ofatumumab; Ubli = ublituximab.

6.43 The indirect treatment comparison of ublituximab versus ocrelizumab via teriflunomide and interferon beta is shown in Table 7. The submission presented only annualised relapse rate data for this comparison (TENERE did not report results for confirmed disability progression). Although the submission stated that it reported "[t]he results of each stepwise comparison used to provide the multistep indirect

ublituximab vs. ocrelizumab comparison" the estimates for the comparison of ocrelizumab and teriflunomide were not provided.

Table 7: ITC ublituximab vs ocrelizumab

	ARR (95% CI)	ARR ratio (95% CI)
TENERE		
Teriflunomide N = 111	0.26 (0.15, 0.44)	1.20 (0.62, 2.30)
Interferon beta N = 104	0.22 (0.11, 0.42)	
OPERA I		
Ocrelizumab N = 410	0.16 (0.12, 0.20)	**0.53 (0.40, 0.72)**
Interferon beta N = 411	0.29 (0.24, 0.36)	
OPERA II		
Ocrelizumab N = 417	0.16 (0.12, 0.20)	**0.53 (0.40, 0.71)**
Interferon beta N = 418	0.29 (0.23, 0.36)	
OPERA Meta-Analysis	-	**0.54 (0.44, 0.66)**
ULTIMATE I/II Meta-Analysis	-	**0.45 (0.34, 0.61)**
ITC Ubli/Ocre	-	1.02 (0.48, 2.15)

Source: Tables 2-27, pp115-116, 2-38, p135, 2-39, p135 2-40, p136, 2-45, p142 of the submission. ARR = annualised relapse rate; CI = confidence interval; ITC. = indirect treatment comparison; Ocre = ocrelizumab; Ubli = ublituximab.

6.44 The indirect treatment comparison for ublituximab versus fingolimod via placebo and teriflunomide is shown in Table 8. Again, although the submission stated that the stepwise estimates were provided, the estimates for the indirect comparison of fingolimod to teriflunomide were not provided.

Table 8: ITC for ublituximab vs fingolimod.

	ARR (95% CI)	ARR ratio (95% CI)	CDP 12 weeks, Hazard Ratio (95% CI)	CDP 24 weeks, Hazard Ratio (95% CI)
FREEDOMS I				
Fingolimod N = 425	0.18 (0.15, 0.22)	**0.46 (0.37, 0.55)**	**0.70 (0.52, 0.96)**	**0.63 (0.44, 0.90)**
Placebo N = 418	0.40 (0.34, 0.47)			
FREEDOMS II				
Fingolimod N = 358	0.21 (0.17, 0.25)	**0.52 (0.40, 0.66)**	0.83 (0.61, 1.12)	0.72 (0.48, 1.07)
Placebo N = 355	0.40 (0.34, 0.48)			
FREEDOMS I/II Meta-Analysis		**0.48 (0.41, 0.57)**	**0.76 (0.62, 0.95)**	**0.67 (0.51, 0.87)**
TEMSO				
Teriflunomide N = 358	0.37 (0.31, 0.44)	**0.68 (0.55, 0.85)**	**0.70 (0.51, 0.97)**	0.75 (0.50, 1.11)
Placebo N = 363	0.54 (0.47, 0.62)			
TOWER				
Teriflunomide N = 370	0.32 (0.27, 0.38)	**0.64 (0.51, 0.79)**	0.68 (0.47, 1.00)	0.84 (0.53, 1.33)
Placebo N = 388	0.50 (0.43, 0.58)			
ULTIMATE I/II Meta-Analysis				
		0.45 (0.34, 0.61)	0.84 (0.50, 1.41)	0.66 (0.36, 1.20)
ITC Ubli/Fin		**0.62 (0.43, 0.90)**	0.77 (0.42, 1.41)	0.78 (0.38, 1.60)

Source: Tables 2-27, pp115-116, 2-29, pp118-119, 2-30, pp119-120, 2-37, p133 of the submission.
ARR = annualised relapse rate; CDP = confirmed disability progression; CI = confidence interval; Fin = fingolimod; Ubli = ublituximab.

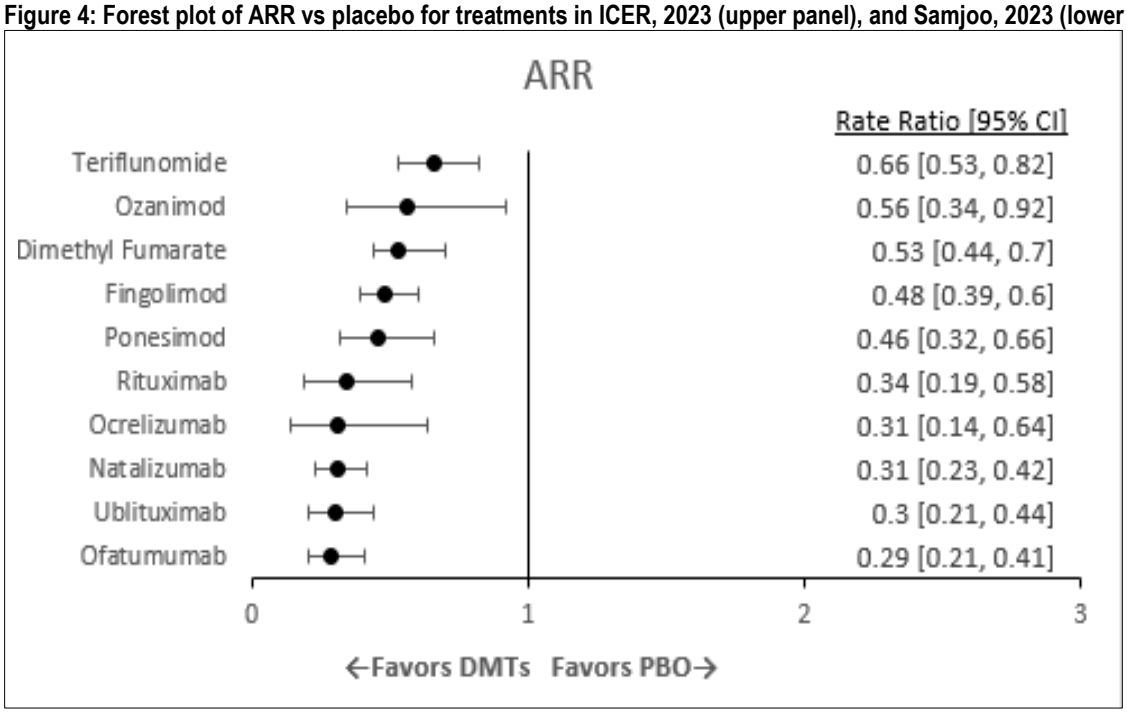
6.45 The Pre-PBAC Response argued the results of the indirect treatment comparison versus fingolimod are reliable and provided an additional attachment to the Response from the University of Melbourne Statistical Consulting Centre, that concluded that based on the results of the comparisons, that a non-blinding bias of more than 25% for the ARR ratio would be required before the superiority conclusion would likely be lost (or a threshold increase in ARR to >0.733). The Response further argued that the possible contribution of biases in the trials reaching this threshold to invalidate the statistical superiority conclusion was unlikely. The PBAC acknowledged the threshold that would be required to achieve statistical non-significance, however considered the multi-step indirect comparison of ublituximab and fingolimod remained inherently uncertain.

Network Meta-Analysis

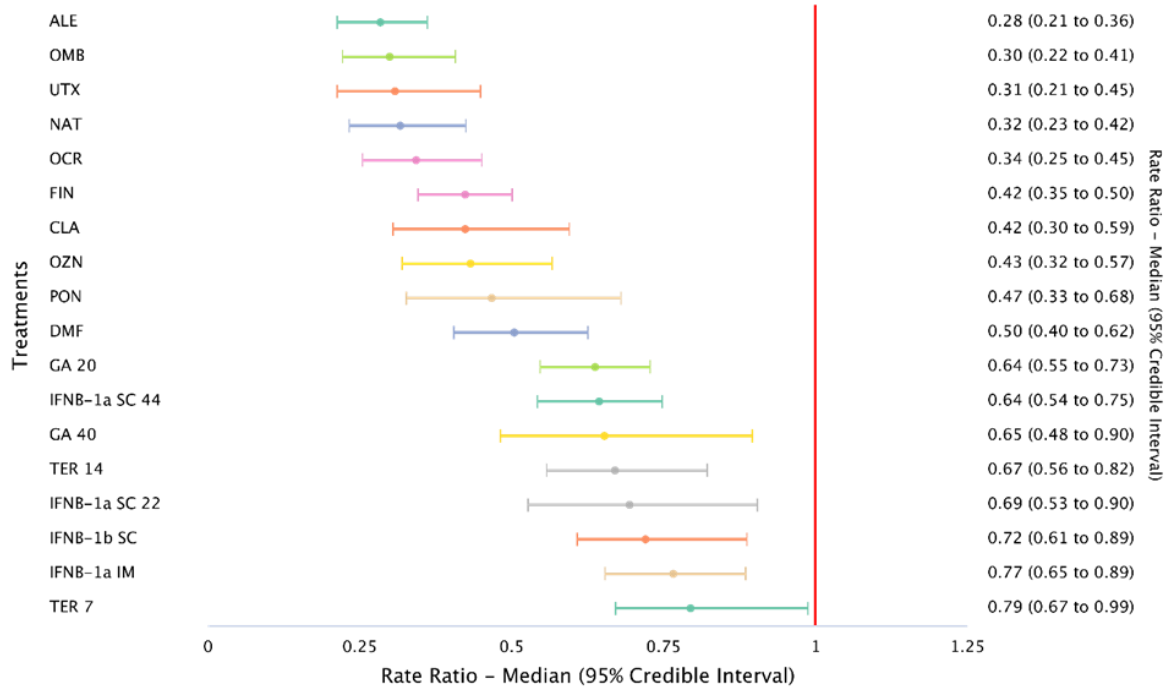
6.46 The submission provided a network meta-analysis (NMA) of some agents for the treatment of relapsing-remitting multiple sclerosis "as supportive information" (ICER, 2023).

6.47 Results for annualised relapse rate (ARR) for the ICER, 2023 NMA and for the NMA of Samjoo, 2023 considered by the PBAC in relation to ofatumumab in March 2024 are shown in Figure 4.

Figure 4: Forest plot of ARR vs placebo for treatments in ICER, 2023 (upper panel), and Samjoo, 2023 (lower panel)



Source: Figure 2-12, p145 of the submission.
ARR = annualised relapse rate; CI = credible interval; DMT = disease modifying therapy; PBO = placebo



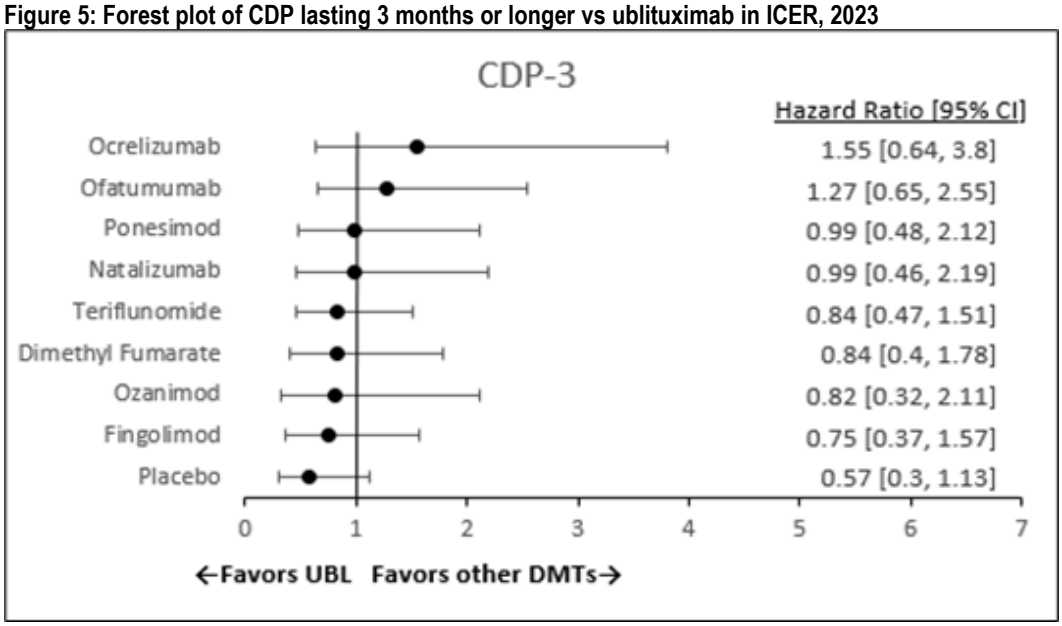
Source: Figure 2, paragraph 6.39, ofatumumab PSD, March 2024 PBAC Meeting. ALE = alemtuzumab; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA 20 = glatiramer 20 mg subcutaneously daily; GA 40 = glatiramer 40 mg subcutaneously three times weekly; IFN = interferon; NAT = natalizumab; OCR = ocrelizumab; OMB = ofatumumab; OZN = ozanimod; PON = ponesimod; SC = subcutaneous; TER7 = teriflunomide 7 mg daily; TER14 = teriflunomide 14 mg daily; UTX = ublituximab;

6.48 There were some differences between the two NMAs, notably the estimate of ARR ratio for fingolimod, which was 0.48 (0.39, 0.6) in ICER, 2023 and 0.42 (0.35, 0.50) in Samjoo, 2023.

6.49 Because of the overlapping 95% CIs, the methodological issues with the TEMSO, TOWER and TENERE trials, and the changes in diagnosis of multiple sclerosis and use of DMTs over time, the PBAC rejected the claim that the Samjoo, 2023, NMA justified a conclusion that ofatumumab was superior to fingolimod (paragraphs 6.41, 6.42, 6.45, 6.46, ofatumumab PSD, March 2024 PBAC Meeting). The results of the ICER, 2023 NMA, do not provide any reason to change that conclusion. The ESC considered the evidence underpinning the superiority claim for ublituximab over fingolimod, including the results of the NMAs, did not appear to be stronger or more robust than that relied upon in the earlier ofatumumab submission to inform a similar claim. Therefore, the ESC considered it was likely reasonable to draw a similar therapeutic conclusion (non-inferiority) for the comparative effectiveness of ublituximab to fingolimod based on the available evidence.

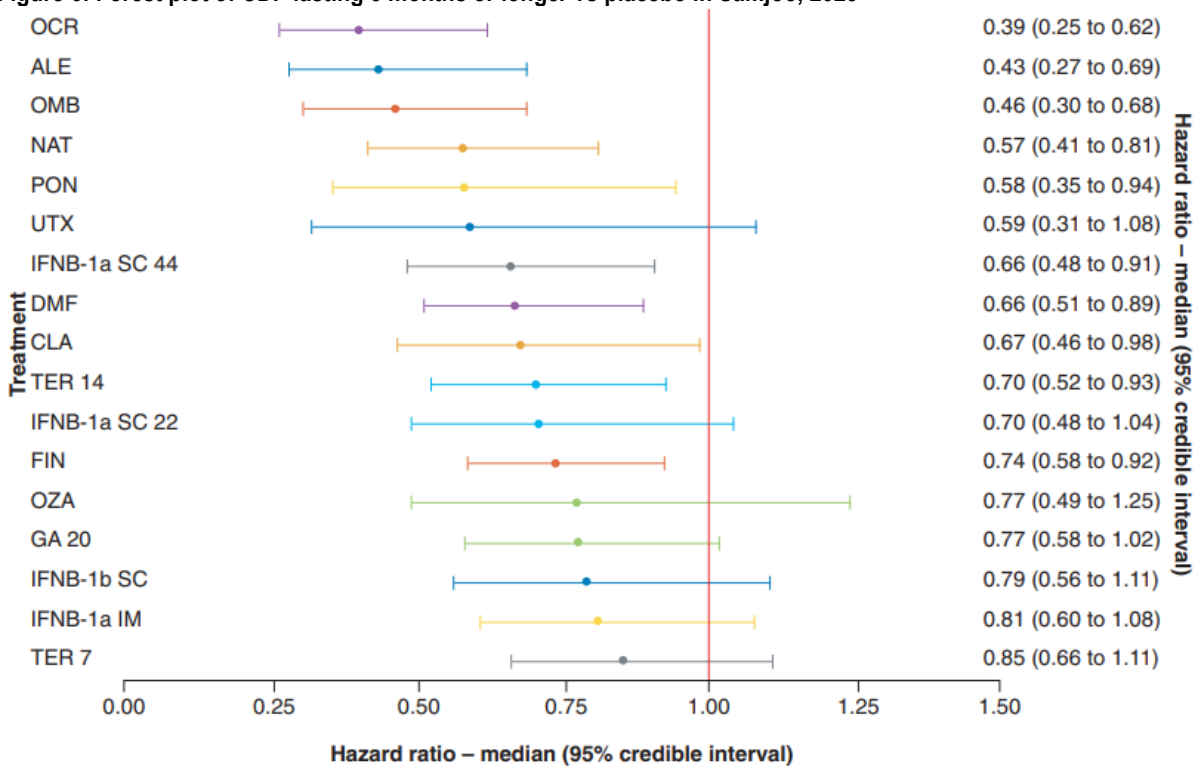
6.50 The next most widely reported outcome in the trials is confirmed disability progression lasting 3 and 6 months. The submission presented estimates for confirmed disability progression (CDP) lasting 3 months or longer from ICER, 2023 (shown in Figure 5 with ublituximab as reference). The analogous plot in the ofatumumab PSD from March 2024 presenting estimates vs placebo is shown in Figure 6.

Figure 5: Forest plot of CDP lasting 3 months or longer vs ublituximab in ICER, 2023



Source: Figure 2-14, p148 of the submission.

Figure 6: Forest plot of CDP lasting 3 months or longer vs placebo in Samjoo, 2023

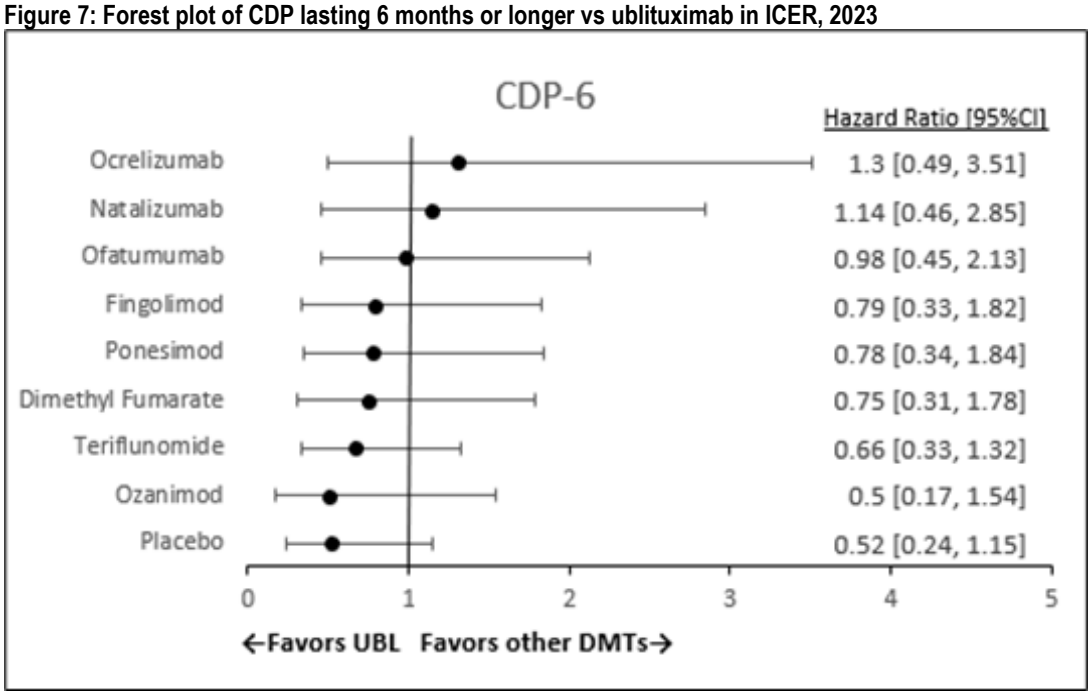


ALE = alemtuzumab; CDP = confirmed disability progression; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB = interferon beta; IM = intramuscular; NAT= natalizumab; OCR = ocrelizumab; OMB = ofatumumab; OZA = ozanimod; PON = ponesimod; SC = subcutaneous; TER7 = teriflunomide 7 mg daily; TER14 = teriflunomide 14 mg daily; UTX = ublituximab.

6.51 The results of ICER, 2023 and Samjoo, 2023 for CDP lasting 3 months or longer were consistent. The most notable finding was that ocrelizumab, ofatumumab and fingolimod were associated with statistically significant reductions in the risk of confirmed disability progression lasting 3 months or longer and ublituximab was not.

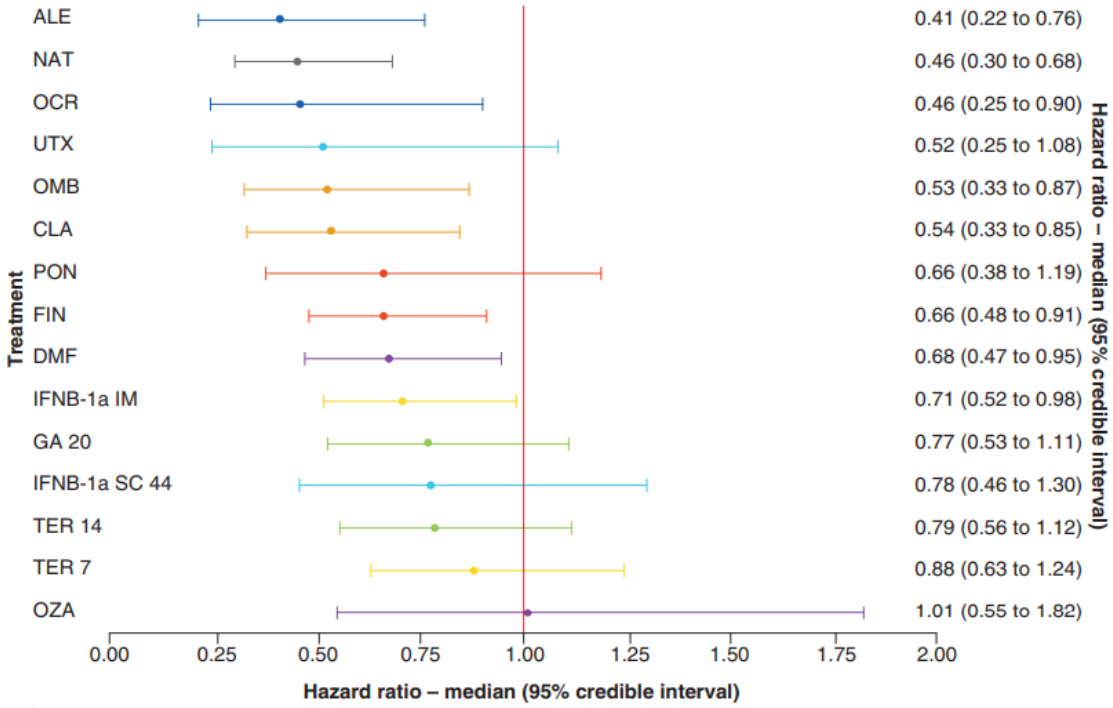
6.52 The submission also presented estimates for confirmed disability progression (CDP) lasting 6 months or longer from ICER, 2023 (shown in Figure 7Figure with ublituximab as reference). The analogous plot in the ofatumumab PSD from March 2024 presenting estimates vs placebo is shown in Figure 8.

Figure 7: Forest plot of CDP lasting 6 months or longer vs ublituximab in ICER, 2023



Source: Figure 2-15, p148 of the submission.
CDP-6 = confirmed disability progression lasting 6 months or longer; CI = credible interval; DMT = disease-modifying therapy; UBL = ublituximab.

Figure 8: Forest plot of CDP lasting 6 months or longer vs placebo in Samjoo, 2023



Source: Figure 5, paragraph 6.49, ofatumumab PSD, March 2024 PBAC Meeting.
ALE = alemtuzumab; CDP = confirmed disability progression; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB = interferon beta; IM = intramuscular; NAT= natalizumab; OCR = ocrelizumab; OMB = ofatumumab; OZN = ozanimod; PON = ponesimod; SC = subcutaneous; TER =, teriflunomide; UTX = ublituximab.

6.53 The results of the two NMAs are consistent; ocrelizumab, ofatumumab and fingolimod were associated with statistically significant reductions in the risk of confirmed disability progression lasting 6 months or longer and ublituximab was not.

Comparative harms

6.54 Adverse events in ULTIMATE I and II are shown in Table 9. Data were presented only for patients with at least one event, not the total number of events, which for some adverse events, such as infusion reactions, may under-represent the burden of adverse events.

6.55 Adverse events of Grade 3 or higher, serious adverse events, and adverse events leading to interruption or discontinuation of study treatment were common, and more frequent in ublituximab-treated than in teriflunomide-treated patients.

Table 9: Adverse events in ULTIMATE I and II

	ULTIMATE I		ULTIMATE II	
	Ublituximab N = 273	**Teriflunomide N = 275**	**Ublituximab N = 272**	**Teriflunomide N = 273**
Patients with TEAE, n (%)	235 (86.1%)	245 (89.1%)	251 (92.3%)	256 (93.8%)
Patients with TEAE Grade 3 or higher, n (%)	72 (26.4%)	43 (15.6%)	44 (16.2%)	34 (12.5%)
Patients with TESAE, n (%)	31 (11.4%)	19 (6.9%)	28 (10.3%)	21 (7.7%)
Patients with TEAE leading to interruption of study drug, n (%)	48 (17.6%)	17 (6.2%)	42 (15.4%)	34 (12.5%)
Patients with TEAE leading to discontinuation of study drug, n (%)	18 (6.6%)	2 (0.7%)	5 (1.8%)	2 (0.7%)
Fatal TEAE, n (%)	2 (0.7%)	0	1 (0.4%)	0
Patients with infusion-related AE, n (%)	8 (2.9%)	1 (0.4%)	19 (7.0%)	2 (0.7%)
Patients with systemic infusion reactions, n (%)	119 (43.6%)	31 (11.3%)	144 (52.9%)	41 (15.0%)
Patients with serious infection, n (%)	15 (5.5%)	6 (2.2%)	12 (4.4%)	10 (3.7%)
Patients with alopecia, n (%)	6 (2.2%)	31 (11.3%)	13 (4.8%)	48 (17.6%)
Patients with cytopenia Grade ≥3 n (%)	40 (14.7%)	8 (2.9%)	29 (9.6%)	5 (1.8%)

Source: Table 2-33, pp126-127, Table 2-34, p127 of the submission; ULTIMATE I CSR, Table 45, pp153-155, pp159-160; ULTIMATE II CSR, Table 45, pp155-157, pp160-161. TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

6.56 Adverse events in the trials of ocrelizumab, ofatumumab and fingolimod are shown in Table 10.

Table 10: Adverse events in trials of ocrelizumab, ofatumumab and fingolimod

	OPERA I/II Ocrelizumab N = 827	OPERA I/II Interferon Beta N = 828	ASCLEPIOS I/II Ofatumumab N = 946	ASCLEPIOS I/II Teriflunomide N = 936	FREEDOMS I/II Fingolimod N = 854	FREEDOMS I/II Placebo N = 418
Patients with any AE, n (%)	687 (83.1%)	688 (83.1%)	762 (80.5%)	788 (84.2%)	805 (94.3%)	387 (92.6%)
Patients with any SAE, n (%)	57 (6.9%)	72 (8.7%)	86 (9.1%)	74 (7.9%)	94 (11.0%)	56 (13.4%)
Patients with serious infection, n (%)	11 (1.3%)	24 (2.9%)	24 (2.5%)	17 (1.8%)	<2	<2
AE leading to discontinuation of study treatment, n (%)	29 (3.5%)	51 (6.2%)	54 (5.7%)	49 (5.2%)	93 (10.9%)	32 (7.7%)
Injection-site AE, n (%)	NR	NR	103 (10.9%)	52 (5.6%)	NA	NA
Systemic reactions to infusion or injection, n (%)[1]	286 (34.6%)	80 (9.7%)	191 (20.2%)	140 (15.0%)	NA	NA

Source: Kappos, NEJM 2010; 362:387-401, Table 3; Hauser, NEJM 2017; 376:221-234, Table 3; Hauser, NEJM 2020; 383:546-557, Table 3.

[1] Fever, tachycardia, influenza-like syndrome AE = adverse event; NR = not reported; SAE = serious adverse event.

6.57 Systemic reactions to monoclonal antibody administration may have been less common with ocrelizumab than with ublituximab and were clearly less common with ofatumumab. The submission lists "Infusion-related AEs" as NA (= not applicable) for ofatumumab, but this is misleading because systemic reactions occur after sub-cutaneous as well as after intravenous administration, and were reported in Hauser, 2017. The ULTIMATE I and II CSRs and the ASCLEPIOS I/II published paper reported systemic reactions and infusion/injection related AEs separately, but the OPERA I/II published report did not.

6.58 Adverse events leading to discontinuation of study treatment were probably less common with ublituximab, ocrelizumab and ofatumumab than with fingolimod.

6.59 Safety outcomes were not assessed in the indirect treatment comparisons provided by the submission. The submitted network meta-analysis analysed adverse events "in a qualitative manner" (ICER, 2023, p18).

Harms in the Open Label Extension of ULTIMATE I/II

6.60 Adverse events were incompletely reported for the open-label extension, and in particular, no estimates of the rate of systemic reactions to infusions or of Grade 3 or worse cytopenia were provided. No new safety signals emerged during the open-label phase.

Extended assessment of Safety

6.61 The mechanism of action of ublituximab has given rise to concerns about risks of infection and neoplasia with long-term treatment. The trials excluded patients considered to be at high risk of adverse events related to infection (e.g., positive serology for Hepatitis B or C), while real-world use may include some of these patients.

6.62 No Periodic Safety Update Report has been prepared for ublituximab because there has not been sufficiently prolonged use outside trials.

Benefits/harms

6.63 A benefits and harms table is not presented versus ofatumumab and ocrelizumab as the submission made a claim of non-inferiority.

6.64 With respect to the superiority claim versus fingolimod, if these were to be accepted, based on the evidence presented in the submission, treatment with ublituximab was associated with:

- A 38% lower annualised relapse rate; and
- No difference in risk of confirmed disability progression at either 12 or 24 weeks.

6.65 Due to the substantial inherent uncertainty with the presented evidence underpinning comparison with fingolimod, the PBAC did not accept the contention that ublituximab was associated with clear benefits over fingolimod.

Clinical claim

6.66 The submission described ublituximab as superior to fingolimod in terms of effectiveness. This evaluation considered this claim was not adequately supported. The key issue was, as PBAC has previously advised (in its consideration of ofatumumab in March 2024), the weaknesses of the trials making up the multi-step indirect treatment comparison likely means the available evidence is not sufficiently reliable for the purposes of establishing superiority. However, the evaluation considered the available evidence does not suggest ublituximab is likely to be less effective than fingolimod. The PSCR argued the indirect treatment comparison results for ARR support the superiority claim for ublituximab over fingolimod. The ESC agreed with the evaluation concerns around the robustness of the multi-step indirect treatment comparisons of ublituximab versus fingolimod. Based on the available evidence, the ESC considered that ublituximab's superiority claim over fingolimod was not adequately supported, and that a claim of non-inferior comparative effectiveness was likely more reasonable.

6.67 The submission described ublituximab as non-inferior to ocrelizumab and ofatumumab in terms of effectiveness. Taking the evidence as a whole, the evaluation and ESC considered these claims were probably reasonable, however the ESC considered the comparison versus ocrelizumab had inherent uncertainty due to the

multi-step indirect treatment comparison approach using a teriflunomide bridging study with a substantial methodological issues.

6.68 The submission described ublituximab as non-inferior in terms of safety compared to fingolimod, ocrelizumab and ofatumumab. Taking the evidence as a whole, the evaluation and ESC considered these claims were probably reasonable.

6.69 The PBAC agreed with the evaluation and ESC and considered the claim of superior comparative effectiveness to fingolimod was not adequately supported. The Committee considered the comparison versus ofatumumab was the most robust and that a claim of non-inferior comparative effectiveness of ublituximab and ofatumumab was likely reasonable. The PBAC considered it was more reasonable to then extrapolate the non-inferiority therapeutic relativities established for ofatumumab to the other higher efficacy tier agents for RRMS on the PBS, including fingolimod and ocrelizumab, to ublituximab.

6.70 The PBAC considered the available safety data did not suggest that ublituximab was likely to have a worse safety profile than fingolimod, ofatumumab and ocrelizumab and considered the claims of non-inferior comparative safety were reasonable.

Economic analysis

6.71 The submission presented a cost analysis to construct a proposed price for ublituximab and proposed that the price should be a weighted average of the three comparators, ocrelizumab, ofatumumab and fingolimod, with weights determined by current relative PBS prescribing. The submission proposed a [redacted]% price premium over the current fingolimod price as part of the calculations, on the grounds of claimed superiority of ublituximab over fingolimod. As noted above, this claim was not adequately supported by the clinical data and the application of an arbitrary price premium does not establish cost effectiveness over fingolimod at the price proposed, even if the claim of superiority were accepted.

6.72 The submission noted that both ocrelizumab and ofatumumab have Special Pricing arrangements and used the published prices in the analysis, acknowledging that these would need to be recalculated.

6.73 The components of the analysis as presented are listed in Table 11.

Table 111: Key components of the cost analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior to OFA and OCRE and superior to FING
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior
Evidence base	Indirect comparison of proposed medicine and main comparator
Equi-effective doses	Estimated over 2 years based on PI: Ublituximab: 13 *150mg packs Ocrelizumab: 300mg *8 packs Ofatumumab: 20mg *27 Fingolimod: 0.5mg per day, calculated as 13.04 *28 day packs per year
Direct medicine costs	As calculated
Other costs or cost offsets	administration costs, premedication costs

Source: Section 3 of the submission.

6.74 The equi-effective doses for ublituximab 13 x 150 mg packs over 2 years were estimated as:

- Ocrelizumab 8 x 300 mg injection packs over 2 years, with the first dose of 600 mg split into 2 doses 2 weeks apart;
- Ofatumumab 27 x 20 mg injections over 2 years, and
- Fingolimod 0.5 mg/day.

In the case of fingolimod, the submission estimated the dose based on the current distribution of use of different strength fingolimod capsules (the price used for the 0.25 mg capsule 28 day pack is currently higher than the 0.5 mg capsule). The submission inappropriately also used the full MBS item fees in its calculations.

6.75 The dose equivalence over 2 years (104 weeks), based on the trial data, should be:

- Ublituximab 16 x 150 mg injections, provided as 1 x 4 injection pack for the first 2 doses at week 0 and week 2, then 4 x 3 injection packs for infusions at weeks 26, 50, 74 and 98;
- Ocrelizumab 5 x 600 mg infusion packs (2 x 300 mg vials per script), with the first dose split into 300 mg at each of week 0 and 2, with subsequent doses of 600 mg every 24 weeks, i.e. at week 28, 52, 76 and 100;
- Ofatumumab 28 x 20 mg doses, with doses at week 0, 1,2,4 and 4 weekly thereafter (last dose over 2 years at week 100); and
- Fingolimod 0.5 mg/day, calculated as 13.04 x 28 day packs per year.

6.76 The PSCR disagreed with the commentary's equi-effective dosing calculations in relation to the number of injections required for ublituximab and ocrelizumab over a two year time period, on the basis of partial accounting.

6.77 The results of the cost analyses (using published AEMP) as presented in the submission are shown in Table 12 with the price of ublituximab calculated to be cost minimised against each comparator.

Table 122: Cost minimisation calculations using published AEMP as presented in the submission.

	ublituximab	ocrelizumab	ublituximab	ofatumumab	ublituximab	fingolimod
Drug cost	$5,125.61	$8,328.18	$4,235.22	$2,058.29	$[redacted]	$830.63[6]
Packs per 2 years	13	8	13	27	13	26.08
Cost per 2 years	$66, 632.96	$66,625.44	$55,057	$55,573.83	$21,287.76	$21,655.72
Concomitant medications				0		0
Corticosteroid	$0.65[1]	$8.17[2]	$0.65[1]		$0.65[1]	
diphenhydramine	$0.16[3]	$0.16[3]	$0.16[3]		$0.16[3]	
Other costs: IV infusion costs/injection costs per 2 years monitoring	$558.00[4]	$558.00[4]	$558.00[4]	$42.85[5]	$558.00[4]	$190.85[7]
Total cost over 2 years	$67,191.77	$67,191.77	$55,616.68	$55,616.68	$21,846.57	$21,846.57

Source: Tables 3.2, 3.3 and 3.4, pp171, 172 and 173 of the submission. Shaded cells show calculated prices for each comparison.
[1] Cost of dexamethasone.
[2] Cost of IV methylprednisolone.
[3] Cost of 25 mg diphenhydramine.
[4] Calculated as 5 * MBS item 14245, $111.60, full fee.
[5] MBS item 23, full fee, as first injection should be performed under the guidance of a health professional.
[6] Weighted average price of 0.25 mg and 0.5 mg fingolimod capsules.
[7] MBS item 11716, first dose cardiac monitoring.

6.78 As noted above, the analyses included a [redacted]% price premium for ublituximab compared to fingolimod, on the basis of the claim of superior effectiveness, which was not adequately supported. The ESC considered that as ublituximab's superiority claim to fingolimod was not supported, a price premium of any magnitude against fingolimod was unjustified.

6.79 The submission used these calculations to derive a weighted average price for ublituximab, as shown in Table 13.

Table 133: Weighted average price calculations based on published prices

Comparator	PBS scripts per patient p.a.	PBS Services (2023-24)		Mths of Treatment per script	No. of months of treatment		Number of patients (derived = weighting)		Individual Cost analysed price	Weighted average price (AEMP)
Ocrelizumab 6 monthly IV	2	All	13,730	6	82,380		6,865	58%	$5,125.61	$[redacted]
Ofatumumab monthly SC	12	Initial	1,246	1	1,246	26,286	2,191	18%	$4,235.22	
		Cont	25,040	1	25,040					
Fingolimod daily oral	13.04	All	37,233	0.92	34,275		2,856	24%	$[redacted]	
Total			77,249		142,941		11,912	100%		

Source: Table 3.5, p 175 of the submission.

6.80 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with ublituximab would be no more than the cost per patient of the alternative therapies, which includes the nominated comparators of ocrelizumab, ofatumumab and fingolimod and may also include other high efficacy tier drugs including natalizumab, alemtuzumab, cladribine and ozanimod. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian

Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

6.81 No compelling evidence was provided that ublituximab provides a significant improvement in efficacy and/or safety over ocrelizumab, ofatumumab or fingolimod.

6.82 In the context of the clinical conclusion, the ESC advised that the weighted cost analysis presented in the submission was not justified and a cost-minimisation against the least-costly alternative DMT within the pool of existing 'higher-tier' RRMS agents, consistent with Section 101(3B) of the *National Health Act 1953* was likely more appropriate.

Drug cost/patient/year

6.83 Using the weighted average AEMP as calculated in Table 13 based on the published prices of the comparators, the cost per patient per year would be $[redacted].

Estimated PBS usage & financial implications

6.84 This submission was not considered by DUSC. The submission appropriately used a market share approach to estimate the use and financial implications of listing ublituximab. The key inputs used in the estimates are shown in Table 144.

Table 144: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Market data	Medicare/PBS Item reports	Appropriate
Uptake rate	Sponsor assumption for each comparator. fingolimod / Ocrelizumab / ofatumumab Year 1: [redacted]% / [redacted]% / [redacted]% Year 2: [redacted]% / [redacted]% / [redacted]% Year 3: [redacted]% / [redacted]% / [redacted]% Year 4: [redacted]% / [redacted]% / [redacted]% Year 5: [redacted]% / [redacted]% / [redacted]% Year 6: [redacted]% / [redacted]% / [redacted]%	Most likely to replace ocrelizumab rather than fingolimod or ofatumumab therefore market share may be overestimated. Tested in sensitivity analyses.
Compliance rate	Assumes 100%	May be an overestimate; tested in sensitivity analyses
offsets for concomitant therapies	PBS items: 1928L- methylprednisolone injection, $8.17 2507Y – dexamethasone 4mg tablet, $0.65	Consistent with Section 3, but assumes all patients will use dexamethasone pre med rather than IV steroids – likely overestimate.
MBS item	MBS item 14245 – IV infusion, $111.60 MBS item 11716, continuous ambulatory ECG, $190.85 MBS Item 23, GP consult level B, $42.85	Consistent with Section 3. IV infusion costs may be appropriate. ECG and GP costs inappropriate and an overestimate.

Source: compiled form Section 4 of the submission.

6.85 The estimated number of scripts and total financial impact as presented in the submission using published prices is shown in Table 155.

Table 155: Estimated use and financial implications based on published prices, DPMQ

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Number of scripts dispensed[a]	[redacted] 1	[redacted] 1	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2
Estimated financial implications of ublituximab						
Cost to PBS/RPBS less copayments	$[redacted] 3	$[redacted] 4	$[redacted] 5	$[redacted] 6	$[redacted] 6	$[redacted] 6
Estimated financial implications for fingolimod, ocrelizumab and ofatumumab						
Number of scripts replaced - fingolimod	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Number of scripts replaced - ocrelizumab	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 2	[redacted] 2	[redacted] 2
Number of scripts replaced - ofatumumab	[redacted] 1	[redacted] 2	[redacted] 2	[redacted] 7	[redacted] 7	[redacted] 7
Total number of scripts replaced	[redacted] 2	[redacted] 7	[redacted] 7	[redacted] 8	[redacted] 8	[redacted] 8
Total number of concomitant medicines scripts replaced[b]	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Cost to PBS/RPBS less copayments	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9
Net financial implications						
Net cost to PBS/RPBS	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9
Net cost to MBS/ Services Australia/other	$[redacted] 10	$[redacted] 10	$[redacted] 10	$[redacted] 10	$[redacted] 10	$[redacted] 10
Net cost to Government	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9	-$[redacted] 9

Source: Constructed form Section 4 and the Section 4 Excel workbook in the submission.

[a] Assumes 2 scripts per year and 100% adherence.

[b] includes methylprednisolone and dexamethasone

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] 5,000 to < 10,000

[3] $30 million to < $40 million

[4] $60 million to < $70 million

[5] $90 million to < $100 million

[6] $100 million to < $200 million

[7] 10,000 to < 20,000

[8] 20,000 to < 30,000

[9] net cost saving

[10] $0 to < $10 million

6.86 The inclusion of the cost of methylprednisolone being replaced by dexamethasone likely underestimates the cost as both steroids can be used as premedication. Inclusion of a change in the use of cardiac monitoring due to reduction in fingolimod use might be reasonable, but a reduction in the use of health professional consultations for training in subcutaneous injections is probably an overestimate.

6.87 The submission presented sensitivity analyses varying the assumptions about market uptake and compliance.

Table 16: Summary of Sensitivity Analysis (at published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base Case						
Number of Ublituximab Rx	[redacted] [1] Rx	[redacted] [1] Rx	[redacted] [2] Rx	[redacted] [2] Rx	[redacted] [2] Rx	[redacted] [2] Rx
Net Cost of Ublituximab to PBS/RPBS	$[redacted] [3]	$[redacted] [4]	$[redacted] [5]	$[redacted] [6]	$[redacted] [6]	$[redacted] [6]
Net Savings to PBS/RPBS from displaced medications	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]
Net Savings to PBS/RPBS	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]
Net Cost to MBS	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]
Net Savings to Government	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]
SS1: Higher market uptake rate						
Number of Ublituximab Rx	[redacted] [1] Rx	[redacted] [2] Rx	[redacted] [2] Rx	[redacted] [2] Rx	[redacted] [2] Rx	[redacted] [9] Rx
Net Cost of Ublituximab to PBS/RPBS	$[redacted] [10]	$[redacted] [11]	$[redacted] [5]	$[redacted] [6]	$[redacted] [6]	$[redacted] [6]
Net Savings to PBS/RPBS from displaced medications	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]
Net Cost to PBS/RPBS	$[redacted] [8]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]
Net Cost to MBS	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]
Net Cost to Government	**$**[redacted] [8]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]
SS2: Reduced comparator adherence						
Number of Ublituximab Rx	[redacted] [1] Rx	[redacted] [1] Rx	[redacted] [2] Rx	[redacted] [2] Rx	[redacted] [2] Rx	[redacted] [2] Rx
Net Cost of Ublituximab to PBS/RPBS	$[redacted] [3]	$[redacted] [4]	$[redacted] [5]	$[redacted] [6]	$[redacted] [6]	$[redacted] [6]
Net Savings to PBS/RPBS from displaced medications	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]
Net Cost to PBS/RPBS	$[redacted] [8]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]	-$[redacted] [7]
Net Cost to MBS	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]	$[redacted] [8]
Net Cost to Government	**$**[redacted] [8]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]	**-$**[redacted] [7]

Source: Table 4.17, p196 of the submission.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*
[2] *5,000 to < 10,000*
[3] *$30 million to < $40 million*
[4] *$60 million to < $70 million*
[5] *$90 million to < $100 million*
[6] *$100 million to < $200 million*
[7] *net cost saving*
[8] *$0 to < $10 million*
[9] *10,000 to < 20,000*
[10] *$40 million to < $50 million*
[11] *$70 million to < $80 million*

Quality Use of Medicines

6.88 The submission stated that there will be a quality use of medicines program including health professional education sessions, patient support material and a post marketing surveillance study.

Financial Management – Risk Sharing Arrangements

6.89 The submission did not propose a Risk Share agreement but did request a Special Pricing Arrangement on the grounds that ocrelizumab and ofatumumab have SPAs.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program – Public and Private Hospitals), Authority Required (Streamlined) listing of ublituximab for the treatment of relapsing-remitting multiple sclerosis (RRMS). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of ublituximab would be acceptable if it were cost-minimised to the least costly alternative therapy available on the PBS for RRMS previously classified into the high efficacy tier (at time of PBAC consideration, this group includes fingolimod, cladribine, ozanimod, natalizumab, alemtuzumab, ocrelizumab and ofatumumab).

7.2 In making this recommendation, the PBAC noted the submission made a claim of superior comparative effectiveness over fingolimod, however considered the clinical evidence presented was not sufficiently reliable for the purposes of establishing superiority over fingolimod (or any of the other comparators). The PBAC's view of the presented evidence and clinical claims are discussed further below.

7.3 The PBAC considered the nominated comparators (ocrelizumab, ofatumumab and fingolimod) were reasonable proxies for the other disease modifying therapies (DMTs) in the high efficacy tier.

7.4 The PBAC advised the equi-effective doses of ublituximab and the nominated comparators are as follows:

- Ublituximab 150 mg by intravenous (IV) infusion at week 0, followed by a second dose of 450 mg IV infusion at week 2 and subsequent doses of 450 mg IV infusion every 24 weeks thereafter;
- Ocrelizumab 5 x 600 mg infusion packs (2 x 300 mg vials per script), with the first dose split into 300 mg at each of week 0 and 2, with subsequent doses of 600 mg every 24 weeks;
- Ofatumumab 28 x 20 mg doses, with doses at week 0, 1,2,4 and 4 weekly thereafter; and
- Fingolimod 0.5 mg /day.

Furthermore, the PBAC advised the equi-effective dosing for all other alternative therapies in the high efficacy tier could be derived with reference to the relevant TGA Product Information and the latest PBS Public Summary Documents in order to ascertain the least costly alternative therapy over 2 years.

7.5 The PBAC considered it was appropriate for the listing to be consistent with other RRMS DMTs, and that as an infusible agent, ocrelizumab was the most applicable similar listing. The Committee considered that it was reasonable for the listing to not be prescriptive about the class of antihistamine to be used as pre-medication, however noted diphenhydramine was used in the clinical trials.

7.6 The PBAC noted there was no direct comparative evidence between ublituximab and any of the nominated comparators, and noted the pivotal trials (ULTIMATE I/II) were randomised controlled trials versus teriflunomide, which it recalled was categorised into the lower efficacy tier of RRMS therapies. Based on the presented evidence, the PBAC was satisfied that ublituximab provides, for some patients, a significant improvement in effectiveness over teriflunomide for the purposes of Section 101(3B) of the *National Health Act 1953* and also considered, based on previously determined relativities, that ublituximab also provides, for some patients, a significant improvement in effectiveness over the other lower tier therapies (interferon beta-1a/1b, peginterferon beta-1a, glatiramer acetate, dimethyl fumarate and diroximel fumarate).

7.7 Overall, the PBAC considered the single-step indirect treatment comparison versus ofatumumab to be the most robust and most compelling evidence to assess the comparative effectiveness of ublituximab to both ofatumumab and the alternative therapies. The Committee considered that both the ublituximab trials (ULTIMATE I/II) and ofatumumab trials (ASCLEPIOS I/II) were high quality and at low risk of bias, and also noted the common comparator of teriflunomide allowed for a single step indirect comparison. The PBAC noted the results of the indirect treatment comparisons found no statistically significant differences in annualised relapse rate ratio (RR 0.98, 95% CI 0.68, 1.40), or hazard of confirmed disability progression at either 12 weeks (HR 1.29, 95% CI 0.72, 2.30) or 24 weeks (HR 0.97, 95% CI 0.49, 1.92), and considered that overall, the available evidence likely supported a conclusion of non-inferior comparative effectiveness of ublituximab and ofatumumab.

7.8 The PBAC noted the submission made a claim of superior comparative effectiveness over fingolimod, and claims of non-inferior comparative effectiveness to ofatumumab and ocrelizumab. The PBAC recalled that in March 2024, it considered a submission for ofatumumab which sought to separate the current higher efficacy tier of RRMS DMTs into two distinct efficacy tiers. The Committee further recalled it did not support the change at that time, on the basis the clinical evidence presented did not adequately support the submission's underlying claim that ofatumumab has superior comparative effectiveness versus fingolimod, as the submission lacked direct comparative evidence and relied on a two-step indirect treatment comparison that, in its view, had substantial transitivity issues and some of the included trials had an unknown amount of bias (paragraph 7.1, ofatumumab PSD, March 2024 PBAC meeting). The PBAC noted the fingolimod trials presented (FREEDOMS I/II) to inform the ublituximab submission's claim of superior comparative effectiveness over fingolimod was the same as in the ofatumumab submission, including the reliance on the same teriflunomide bridging studies (TEMSO and TOWER) it had considered to be at a high risk of bias for the two-step indirect comparison, and considered therefore the comparison of ublituximab and fingolimod suffered from the same inherent uncertainties and weaknesses. The PBAC noted the comment and statistical analysis regarding the impact of the potential bias on the comparison (paragraph 6.45 refers).

In drawing its conclusions, the PBAC took into account the statistical analyses and associated comments regarding the potential bias on the comparison.

7.9 The PBAC also noted the submission presented an additional network meta-analysis (NMA) and agreed with the ESC that the NMA presented in the current submission (ICER 2024) did not appear to provide additional certainty to inform a claim of superiority than the NMA used to support the similar claim for ofatumumab in March 2024 (Samjoo 2023) i.e. given the consistently overlapping 95% confidence intervals, these analyses did not support a conclusion of superiority for ublituximab over fingolimod (paragraph 6.49).

7.10 With respect to the analyses and clinical claim of non-inferior comparative effectiveness versus ocrelizumab, the PBAC considered the two-step indirect treatment comparison via interferon beta 1-a was also inherently uncertain given the risk of bias concerns with the bridging trial of teriflunomide and interferon beta-1a (TENERE). However, the Committee considered that as the comparison was used to support a claim of non-inferiority (rather than superiority), the evidence tended to be more supportive for such a claim but still included substantial uncertainty.

7.11 Given its view on the comparative effectiveness of ublituximab to the nominated comparators of fingolimod, ofatumumab and ocrelizumab, the PBAC recalled it had considered a submission for ofatumumab for RRMS in March 2024 that made a claim of superior comparative effectiveness over fingolimod and requested the formation of a third ('mid') efficacy tier in RRMS and that it did not accept either of those claims/requests. The PBAC also recalled that when it first considered ofatumumab in March 2021, its recommendation established relativities of non-inferiority of ofatumumab to the other higher efficacy tier drugs established when it first considered ofatumumab for RRMS in March 2021 (paragraph 7.1, ofatumumab PSD, March 2021 PBAC meeting). Overall, the PBAC considered it was reasonable to conclude that, given its view on the comparative effectiveness of ublituximab and ofatumumab, ublituximab was also likely to be of non-inferior comparative effectiveness to the other therapies in the higher efficacy tier, including ofatumumab, ocrelizumab, fingolimod, cladribine, ozanimod, natalizumab and alemtuzumab.

7.12 The PBAC noted the submission made a claim of non-inferior comparative safety to ofatumumab, fingolimod and ocrelizumab. The Committee considered the safety data presented indicated similar rates of adverse events between therapies, and whilst the adverse event profiles of these therapies differ, considered overall that the submission claim of non-inferior comparative safety was likely to be reasonable.

7.13 The PBAC noted the submission presented a weighted cost minimisation approach (CMA) based on proportional replacement of fingolimod (24%), ofatumumab (18%) and ocrelizumab (58%), with an additional [redacted]% premium requested over fingolimod given the claim of superior comparative effectiveness. The PBAC considered this approach was inconsistent with recent previous recommendations for RRMS DMTs which have been based on a CMA to the least costly alternative therapy (including

ofatumumab). Given its view on the clinical claim of superior comparative effectiveness versus fingolimod not being adequately supported, the PBAC considered a price premium over fingolimod was not justified. Furthermore, the PBAC considered there was no clear population identified for whom ublituximab is a suitable therapy where fingolimod, ofatumumab, ocrelizumab or the other alternatives are not, and as a result the PBAC did not support the rationale for the weighted pricing approach. Therefore, the PBAC considered it was appropriate for the CMA to be conducted over two years versus the least costly alternative using approved ex-manufacturer prices, with costs based on the equi-effective doses recommended in paragraph 7.4 above, and that cost of other higher efficacy tier therapies could be established per the method outlined in paragraph 7.4 to establish the least costly alternative therapy. The PBAC also considered the CMA should account for administration and pre-medication costs as outlined in the CMA presented in the evaluation, where relevant.

7.14 The PBAC considered the market share approach used in the submission and noted that the utilisation and financial expenditure of ublituximab will be primarily determined by the least-costly alternative RRMS therapies substituted. The PBAC noted that the base case resulted in a net save arising from the weighted CMA approach to derive the price of ublituximab and the assumed rates of substitution of fingolimod, ofatumumab and ocrelizumab, but considered the estimates should be based on the equi-effective doses outlined in 7.4. The Committee also noted the estimates were based on published prices of these agents, where such Special Pricing Arrangements exist. The PBAC also considered that, whilst there may be some limited substitution from lower tier agents, the listing of ublituximab would not materially alter the nature of the RRMS market. Overall, the Committee considered that, if listed on a cost minimisation basis with the least costly alternative higher efficacy tier therapy, that the listing would likely be cost neutral or modestly cost saving to the PBS, as it would effectively only replace therapies that are of equivalent cost or more expensive, and the substitution of lower cost, lower tier therapies would be very low.

7.15 The PBAC advised that, under section 101(3BA) of the *National Health Act 1953* ublituximab should be treated as interchangeable with ofatumumab, ocrelizumab, fingolimod, ozanimod, cladribine, natalizumab and alemtuzumab.

7.16 The PBAC advised that ublituximab is not suitable for prescribing by nurse practitioners, consistent with other RRMS DMT listings.

7.17 The PBAC recommended that the Early Supply Rule should not apply as it cannot currently be applied to Section 100 Highly Specialised Drugs (Public and Private Hospitals) listings.

7.18 The PBAC considered the context in which RRMS DMTs are listed on the PBS is important. The Committee noted that in other jurisdictions, treatment algorithms are published that direct prescribers towards a more limited list of therapies under certain

clinical scenarios (such as the NICE published algorithm from 2023[5]), while the PBS has no such restrictions and allows prescribers and patients the flexibility to select from any available therapy for first line treatment, including with higher efficacy (and higher cost) therapies and to move to any other available therapy if sustained progression of disability or intolerance occurs. The PBAC considered its preference would be for this flexibility to remain in place, however also recalled that substantial price disparity between the RRMS DMTs has developed over time as older therapies are subject to pricing policies and as generics and biosimilars enter the market. The Committee considered it would be informative to better understand how these therapies are being used on the PBS, with a potential view to a further review to ensure the listings and therapeutic relativities remain consistent with the contemporary evidence base.

7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ublituximab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the existing alternative therapies, or not expected to address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initiation therapy

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
UBLITUXIMAB					
Ublituximab 150mg/6mL injection, 1 x 6mL vial	NEW S100 Public (HB)	4	4	0	Briumvi
Ublituximab 150mg/6mL injection, 1 x 6mL vial	NEW S100 Private (HS)	4	4	0	Briumvi
Restriction Summary [new variation of 9523] / Treatment of Concept: [new variation of 9523]					
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (Streamlined) [NEW]					
Authority type: ☒ Non-complex Authority Required (non-CAR)					

[5] https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf

Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Multiple sclerosis
Treatment phase: Initial treatment
Clinical criteria:
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; **OR**
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition
AND
Clinical criteria:
Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition
AND
Clinical criteria:
Patient must be ambulatory (without assistance or support)
AND
Treatment criteria
Must be treated by a neurologist
Prescribing instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

Continuation therapy

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
UBLITUXIMAB					
Ublituximab 150mg/6mL injection, 1 x 6mL vial	NEW S100 Public (HB)	3	3	0	Briumvi
Ublituximab 150mg/6mL injection, 1 x 6mL vial	NEW S100 Private (HS)	3	3	0	Briumvi
Restriction Summary [new variation of 9635] / Treatment of Concept: [new variation of 9635]					
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (Streamlined) [NEW]					
Authority type: ☒ Non-complex Authority Required (non-CAR)					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Multiple sclerosis					
Treatment phase: Continuation treatment					
Clinical criteria:					

Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not show continuing progression of disability while on treatment with this drug
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition
AND
Clinical criteria:
Patient must have demonstrated compliance with, and an ability to tolerate this therapy
AND
Treatment criteria
Must be treated by a neurologist

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.