

5.13 OFATUMUMAB, Injection 20 mg in 0.4 mL single use pre-filled pen, Kesimpta[®], Novartis Pharmaceuticals Australia Pty Ltd

1 Purpose of Application

- 1.1 The submission requested a General Schedule, Authority Required (STREAMLINED) listing for ofatumumab (OFA) for treatment of relapsing-remitting multiple sclerosis (RRMS). This is the first submission for ofatumumab in RRMS.
- 1.2 The listing is requested on a cost-minimisation basis to fingolimod, as a reference comparator for the nominated comparators fingolimod, cladribine, ocrelizumab, and natalizumab.
- 1.3 Table 1 presents key components of the clinical issue addressed by the submission.

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

Component	Description
Population	Patients with relapsing forms of multiple sclerosis
Intervention	Ofatumumab 20mg SC monthly, following initial doses at week 0, 1, 2 and week 4
Comparator	Main comparators are high efficacy DMTs: fingolimod, ocrelizumab, natalizumab, cladribine. Other and near market comparators are also considered
Outcomes	ARR; proportion (%) free from relapse; 3- and 6-month confirmed disability progression/worsening; and safety (any adverse event)
Clinical claim	In patients with relapsing forms of multiple sclerosis, ofatumumab is non-inferior to fingolimod, ocrelizumab, natalizumab and cladribine with respect to efficacy and safety

Source: Table 1.1, p18 of the submission.

ARR = annualised relapse rate; DMT = disease modifying therapy; SC = subcutaneous

- 1.4 The key ofatumumab and many of the comparator trials included patients with relapsing forms of MS (RMS), including RRMS and a small number of patients with secondary progressive MS (SPMS). The submission requested listing only for patients with RRMS.

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Ofatumumab					Kesimpta, Novartis
20mg/0.4ml injection (pen device) initial	4	4	0	Published: ^a \$8,394.34 Effective: ^b \$	
20mg/0.4ml injection (pen device) continuing	1	1	5	Published: ^a \$2,178.85 Effective: ^b \$	
Initial Restriction					
Episodicity:	Chronic				
Severity:	Nil				
Condition:	Multiple sclerosis				
PBS Indication:	Multiple sclerosis				
Treatment phase:	Initial				
Restriction:	<input checked="" type="checkbox"/> Streamlined				
Clinical criteria:	<p>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR</p> <p>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</p> <p>The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND</p> <p>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</p> <p>Patient must be ambulatory (without assistance or support).</p> <p>Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical record.</p>				
Administrative Advice:	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>				
Continuing restriction					
Episodicity:	Chronic				
Severity:	Nil				
Condition:	Multiple sclerosis				
PBS Indication:	Multiple sclerosis				
Treatment phase:	continuing				
Restriction:	<input checked="" type="checkbox"/> Streamlined				
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND</p> <p>Patient must not show continuing progression of disability while on treatment with this drug, AND</p> <p>The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND</p> <p>Patient must have demonstrated compliance with, and an ability to tolerate this therapy.</p>				

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Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
Grandfathering restriction	
Episodicity:	Chronic
Severity:	Nil
Condition:	Multiple sclerosis
PBS Indication:	Multiple sclerosis
Treatment phase:	continuing
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient, AND Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition AND Patient must have received treatment with this drug for this condition prior to [PBS listing date], AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must be ambulatory (without assistance or support). Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical record. AND Patient must not show continuing progression of disability while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Source: Tables 1.8 to 1.11, pp36-41 of the submission.

^a Special Pricing Arrangement (SPA) is requested for listing of ofatumumab on the PBS – to be discussed with the Pricing Section following PBAC recommendation.

^b The proposed Effective price is equivalent to the fingolimod price, after adjusting for first dose monitoring requirements (i.e. continuous ECG)

- 2.1 A Special Pricing Arrangement (SPA) was requested for listing ofatumumab.
- 2.2 The submission stated that all patients initiating ofatumumab were required to follow a set titration schedule consisting of four injections in the first month (week 0, 1, 2 and week 4). This covered two months of treatment, with monthly injections starting after the fourth injection (i.e. fifth dose at week 8). The maintenance phase consists of monthly subcutaneous (SC) injections, with one pack and five repeats covering a six-month treatment duration. A monthly maintenance dosing frequency was not consistent with the pivotal clinical trials in which patients were treated with an injection every four weeks. This has implications for the economic evaluation and financial estimates. The Pre-Sub-Committee Response (PSCR) reiterated the

submission argument that clinicians would be influenced by the dosing information in the Product Information (PI). The ESC noted that the TGA Delegate had requested the ACM provide advice on, the patient population studied, dose and indication sought and the final dosing regimen was not yet available. The Pre-PBAC Response noted that the Product Information was in the final stages of approval and indicated the PI would include a once monthly (rather than once every four weeks) dosing regimen.

- 2.3 The requested PBS restrictions were narrower than the presented evidence and proposed TGA indication (RRMS only rather than relapsing MS [RMS], which may include patients with active secondary progressive MS [SPMS]).
- 2.4 The proposed initial therapy and continuing restrictions for ofatumumab were same as the current PBS restrictions for fingolimod and ocrelizumab. The submission also requested a grandfather restriction for a planned product familiarisation program and estimated approximately < 500 patients would be enrolled.

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

3 Background

Registration status

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Round 1 Clinical Evaluation Report (CER), Delegate's Overview and ACM Advice were available.

4 Population and disease

- 4.1 Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system characterised by inflammation, demyelination and axonal/neuronal destruction, leading to severe disability. MS is characterised by plaques (or lesions) displaying demyelination of white and grey matter in the brain and spinal cord (Trapp 2008). These start with an initial inflammatory response, where lymphocytes enter the central nervous system (CNS) by crossing the blood brain barrier (Sospreda 2005; Hauser 2006). Demyelination results in a progressive loss of structure and function of neurons due to impaired propagation of action potentials across demyelinated axons (Schaeffer et al 2015).
- 4.2 The symptoms of MS vary significantly across patients depending on where in the brain or spinal cord lesions develop. Symptoms can manifest in any combination of the following five major health problems (MS Australia 2020): motor control, fatigue, cognitive difficulties, memory loss and other neurological symptoms - including vertigo, pins and needles, neuralgia and visual disturbances, continence problems, and neuropsychological symptoms - including depression.

- 4.3 There are three main forms of MS, relapsing-remitting (RR), secondary progressive (SP) and primary progressive (PP). RRMS is the most common type of MS and is estimated to affect 85% of newly diagnosed MS patients. Relapsing MS (RMS) is a term used to describe patients with RRMS and those with SPMS who still experience relapse events. Patients with RRMS experience exacerbations ('flare-ups' or relapses) of symptoms, followed by remission of symptoms. Patients with RRMS typically develop irreversible disability over time. The clinical course of MS is varied. The symptoms of MS and accumulation of disability progressively reduce the quality of life for people with MS. (Paragraph 4.2, ozanimod Public Summary Document (PSD) March 2020)
- 4.4 The submission noted that disease-modifying therapies (DMTs) should be considered in any patient with a first episode of demyelination where supporting evidence in the form of magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings strongly support a diagnosis of MS, or when relapsing-remitting MS has been diagnosed.

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

5 Comparator

- 5.1 The submission nominated "high efficacy treatment options", which included fingolimod, natalizumab, ocrelizumab and cladribine as the main comparators. The submission stated that these were nominated on the basis of their pharmacology, therapeutic relativities and relative utilisation in the MS market.
- 5.2 The submission noted that the closest clinical comparator for ofatumumab was ocrelizumab, as both are anti-CD20 monoclonal antibodies and are pharmacological analogues. The submission also noted that ocrelizumab had 21% of the market share of MS DMTs listed on the PBS in 2019-20 based on patient-years of therapy.
- 5.3 The submission stated that fingolimod also maintains a large market share at 24.7%. According to the therapeutic relativity sheets, ocrelizumab was listed based on a cost-minimisation to fingolimod. Other therapies also listed based on a cost-minimisation to fingolimod include cladribine and alemtuzumab. Alemtuzumab was also considered to be non-inferior to natalizumab. The submission expected all of these therapies to be replaced by ofatumumab. In practice, ofatumumab could replace any of the PBS-listed DMTs for RRMS, however the extent to which this may be expected to occur may vary.
- 5.4 Therapeutic relativity sheets showed that other disease modifying treatments (DMTs) (glatiramer, dimethyl fumarate, and teriflunomide) were listed based on cost-minimisation to interferon beta-1a/1b or glatiramer. Fingolimod and natalizumab were recommended based on cost-effectiveness to interferon beta-1a/1bs.
- 5.5 The submission considered that there was a distinct difference in efficacy between the DMTs which were PBS listed based on cost effectiveness compared to interferon beta-

1a/1b (fingolimod and natalizumab) or cost-minimised to fingolimod (ocrelizumab, cladribine, alemtuzumab, i.e. a 'higher' efficacy tier) or and those cost-minimised to interferon beta 1a/1b (glatiramer, dimethyl fumarate, teriflunomide, i.e. a 'lower' efficacy tier).

- 5.6 The submission therefore referred to fingolimod and DMTs that were cost-minimised to fingolimod as 'high efficacy' treatments. The submission noted that this is consistent with terminology used by the ESC in the evaluation of the PBAC application for ocrelizumab in July 2017 (Ocrelizumab PSD July 2017).
- 5.7 Under Section 101(3B) of the *National Health Act (1953)*, the PBAC cannot recommend listing a therapy that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy and/or reduction in toxicity. The submission presented direct evidence demonstrating superior comparative efficacy versus teriflunomide (a lower tier drug). On that basis, it may be reasonable to conclude that ofatumumab is also superior to other DMTs in the same efficacy tier as teriflunomide, including interferon beta-1a/1b (SC and IM presentations), peginterferon beta-1a, glatiramer acetate and dimethyl fumarate. On that basis, a comparison to the higher efficacy tier drugs may be reasonable.
- 5.8 Whilst the indirect comparisons with both higher tier drugs (fingolimod, natalizumab, alemtuzumab, ocrelizumab and cladribine) and lower tier drugs (interferon beta-1a) had numerous issues due to the multi-step indirect comparison approach and issues with some bridging clinical trials, the evidence presented likely supported a claim of non-inferior comparative efficacy to these higher tier drugs.
- 5.9 The submission did not include alemtuzumab as a main comparator as it represented only 1.1% of the market for all PBS-listed DMTs and therefore unlikely to be replaced by ofatumumab to any substantial amount. Though this was an insufficient reason to exclude consideration of alemtuzumab, the conclusion that replacement would make up a small proportion of use was reasonable. Additionally, though alemtuzumab was not nominated as a main comparator, a clinical comparison against alemtuzumab was still included, and alemtuzumab scripts were assumed to be replaced by a listing of ofatumumab in the financial estimates.
- 5.10 Ozanimod was also considered as an additional near market comparator. The PBAC recommended ozanimod at its September 2020 intracycle meeting (Ozanimod PSD, September 2020 PBAC intracycle meeting). The PBAC considered ozanimod was a relevant alternative and potential comparator, however also considered its inclusion as a main comparator would not materially alter its view of the submission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the importance of having additional treatment options available for RRMS. The PBAC also noted the advice received from MS Australia and the Australian and New Zealand Association of Neurologists (ANZAN) that highlighted the effectiveness of ofatumumab and the benefits of having a treatment option similar to ocrelizumab that can be self-administered, particularly for rural, remote and other patients who may find it difficult to attend infusion clinics.

Clinical trials

6.3 The submission was based on two trials of ofatumumab versus teriflunomide. ASCLEPIOS I (N=927) and II (N=955) were randomised and double blinded, double dummy trials with identical trial designs. Patients were randomised 1:1 to receive either ofatumumab 20 mg SC injections every 4 weeks (after initial loading regimen of three weekly 20 mg doses in the first 14 days and one in Week 4) or teriflunomide 14 mg orally once daily. Patients were followed up for two and a half years (30 months).

6.4 The submission was also based on 20 trials serving as evidence for the nominated comparators, bridging comparators for the multi-stepped indirect comparison and additional comparators (i.e. alemtuzumab and ozanimod).

6.5 For the nominated comparators in RMS/RRMS, the comparator trials included:

- two interferon-beta 1-a controlled trials for ocrelizumab (OPERA I/II);
- two placebo controlled trials (FREEDOMS I and FREEDOMS II) and one interferon beta-1a controlled trial (TRANSFORMS) for fingolimod;
- one placebo controlled trial for cladribine (CLARITY); and
- one placebo controlled trial for natalizumab (AFFIRM).

6.6 For the bridging comparators to inform the indirect comparison, the bridging comparator trials include:

- three placebo controlled trials for interferon beta-1a (MSCRG, PRISMS and BRAVO); and
- two placebo controlled trials (TEMPO and TOWER); and one interferon beta-1a controlled trial (TENERE) for teriflunomide.

- 6.7 Additionally, even though they were not nominated comparators, the submission identified the following trials for other and near market comparators which formed part of the multistep indirect comparison:
- three interferon beta-1a controlled trials for alemtuzumab (CAMSS223, CARE-MSI and CARE-MSII);
 - two interferon beta-1a controlled trials for ozanimod (SUNBEAM and RADIANCE); and
 - two placebo controlled trials for dimethyl fumarate (DEFINE and CONFIRM).
- 6.8 The PBAC has previously considered all of the included studies for all of the nominated, bridging and supplementary comparators.
- 6.9 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ofatumumab trials		
ASCLEPIOS I/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).	December 2019:
	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)	December 2019:
	Hauser, S. L., et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis.	NEJM. 2020; 383(6): 546-557
Ocrelizumab trials		
OPERA I/II	Hauser, S. L., et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis.	NEJM. 2017; 376(3): 221-234.
Fingolimod trials		
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 NEJM. 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.
TRANSFORMS	Cohen, J. A., et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis.	NEJM. 2010; 362(5): 402-415.
Cladribine trial		
CLARITY	Giovannoni, G., et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis.	NEJM. 2010; 362(5): 416-426
Natalizumab trial		
AFFIRM	Polman, C. H., et al. (2006). A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis.	NEJM. 2006; 354(9): 899-910.
Interferon beta 1a trials		
MSCRG	Jacobs, L. D., et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG).	Annals of Neurology. 1996; 39(3): 285-294
PRISMS	Ebers. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group.	Lancet. 1998; 352(9139): 1498-1504
BRAVO	Vollmer, T. L., et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis.	Journal of Neurology. 2014; 261(4): 773-783
Teriflunomide trials		
TEMSO	O'Connor, P., et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis.	NEJM. 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.	The Lancet. 2014; Neurology 13(3): 247-256

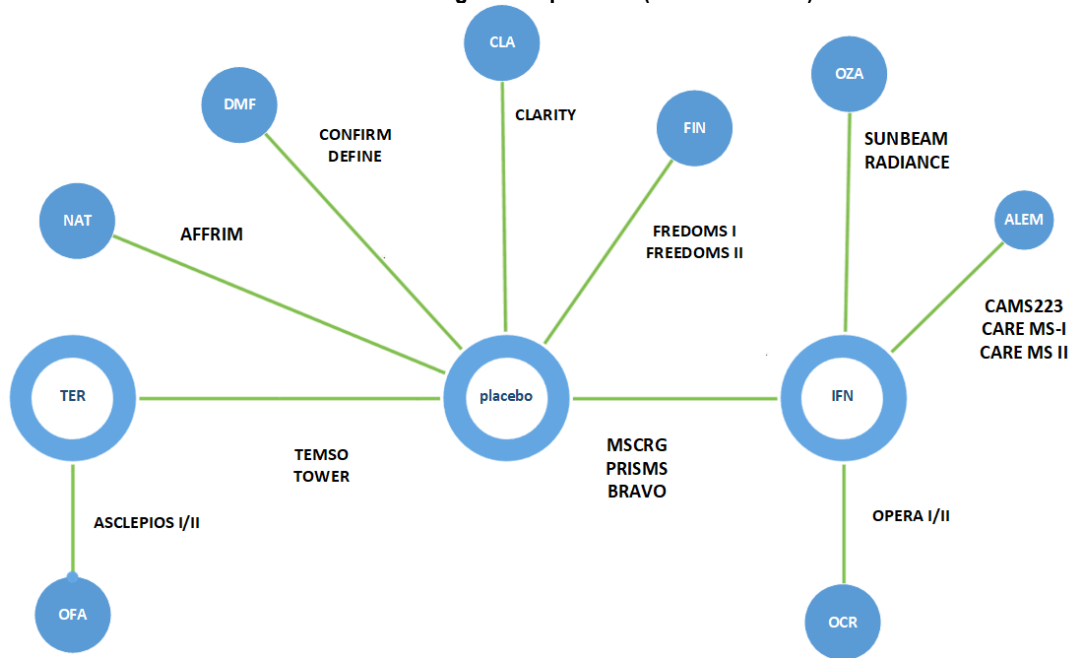
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Trial ID	Protocol title/ Publication title	Publication citation
TENERE	Vermersch, P., et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: A randomised, controlled phase 3 trial.	Multiple Sclerosis Journal. 2014; 20(6): 705-716
Alemtuzumab trials		
CAMS223	Coles, A. J., et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis.	NEJM. 2008; 359(17): 1786-1801
CARE-MSI	Cohen, J. A., et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial.	Lancet. 2012; 380 (9856): 1819-1828.
CARE-MSII	Coles, A. J., et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial.	Lancet. 2012; 380 (9856): 1829-1839.
Ozanimod trials		
SUNBEAM	Comi, G., et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial.	Lancet. 2019; Neurology 18(11): 1009-1020
RADIANCE	Cohen, J. A., et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial	Lancet. 2019; Neurology 18(11): 1021-1033
Dimethyl fumarate trials		
DEFINE	Gold, R., et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis.	NEJM. 2012; 367(12): 1098-1107
CONFIRM	Fox, R. J., et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis.	NEJM. 2012; 367(12): 1087-1097

Source: Table 2.7, pp52-53 of the submission. NR = not reported

- 6.10 The trials were used to inform multi step comparisons of ofatumumab versus fingolimod, cladribine, and natalizumab via placebo and the bridging comparator teriflunomide (ofatumumab versus teriflunomide versus placebo versus fingolimod, cladribine, natalizumab or dimethyl fumarate).
- 6.11 The trials were also used to inform multi step comparisons versus ocrelizumab ozanimod and alemtuzumab via teriflunomide and interferon beta 1a (ofatumumab versus teriflunomide versus interferon beta 1a versus ocrelizumab, ozanimod or alemtuzumab).
- 6.12 Figure 1 presents an illustration of the submission's indirect comparison network including all trials of all main, bridging and supplemental comparators.

Figure 1: Network of RCTs - Full network including all comparators (main and other)



Source: Figure 2.3, p59 of the submission.

ALEM = alemtuzumab; CLA = cladribine; DMF = dimethyl fumarate; FIN= fingolimod; IFN = interferon beta-1a; NAT = natalizumab; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; TER = teriflunomide

6.13 Despite being selected for inclusion, neither TRANSFORMS (fingolimod versus interferon beta-1a) nor TENERE (teriflunomide versus interferon beta-1a) were included in the multistep indirect comparison but were included only as a sensitivity analysis. The reason for this appeared to be because TENERE did not report CDP as an outcome, and the randomised phases were limited to 52 weeks and 48 weeks for TRANSFORMS and TENERE, respectively. However, it was noted that TOWER (teriflunomide versus placebo), which also reported data at only 48 weeks, was included in the multistep indirect comparison.

6.14 Table 3 presents key features of the included evidence in the indirect comparison.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Ofatumumab vs. teriflunomide					
ASCLEPIOS I	927	R, DB, 30 months	Low	RMS (RRMS or SPMS) (94% RRMS)	ARR, 3/6 month CDP*, proportion relapse free
ASCLEPIOS II	955	R, DB, 30 months	Low	RMS (RRMS or SPMS) (94% RRMS)	
Teriflunomide versus placebo (bridging comparison)					
TEMPO	1088	R, DB, 96 weeks	High	RMS (RRMS, SPMS, or PRMS) (91% RRMS)	ARR, proportion relapse free
TOWER	1169	R, DB, 48+ weeks	High	RMS (RRMS, SPMS, or PRMS) (97% RRMS)	
Placebo versus Fingolimod					
FREEDOMS I	1272	R, DB, 24 months	Low	RRMS	ARR, 3/6 month CDP, proportion relapse free
FREEDOMS II	1083	R, DB, 24 months	Low	RRMS	
Placebo versus cladribine					
CLARITY	1326	R, DB, 96 weeks	Low	RRMS	ARR, 3/6 month CDP, proportion relapse free
Placebo versus natalizumab					
AFFIRM	942	R, DB, 2 + years	Low	RRMS	ARR, 3/6 month CDP, proportion relapse free
Placebo versus DMF					
CONFIRM	1430	R, DB (except vs GA), 2 years	High	RRMS	ARR, 3/6 month CDP, proportion relapse free
DEFINE	1237	R, DB, 2 years	High	RRMS	
Placebo versus IFN (Bridging comparison)					
MSCRG	301	R, DB, 2 years	Unknown	RMS (not chronic-progressive MS)	ARR, 3/6 month CDP, proportion relapse free
PRISMS	560	R, DB, 2 years	Low	RRMS	
BRAVO	1331	R, OL, 2 years	Low	RRMS	
Ocrelizumab versus IFN					
OPERA I	821	R, DB, 96 weeks	Low	RMS (not PPMS)	ARR, 3/6 month CDP, proportion relapse free
OPERA II	835	R, DB, 96 weeks	Low	RMS (not PPMS)	
Alemtuzumab versus IFN					
CAMMS223	334	R, OL, 3 years	High	RRMS	ARR, 3/6 month CDP, proportion relapse free
CARE-MS1	581	R, OL, 2 years	High	RRMS	
CARE-MS-2	840	R, OL, 2 years	High	RRMS	
Ozanimod versus IFN					
SUNBEAM	1346	R, DB ≥ 12 months	Low	RMS	ARR, 3/6 month CDP, proportion relapse free
RADIANCE	1313	R, DB, 24 months	Low	RMS	

Source: Table 4.1, p25 of Technical document 5. GA = glatiramer acetate; IFN = interferon; MS = multiple sclerosis; NR = not reported; OL = open label; PPMS = primary progressive multiple sclerosis; PRMS = progressive-relapsing multiple sclerosis; R = randomised; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis
*the ASCLEPIOS I/II trials and the submission called this confirmed disability worsening (CDW)

6.15 Overall, the risk of bias of the comparator trials varied greatly. The TEMPO trial comparing teriflunomide to placebo had low risks of selection and performance bias (adequate randomisation, and allocation concealment) but had high risk of detection bias (as relapse outcomes identified by a blinded assessor had to be confirmed by unblinded treating neurologist, meaning that the assessment was effectively

unblinded), had unknown risk of attrition bias, high risk of reporting bias and high risk of other biases. The TOWER trial had a similar assessment of risk of bias except it had an unknown risk of detection bias, a high risk of attrition bias and a low risk of reporting bias.

- 6.16 Given that TEMSO and TOWER were critical in the submission’s multi-step indirect comparison (serving as a bridging comparator from teriflunomide to placebo, to allow comparisons with ocrelizumab, fingolimod, cladribine and natalizumab) a high risk of bias in these trials may limit the interpretability of the submission’s indirect comparisons.
- 6.17 The submission inappropriately assumed that the intramuscular (IM) and subcutaneous (SC) forms of interferon beta-1a were comparable and combined all interferon beta-1a studies irrespective of how it was administered in their indirect analysis and network meta-analysis. While it was noted that SC interferon beta-1a (tradenname Rebif) was listed on the PBS based on a cost minimisation to the IM interferon beta-1a (tradenname Avonex) according to the therapeutic relativity sheets, it may not have been appropriate to combine all interferon beta-1a trials without any regard for the route of administration and regimen. However, the comparisons against fingolimod, the reference comparator for the cost-minimisation did not rely on interferon beta 1a evidence in the multistep indirect comparison.

Comparative effectiveness

- 6.18 Table 4 presents the results of annualised relapse rate (ARR) in the ASCLEPIOS I and II trials.

Table 4: Results of annualised relapse rates in ASCLEPIOS I & II (ITT)

Treatment	N	Adjusted ARR (95%CI) ^a	Rate reduction	ARR ratio (95%CI) ^a	P value
ASCLEPIOS I					
ofatumumab	454	0.11 (0.09,0.14)	50.5%	0.495 (0.374, 0.654)	<0.001
teriflunomide	452	0.22 (0.18,0.26)			
ASCLEPIOS II					
ofatumumab	469	0.11 (0.08,0.13)	58.5%	0.415 (0.308, 0.559)	<0.001
teriflunomide	469	0.25 (0.21,0.30)			
Pooled^b					
ofatumumab	923	0.11 (0.09,0.13)	54.0%	0.460 (0.38, 0.57)	<0.001
teriflunomide	921	0.24 (0.21,0.27)			

Source: Table 2.36, p148 of the submission. ARR = annualised relapse rate; CI = confidence interval; ITT = intention to treat

Values in bold indicate statistically significant differences

^a Obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd enhancing lesions and the patient’s age at baseline as covariates. The natural log of the time-in-study was used as offset to annualize the relapse rate

^b Obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for study, region, treatment, and treatment by study interaction as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesion and age at baseline as covariates. The natural log of the time-in-study was used as offset to annualize the relapse rate

- 6.19 In the ASCLEPIOS I/II studies and pooled results, ofatumumab was associated with statistically significant improvements in ARR compared to teriflunomide.

6.20 Table 5 presents the proportion of patients free from relapse (confirmed) in ASCLEPIOS I and II.

Table 5: Proportion (%) of patients free from relapse (confirmed) (ASCLEPIOS I/II)

Trial ID	Ofatumumab			Teriflunomide			OR (95% CI) ^a , p value
	n	N	%	n	N	%	
ASCLEPIOS I	386	465	83.0	330	462	71.4	1.95 (1.43, 2.68), p<0.00001
ASCLEPIOS II	409	481	85.0	336	474	70.9	2.33 (1.70, 3.21), p<0.00001
Pooled	795	946	84.0	666	936	71.2	2.13 (1.70, 2.67), p<0.00001

Source: Table 2.39, p151 of the submission. CI=confidence interval; n=number of subjects with events; N=number of subjects in the analysis, OR = odds ratio

Values in bold indicate statistically significant differences

Number from relapse = N – patients with confirmed relapse (79 and 132 for ofatumumab and teriflunomide respectively for ASCLEPIOS I, 72 and 138 for ofatumumab and teriflunomide respectively for ASCLEPIOS III)

6.21 The results showed a statistically significant increase in the odds of being relapse free in patients randomised to ofatumumab compared to patients randomised to teriflunomide in both ASCLEPIOS I and II.

6.22 Table 7 and Table 8 presents the trial results for confirmed disease worsening (CDW) at three months and at six months in the ASCLEPIOS I and II trials. The submission noted that the OR values were the estimates of relative effect relied on in the indirect comparisons. CDW was used interchangeably with confirmed disease progression (CDP) by the submission.

6.23 The submission stated that CDW measure through changes in EDSS was analogous to CDP, which was used in the comparator trials in relapsing MS. It was noted that the definition of CDW in ASCLEPIOS I and II did not align precisely with the definition of CDP in other trials. For example, the definition of CDP in the ocrelizumab trials (OPERA I and II) compared to CDW in ASCLEPIOS I and II is presented in Table 6.

Table 6 Comparison of definition of CDP in OPERA I and II and CDW in ASCLEPIOS I and II

Definition	OPERA I and II	ASCLEPIOS I and II
Three and six month CDW/CDP definition	Increase in EDSS of <ul style="list-style-type: none"> • ≥ 1.0 point with a baseline EDSS of ≤ 5.5; or • ≥0.5 points, with a baseline EDSS of >5.5 That was sustained for at least 12 or 24 weeks.	Increase in EDSS of <ul style="list-style-type: none"> • ≥ 1.5 point, with a baseline EDSS of 0, or • ≥ 1.0 point, with a baseline EDSS of 1-5.0, or • ≥ 0.5 point, with a baseline EDSS ≥5.5 After a scheduled or unscheduled visit at which the patient fulfils the disability worsening criterion, all EDSS assessments (scheduled or unscheduled) need to also fulfil the worsening criteria until the worsening (“the event”) can be confirmed at the first scheduled visit that occurs 3-months (or 6 months) after the onset of the worsening, or later.

CDP = confirmed disease progression, CDW = confirmed disease worsening, EDSS = Expanded Disability Status Scale

Source: Tables 2.31, p125-126 and Hauser 2017

6.24 The submission considered that the criteria for measuring disease progression in the ASCLEPIOS I/II trial (i.e. CDW) was the most stringent of the relapsing MS trials, with the addition level of a 1.5 point increase in patients with the lowest disability levels

(i.e. EDSS =0 at baseline). The inclusion of the additional criterion, while more sensitive, was not inherently conservative. Since it may potentially capture disease progression that would not be captured in the comparator trials, this may have led to an increased number of worsening/progression events that may affect the comparability of the trials. The submission’s assumption that these distinct definitions of worsening/ progression can be compared may not be reasonable. The submission’s supplementary network meta-analysis included sensitivity analyses where the definitions of CDP were aligned across the trials.

6.25 Unless otherwise noted, reference to CDW in ASCLEPIOS has been changed in this document to CDP.

Table 7: 3-month CDP in the ASCLEPIOS I/II trials (24 months)

Treatment	n/N	(%)	Risk reduction	Hazard ratio (95%CI) ^a P value	OR (95% CI) P value
ASCLEPIOS I					
ofatumumab	45*/465	9.7	34.8%	0.652 (0.445, 0.957) p=0.029	0.67 (0.45, 1.01) p=0.06
teriflunomide	63/459	13.7			
ASCLEPIOS II					
ofatumumab	43/479	9.0	34.0%	0.660 (0.447, 0.974) p=0.036	0.65 (0.43, 0.98) p=0.04
teriflunomide	62/472	13.1			
pooled					
ofatumumab	88/944	9.3	34.4%	0.656 (0.499, 0.862) P=0.002	0.66 (0.50, 0.89) p=0.005
teriflunomide	125/931	13.4			

Source: Table 2.40, p152 and Table 2.42, p155 of the submission. CI = confidence interval

Values in bold indicate statistically significant differences

^a Results of treatment comparison obtained from a Cox regression adjusted for study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate. Statistical test uses significance (2-sided) level at 0.04875 between treatments according to the multiplicity procedure.

*The submission table included the number 46/465 instead of 45/465. This number did not fit with the numbers of the pooled results, and was changed during the evaluation to be consistent with Table 7.4.4 of the TGA Clinical Evaluator’s Report.

Table 8: 6-month CDP in the ASCLEPIOS I/II trials (24 months)

Treatment	n/N	(%)	Risk reduction	Hazard ratio (95%CI) ^a P value	OR (95% CI) P value
ASCLEPIOS I					
ofatumumab	35/465	7.5	39.3%	0.607 (0.396, 0.930) p=0.022	0.62 (0.40, 0.98) p=0.04
teriflunomide	53/459	11.5			
ASCLEPIOS II					
ofatumumab	36/479	7.5	24.4%	0.756 (0.489, 1.170) p=0.209	0.75 (0.48, 1.19) p=0.22
teriflunomide	46/472	9.7			
Pooled					
ofatumumab	71/944	7.5	32.5%	0.675 (0.498, 0.916) p=0.012	0.68 (0.50, 0.94) p=0.02
teriflunomide	99/931	10.6			

Source: Table 2.41, p153 and Table 2.42, p155 of the submission.

Values in bold indicate statistically significant differences

^a Results of treatment comparison obtained from a Cox regression adjusted for study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate. Statistical test uses significance (2-sided) level at 0.04875 between treatments according to the multiplicity procedure

6.26 Though the upper bounds of confidence intervals for both the HR and OR were close to one in both endpoints in both individual trials, the pooled results indicated

statistically significant reductions in three and six month CDP for patients randomised to ofatumumab compared to patients randomised to teriflunomide.

- 6.27 Health related quality of life (HRQoL) data from ASCLEPIOS I and II were assessed using Multiple Sclerosis Impact Scale (MSIS-29) and the EuroQol 5 dimensions (EQ-5D) instruments. The MSIS-29 is a 29-item, self-administered questionnaire that includes two domains: physical and psychological. Responses were captured on a 4-point ordinal scale ranging from 1 (not at all) to 4 (extremely), with higher scores reflecting greater impact on day to day life.
- 6.28 The MSIS-29 reported statistically significant differences for physical impact in favour of ofatumumab at 12 months (difference between treatment = -2.59 [95% CI -4.54, -0.65] and -1.97 [95% CI -3.91, -0.03]) and 24 months (difference = -3.19 [95% CI -5.56, -0.082] and -3.54 [95%CI -6.05, -1.03]), for ASCLEPIOS I and II respectively, but no statistically significant difference was observed for psychological impact. For EQ-5D, a statistically significant difference was observed only at 24 months in ASCLEPIOS II favouring ofatumumab (difference = 0.03, p = 0.039). It was unclear if this difference in EQ-5D was clinically meaningful, and the lack of statistically significant difference in ASCLEPIOS I at month 24 suggests that this difference may be uncertain.
- 6.29 The TGA Round 1 CER considered that the submitted data provided adequate evidence to support efficacy of ofatumumab in treatment of RMS (.).
- 6.30 The submission presented multi-stepped indirect comparisons for the outcomes of ARR, proportion relapse-free and 3-month CDP to support their clinical claim. Table 9 presents the results of these indirect comparisons against the main comparators.

Table 9: Indirect comparison of ofatumumab versus fingolimod, cladribine and natalizumab via placebo

	Ofatumumab 20mg monthly vs placebo (Ratio/OR 95%CI) ^a	DMT vs placebo (Ratio/OR 95%CI) ^a	Ofatumumab 20mg monthly vs DMT (Ratio/OR 95%CI) ^a	P value
Fingolimod 0.5mg daily (FREEDOMS I and II)				
ARR	0.303 (0.235, 0.390)	0.477 (0.406, 0.561)	0.635 (0.470, 0.858)	0.0031
Proportion (%) relapse free	3.804 (2.620, 5.521)	2.54 (2.05, 3.17)	1.498 (0.973, 2.306)	0.0667
3-month CDP	0.475 (0.323, 0.698)	0.71 (0.55, 0.91)^b	0.669 (0.422, 1.06)	0.0870
Cladribine 3.5mg/kg (CLARITY)				
ARR	0.303 (0.235, 0.390)	0.430 (0.340, 0.540)	0.705 (0.500, 0.993)	0.0455
Proportion (%) relapse free	3.804 (2.620, 5.521)	2.52 (1.86, 3.41)	1.510 (0.934, 2.440)	0.0929
3-month CDP	0.475 (0.323, 0.698)	0.670 (0.460, 0.970)	0.709 (0.415, 1.212)	0.2087
Natalizumab 300mg IV four weekly (AFFIRM)				
ARR	0.303 (0.235, 0.390)	0.320 (0.256, 0.399)	0.947 (0.676, 1.326)	0.7507
Proportion (%) relapse free	3.804 (2.620, 5.521)	2.880 (2.180, 3.810)	1.321 (0.829, 2.104)	0.2415
3-month CDP	0.475 (0.323, 0.698)	0.550 (0.390, 0.760)^b	0.864 (0.519, 1.438)	0.5729
Ocrelizumab 600mg 24 weekly (OPERA I and II)				
ARR	0.303(0.235, 0.390)	0.405 (0.317, 0.517)	0.748 (0.526, 1.064)	0.1063
Proportion (%) relapse free	3.804 (2.620, 5.521)	3.328 (2.170, 5.103)	1.143 (0.648, 2.015)	0.6441
3-month CDP	0.475 (0.323, 0.698)	0.426 (0.276, 0.656)	1.115 (0.625, 1.99)	0.7127

Source: Tables 2.103, 2.105, 2.107 and Table 2.101, pp213-215 ARR=annualised relapse rate, CI=confidence interval; OR=odds ratio; PBO=placebo; DMT = disease modifying therapy, OFA = ofatumumab

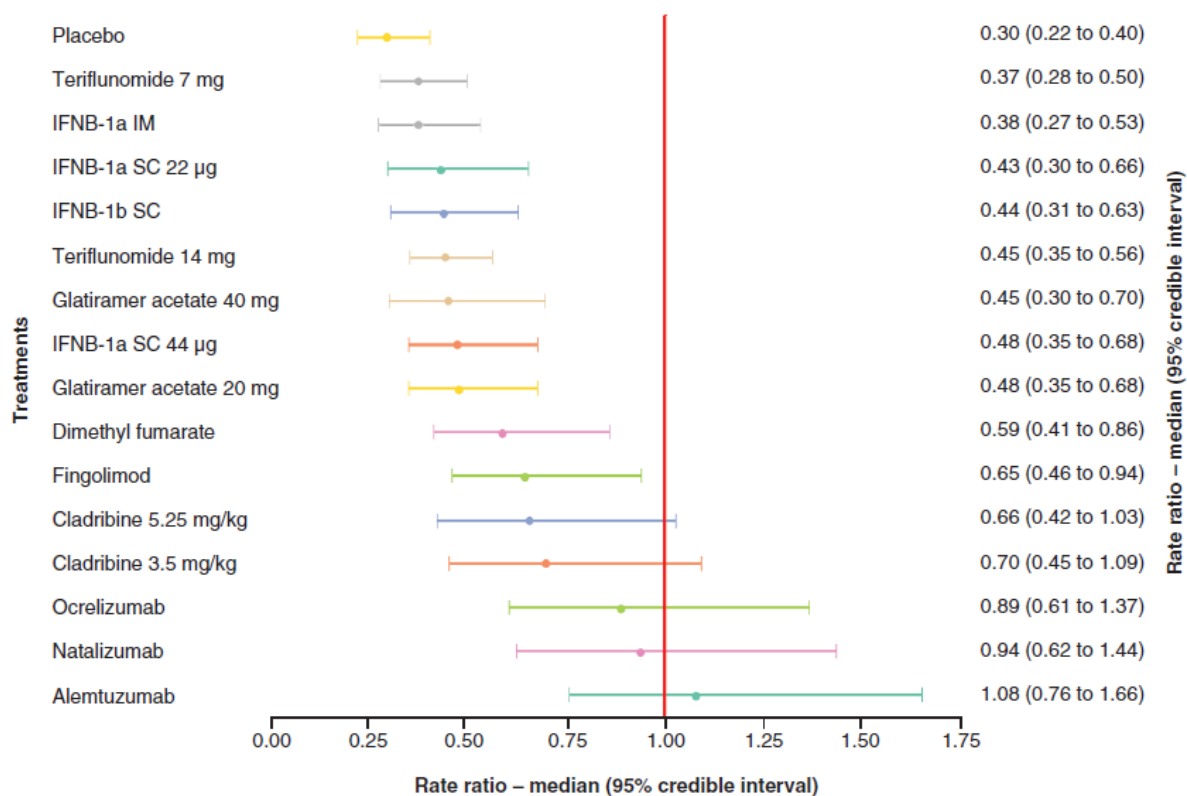
ARR < 1 favours OFA, % relapse free >1 favours OFA, 3 and 6-month CDP < favours OFA

^a Difference in ARR expressed as ARR ratio, difference in proportion relapse free and 3 month CDP expressed as OR

^b Values differed to meta-analysis reported in ocrelizumab July 2017, which reported a meta HR instead of a post hoc OR. It is unclear Text in bold indicates statistical significance.

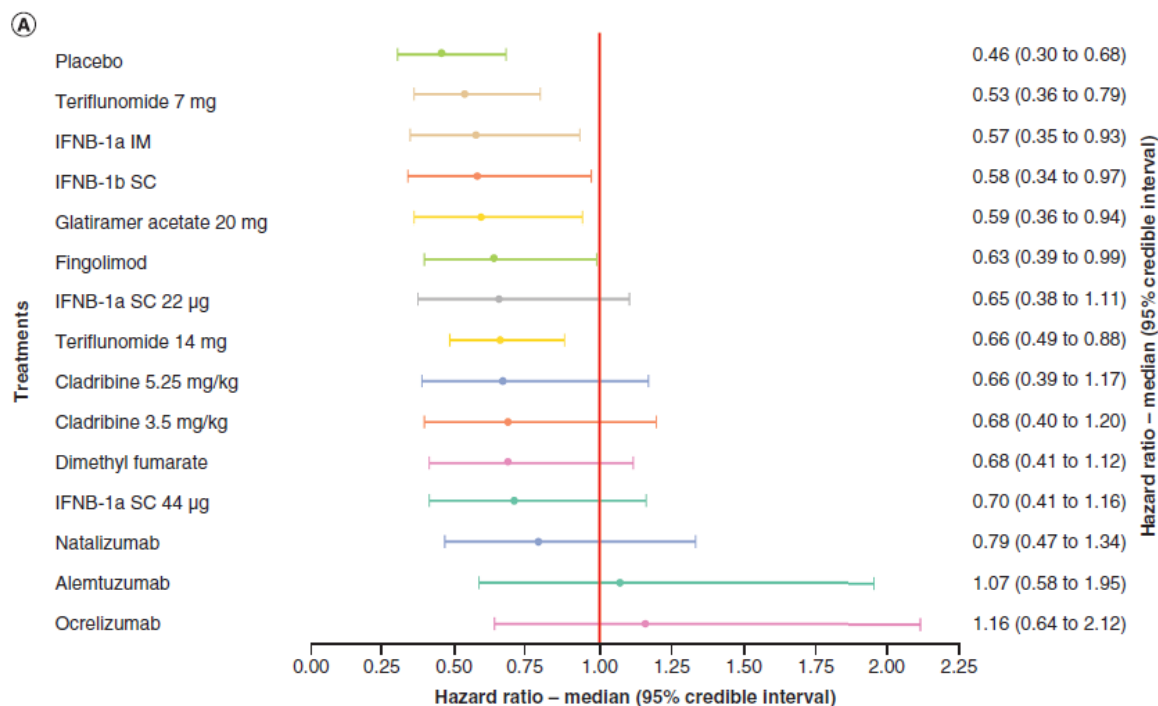
- 6.31 The results of the indirect comparisons showed statistically significant results for the outcome of ARR in the comparisons versus fingolimod and cladribine. Given the multiple steps in the indirect comparison and the differences in trial design, particularly in reference to the bridging comparator teriflunomide trials, these results must be interpreted with caution. All point estimates of the multi-step indirect comparisons favoured treatment with ofatumumab compared to treatment with fingolimod, cladribine, natalizumab or ocrelizumab (albeit with wide confidence margins), and overall there does not appear to be any evidence to suggest that treatment with ofatumumab would be inferior to fingolimod, cladribine, natalizumab or ocrelizumab.
- 6.32 The submission also presented a supplementary network meta-analysis (NMA) for the outcomes of ARR, proportion relapse-free, 3 month CDP, 6 month CDP as well as for some safety outcomes. Key results from the NMA for the outcomes of ARR, 3 month and 6 month CDP are presented in Figure 2, Figure 3 and Figure 4 below.

Figure 2: Results of NMA – (ofatumumab vs comparator) ARR



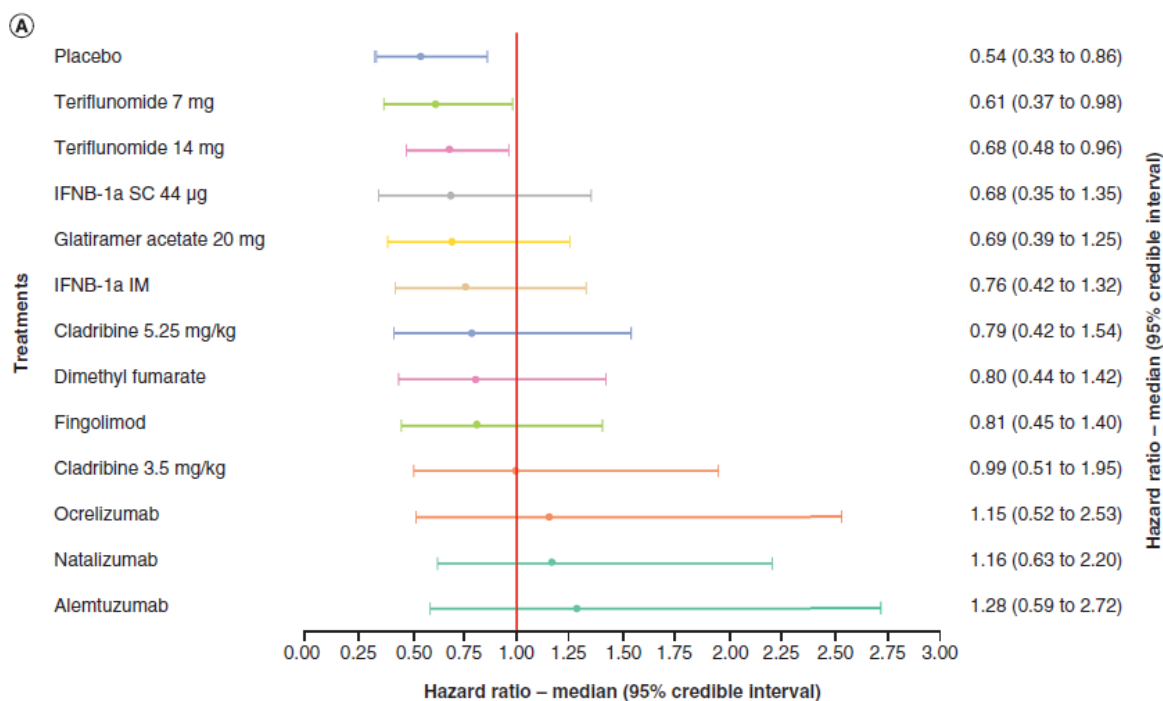
Source: Figure 2.15, p229 of the submission. IM = intramuscular; kg = kilogram; mg = milligram; SC = subcutaneous; µg = microgram

Figure 3: Results of NMA – (ofatumumab vs comparator) CDP – 3 month



Source: Figure 2.18, p233 of the submission. IM = intramuscular; kg = kilogram; mg = milligram; SC = subcutaneous; µg = microgram

Figure 4: Results of NMA – (ofatumumab vs comparator) CDP – 6 month



Source: Figure 2.23, p240. IM = intramuscular; kg = kilogram; mg = milligram; SC = subcutaneous; µg = microgram

- 6.33 The results of the NMA largely supported the results of the multi-stepped indirect comparison.
- 6.34 The PSCR acknowledged the inherent uncertainties of the multi-step indirect comparison approach but argued the results of the supplementary network meta-analysis provided additional certainty of the comparative effectiveness of ofatumumab to the nominated comparators. The ESC agreed and noted the studies included in the comparisons had overall similar designs and recruited populations and considered the plurality of comparisons and overall similarity of the results of the indirect comparisons, as well as the results of the supplementary NMA supported a conclusion that ofatumumab was likely of non-inferior comparative effectiveness to fingolimod, natalizumab, cladribine and ocrelizumab.

Comparative harms

- 6.35 Table 10 presents a summary of notable adverse event outcomes reported in ASCLEPIOS I and II.

Table 10: Notable adverse events outcomes related to the study drug in the ASCLEPIOS I/II trials

Primary system organ class	ASCLEPIOS I			ASCLEPIOS II		
	Ofatumumab 20mg N=465 n (%)	Teriflunomide 14mg N=462 n (%)	RD (95% CI)	Ofatumumab 20mg N=481 n (%)	Teriflunomide 14mg N=474 n (%)	RD (95% CI)
Patients with at least one AE	382 (82.2)	380 (82.3)	0 (-0.05, 0.05)	409 (85.0)	408 (86.1)	0 (-0.04, 0.04)
Patients with at least one Serious AE	48 (10.3)	38 (8.2)	0.02 (-0.02, 0.06)	38 (7.9)	36 (7.6)	0 (-0.03, 0.03)
Patients who discontinued due to an AEs	27 (5.8)	24 (5.2)	0.01 (-0.02, 0.04)	27 (5.6)	25 (5.3)	0 (-0.03, 0.03)
Patients who died	0 (0.0)	0 (0.0)	0(0, 0)	0 (0.0)	0 (0.0)	0(0, 0)
Gastrointestinal Disorders	104 (22.4)	135 (29.2)	-0.07 (-0.13, -0.01)	120 (24.9)	151 (31.9)	-0.07 (-0.13, -0.01)
Skin And Subcutaneous Tissue Disorders	71 (15.3)	116 (25.1)	-0.1 (-0.15, -0.05)	87 (18.1)	122 (25.7)	-0.1 (-0.15, -0.05)

Source: Tables 2.73 and 2.74 p182 and p184 of the submission; AE=adverse event; LFTs=liver function tests; SAE=serious adverse event, RD = risk difference

Risk difference calculated during the evaluation in Microsoft Excel

Text in bold denotes statistically significant differences.

- 6.36 In ASCLEPIOS I and II, a statistically significantly lower proportion of patients treated with ofatumumab reported gastrointestinal disorders and skin and subcutaneous tissue disorders compared to patients treated with teriflunomide. However, the TGA Round 1 CER considered that risk of injection reactions was higher with ofatumumab versus teriflunomide (due to differences in route of administration) and that upper respiratory tract infections and urinary tract infections were the most frequently reported types of infections in patients treated with ofatumumab. The CER also noted that long-term safety of ofatumumab in RMS was not assessed beyond 30 months.
- 6.37 The submission considered that all the injection site reactions were classified as non-serious, Grade 1 or 2, (except for 1 patient with Grade 3 in ASCLEPIOS I) and mostly

self-limiting in nature. There were no discontinuations due to injection site reactions in either treatment groups, in both ASCLEPIOS I and II.

- 6.38 The submission did not present a multistep indirect comparison for adverse event outcomes as for efficacy outcomes. Instead, naïve indirect comparisons of adverse events reported in the identified clinical trials for the nominated comparators were presented, but were difficult to interpret. The submission considered that the safety profiles for ofatumumab and the comparators were different, often related to the differences in mode of action and method of administration, and that it can be difficult to interpret and quantify AE-related outcomes when the safety profiles between drugs are dissimilar.
- 6.39 The PSCR argued that pairwise indirect comparisons could not be completed due to differences in the control/comparator arms in the clinical trials for ofatumumab and the nominated comparators and further argued a network meta-analysis for comparative safety would be limited by differences in classes of events and differences in dosing regimens between agents. The PSCR also reiterated that ofatumumab is a pharmacological analogue of ocrelizumab and it was reasonable to conclude these agents had a similar safety profile which was different but not worse than the other nominated comparators. The ESC considered the comparative safety of ofatumumab was difficult to assess due to the lack of available comparisons and different pharmacological profiles of RRMS DMTs but considered there were no specific issues in the safety data which would indicate ofatumumab had a worse safety profile than the nominated comparators.

Clinical claim

- 6.40 The submission made efficacy and safety claims against each of its nominated comparators as well as additional comparators. These claims were stated as follows.
- 6.41 With respect to efficacy:
- Ofatumumab is non-inferior to ocrelizumab, fingolimod, cladribine and natalizumab in patients with RMS; and
 - Ofatumumab is superior to teriflunomide and interferon beta-1a in patients with RMS.
- 6.42 With respect to safety:
- Ofatumumab is non-inferior to ocrelizumab in patients with RMS, with a similar safety profile; and
 - Ofatumumab is non-inferior to fingolimod, cladribine, natalizumab, teriflunomide and interferon beta-1a in patients with RMS, with a different safety profile.
- 6.43 Overall, the ESC considered the claims of non-inferior comparative efficacy against the nominated comparators of fingolimod, ocrelizumab, cladribine and natalizumab were

likely supported. However, the conclusion should be considered with some caution due to the following issues and limitations:

- all comparisons relied on older teriflunomide trials (TEMISO and TOWER), to serve as bridges between ofatumumab and the placebo controlled fingolimod, cladribine and natalizumab trials,;
- both TEMISO and TOWER were considered to have a high risk of bias;
- TOWER only included 48 week treatment duration compared to around two years for all other included trials;
- The submission inappropriately assumed that IM interferon beta-1a 30µg once weekly results were exchangeable with SC interferon beta-1a 44µg three times weekly results (which may impact the comparison with ocrelizumab); and
- The estimated comparative efficacies relied on multi-step comparisons, in the case of the ocrelizumab comparison, there were three steps.

6.44 Though teriflunomide was not a nominated comparator, the ESC considered the claim of superior efficacy of ofatumumab was well supported by the ASCLEPIOS I and II trials and the TGA clinical evaluator's consideration of effectiveness of ofatumumab versus teriflunomide.

6.45 The claim of superior efficacy versus interferon beta-1a was based on a multistep indirect comparison and therefore had the same limitations as for the comparisons with of fingolimod, ocrelizumab, cladribine and natalizumab. Additionally, it was inappropriate for the submission to have combined IM and SC interferon beta-1a, and while statistically significant differences favouring ofatumumab over interferon beta-1a were estimated for ARR (ratio = 0.399, 95% CI 0.301, 0.529) and proportion relapse free (OR = 2.212, 95%CI 1.315, 3.721) there was no statistically significant difference for 3 month CDP (OR = 0.709, 95% CI 0.435, 1.155).

6.46 Overall, though the ITC and the submission's supplementary NMA indicated non-inferior safety of ofatumumab versus the nominated comparators of ocrelizumab, fingolimod, cladribine and natalizumab, the comparability of the trial populations used in the indirect comparisons was unclear. Moreover, it was difficult to conclude non-inferior safety given the differences in route of administration of the various DMTs. It was reasonable to acknowledge that ofatumumab would have a different safety profile compared to other DMTs.

6.47 The PBAC considered that the claim of non-inferior comparative effectiveness to ocrelizumab, fingolimod, cladribine and natalizumab was reasonable.

6.48 The PBAC considered that the claim of non-inferior safety to ocrelizumab and different (but not worse) safety to fingolimod, cladribine, natalizumab, teriflunomide and

interferon beta-1a was reasonable and noted there were no specific safety signals that would indicate ofatumumab has a worse safety profile than the alternatives.

Economic analysis

6.49 The submission presented a cost-minimisation analysis against the reference comparator fingolimod. Table 11 presents the key components and assumptions of the cost minimisation analysis.

Table 11: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, ofatumumab is non-inferior ocrelizumab, fingolimod, cladribine and natalizumab. The cost of fingolimod is used in the cost-minimisation analysis based on the therapeutic relativities (i.e. ocrelizumab and cladribine were cost-minimised to fingolimod)
Therapeutic claim: safety	Based on evidence presented in Section 2, ofatumumab has a different safety profile to the main comparators. No specific adverse safety issues have been identified in the comparisons suggesting differential claims on safety
Evidence base	The therapeutic relativities are informed by indirect comparison of randomised trials in Section 2
Equi-effective doses	Ofatumumab 20mg SC every month is equivalent to fingolimod 500mcg (0.5mg) daily, over 2 years
Direct medicine costs	Treatment costs for ofatumumab and fingolimod should be the same, at equi-effective doses of ofatumumab 20 mg SC every month and fingolimod 500 micrograms (0.5mg) daily, over 2 years (after titration is complete)
Other costs or cost offsets	First dose monitoring associated with the initiation of fingolimod (i.e. continuous ECG). First SC injection for ofatumumab is administered by a healthcare professional (i.e. nurse/ doctor)

Source: Table 3.1, p277 of the submission.

- 6.50 The equi-effective doses were estimated as ofatumumab 20 mg SC every month being equivalent to fingolimod 0.5 mg daily (at steady state maintenance dosing frequency).
- 6.51 The equi-effective doses of ofatumumab compared with fingolimod were based on the recommended dosing regimens outlined in the fingolimod product information and ofatumumab draft product information.
- 6.52 The number of injections of ofatumumab was inconsistent with the ASCLEPIOS I and II trials, which had a dosing frequency of every 4 weeks (13 doses per year) as opposed to the monthly frequency (12 doses per year) as suggested by the submission. This assumption impacts the proposed equi-effective doses in favour of a higher ofatumumab price. In its consideration of ocrelizumab in July 2017 (Paragraph 6.42, Ocrelizumab July 2017 PSD), the PBAC considered it was appropriate to use the dosing intervals in the clinical trials (once every 24 weeks) rather than that in the TGA Product Information (once every six months) for establishing equi-effective dosing. An analysis assuming dosing every 4 weeks was conducted during the evaluation and is presented as a sensitivity analysis. The PSCR and Pre-PBAC Response argued that monthly dosing was the most appropriate basis for deriving the equi-effective doses as this was consistent with the draft PI and Delegate’s Overview and that clinicians would be most influenced by the PI rather than the clinical trial reports. The ESC considered that the

most appropriate basis for deriving equi-effective doses for the cost minimisation analysis was based on the dose regimen used in the clinical trials.

6.53 Based on the draft PI of ofatumumab, the first injection of ofatumumab should be performed under the guidance of a healthcare professional. Based on the fingolimod PI, fingolimod requires first dose cardiac monitoring. These costs were considered as part of the cost minimisation analysis. All other monitoring costs associated with ongoing treatment with a DMT as considered to be the same for ofatumumab and fingolimod. This was reasonable.

6.54 Table 12 presents the results of the cost minimisation analysis.

Table 12: Cost-minimisation price for ofatumumab

	Cost	Source
Fingolimod (comparator)		
Drug cost	\$ [REDACTED]	Fingolimod– 500mcg tablets × 28 (AEMP)
Packs per year	13.04	Daily administration (365.25 days/28 days)
Drug cost (annual)	\$ [REDACTED]	Drug cost × packs per years
Total monitoring cost	\$172.75	First dose cardiac monitoring - MBS 11716
Total cost over 2 years	\$ [REDACTED]	Drug cost (annual) × 2 + Total monitoring cost
Ofatumumab		
Fingolimod costs	\$ [REDACTED]	Treatment cost equivalent to fingolimod over 2 years
Administration cost (first dose)	\$38.75	First dose administration – MBS 23
Drug cost over 2 years	\$ [REDACTED]	Treatment cost minus administration costs
Injections		
Injections in year 1	14	SC Injections at week 0,1,2 and 4 (4 injections, 2 months) + monthly (10 injections, 10 months)
Injections in year 2	12	SC Injections monthly (12 months)
Injections over 2 years	26	Year 1 + Year 2
Cost per 20mg injection (AEMP) assuming dosing every month	\$ [REDACTED]	Total cost over 2 years / no. injection over 2 years (Treatment cost minus administration costs)
Sensitivity analysis – Trial-based equi-effective doses (OFA maintenance once every four weeks)		
Cost per 20mg injection (AEMP) assuming dosing every 4 weeks	\$ [REDACTED]	Include 15 doses in year 1 and 13 doses in year 2 instead of 14 and 12, respectively

Source: Table 3.3, p279 of the submission. AEMP = Australian ex manufacturer price; SC=subcutaneous; OFA = ofatumumab

6.55 This cost minimisation analysis was conducted on a time horizon of two years of treatment. This was consistent with previous RRMS cost-minimisation analyses assessed by the PBAC such as ocrelizumab (paragraph 6.43, ocrelizumab PSD July 2017) and cladribine (paragraph 5.17, cladribine PSD July 2018). However, given the increased number of injections in the first month of treatment and consequently the higher cost of the first month of treatment associated with ofatumumab, the time horizon of the cost minimisation analysis is an important consideration when cost minimising against fingolimod, which requires no specific initiation regimen.

6.56 In this context, a longer time horizon would lead to a higher price per ofatumumab script, and a shorter time horizon would lead to a lower price per ofatumumab script.

6.57 It was noted that mean treatment duration in the ofatumumab arms of the ASCLEPIOS I and II trials were 586 days and 563 days, or approximately 1.6 years and 1.5 years,

respectively. Reducing the time horizon to 1.5 years would require a lower ofatumumab cost to achieve cost-minimisation to fingolimod.

- 6.58 The proposed cost minimisation with fingolimod included offsets for first dose cardiac monitoring, which was inconsistent with the inputs for the cost-effectiveness model for fingolimod, which did not include did not attribute any costs to first-dose cardiac monitoring (Table 90 of the fingolimod submission, March 2011). Further, the ozanimod submission (March 2020) did not claim any offsets for reduced cardiac monitoring in its cost minimisation approach versus fingolimod (paragraph 6.27, ozanimod PSD, September 2020 PBAC meeting).
- 6.59 As the PBAC has previously accepted that, alemtuzumab, cladribine and ocrelizumab are non-inferior to fingolimod (natalizumab was listed on a cost-effectiveness basis with interferon beta) and the ESC considered that as there was no evidence to indicate ofatumumab is better than any of the alternatives it may be reasonable for the PBAC to consider the cost minimisation analysis should be based on (and cost no more than) the least expensive of alemtuzumab, cladribine, ocrelizumab and fingolimod.

Drug cost/patient/two years

- 6.60 Based on price per 20 mg injection (\$ [REDACTED]) times number of injections over two years (26 injections, assuming maintenance dosing every month as in submission) the cost was \$ [REDACTED].
- 6.61 The calculations of ofatumumab and fingolimod (reference comparator) costs based on inputs and assumptions from the relevant trial data, cost minimisation analysis and financial estimates are presented in Table 13. The difference between cost/patient/year for ofatumumab and fingolimod was due to differences in MBS item costs for first dose administration and monitoring.

Table 13: Drug cost per patient for proposed and comparator drugs

	Ofatumumab Trial dose and duration	Ofatumumab CMA	Ofatumumab Financial estimates	Fingolimod* Trial dose and duration	Fingolimod CMA	Fingolimod Financial estimates
Mean dose	20mg doses on weeks 0,1,2 and 4 and every 4 weeks thereafter*	20mg doses on weeks 0,1,2 and 4 and 20mg monthly thereafter		0.5mg daily	0.5mg daily	0.5mg daily
Number of injections /packs over 2 years	28 injections: 15 in year 1 13 in year 2	26 injections: 14 in year 1 12 in year 2		13.04 packs per year. 26.08 over 2 years		
Cost/ injection or tablet	\$ [REDACTED]			\$ [REDACTED]		
Cost/patient/ year	\$ [REDACTED]		\$ [REDACTED]			

Source: Table 2.25 and Table 2.26, p108 and p110 of the submission; Table 3.3, p279 of the submission; "Att_21_Section 3_Cost-min_OFA.xlsx" and "utilisation and financial estimates_ofatumumab_Nov2020.xlsx"

CMA = cost minimisation analysis; mg = milligram.

*Fingolimod is reference comparator, but not the only efficacy comparator.

Estimated PBS usage & financial implications

- 6.62 This submission was not considered by DUSC. The submission took a market share approach to estimating financial impact.
- 6.63 The submission assumed that grandfathered patients would be captured in the market share model, as ofatumumab was not expected to grow the market and patients in transitioning from a patient familiarisation program were currently treated for RRMS.
- 6.64 Table 14 presents key data sources and parameter values for the financial estimates.

Table 14: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Treatment utilisation			
Ofatumumab uptake rate	Yr 1: 6% Yr 2: 10% Yr 3: 15% Yr 4: 20% Yr 5: 20% Yr 6: 25%	Set to half of ocrelizumab uptake in first two years, following increasing trend up to 25%	Source of uncertainty, tested and reasonably explained in submission sensitivity analysis.
Switch from cladribine/alemtuzumab	Yr 1: 3% Yr 2: 6% Yr 3: 10% Yr 4: 15% Yr 5: 20% Yr 6: 22%	Assumed based on lower switching due to long term dosing regimen of these comparators.	
Scripts per year	11.59	Weighted average of 11 scripts in first year and 12 scripts in 5 subsequent years	The submission stated that the financial model template did not allow for different substitution rates at different stages of treatment and may have resulted in slight overestimation of scripts in years 1 and 2 and a slight underestimation of scripts in years 3 to 6. May also be underestimated if ofatumumab is used four weekly instead of monthly
Costs			
Ofatumumab	Initial: \$ [REDACTED] Continuing: \$ [REDACTED]	Initial script include four injections	Reasonable.
Fingolimod	\$2058.29 [Published]	Effective price known to Sponsor	
Ocrelizumab	\$8766.50	Listed on CMA basis to Fingolimod, based on a comparison of annual cost of therapy with fingolimod	
Alemtuzumab	\$10824.30		
Cladribine	\$3833.04 [Published]	Shares subsidisation caps with fingolimod. Effective price derived from supporting data provided with rebate invoices to Sponsor by Department of Health.	
Natalizumab	\$1340.68	No difference between published and effective prices.	
teriflunomide	\$511.19		
Interferon beta 1a	\$763.52		
Peg interferon beta 1a	\$893.01		
Glatiramer	\$891.54		
DMF	AEMP: \$1169.40 [Published]	Listed on CMA basis to older therapies weighted price calculated based on current market share of these therapies	

Source: Table 4.1, p282 of the submission and "Utilisation and financial estimates_ofatumumab_Nov202.xlsx" AEMP = Australian ex-manufacturer price; CMA = cost minimisation analysis; DMF = dimethyl fumarate; DPMQ = dispensed price per maximum quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.

6.65 The submission noted that in the first year of therapy, the loading dose is covered by one script and lasts for the first two months of therapy, following which 10 scripts of

continuing treatment are left in the year for initiating patients, and thus 11 total scripts. In subsequent years, there are 12 scripts of ofatumumab per year as it follows a monthly dosing regimen. The weighted average number of scripts of ofatumumab for the first 6 years of listing was calculated as 11.59 scripts per year. The dosing frequency of ofatumumab in ASCLEPIOS I and II was every four weeks, which would translate to 13 scripts per year. The submission’s assumption of 12 scripts per year was likely to be an underestimate.

6.66 Table 15 presents the submissions estimates of use and financial implications.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of ofatumumab						
Initiating scripts	1	1	1	1	1	1
Continuing scripts	2	3	4	5	6	7
Total scripts	2	3	4	5	6	7
Estimated financial implications of ofatumumab						
Cost to PBS/RPBS	\$ 8	\$ 9	\$ 10	\$ 11	\$ 12	\$ 13
Copayments	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17
Cost to PBS/RPBS less copayments	\$ 8	\$ 9	\$ 10	\$ 11	\$ 12	\$ 13
Estimated financial implications for replaced medicines						
Cost to PBS/RPBS	-\$ 14	-\$ 9	-\$ 15	-\$ 16	-\$ 11	-\$ 13
Copayments	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17
Cost to PBS/RPBS less copayments	-\$ 14	-\$ 9	-\$ 15	-\$ 16	-\$ 11	-\$ 12
Net financial implications						
Net cost to PBS/RPBS	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17
Net cost to MBS	-\$ 17	-\$ 17	-\$ 17	-\$ 17	-\$ 17	-\$ 17
Net cost to Government health budgets	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17	\$ 17

Source: Table 4.12, p289 of the submission; Tables 4.17 and 4.18, p292 of the submission; Table 4.22, p296 of the submission; Table 4.26, p299 of the submission; Table 4.33, p302 of the submission. MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 10,000 to < 20,000
- ³ 20,000 to < 30,000
- ⁴ 30,000 to < 40,000
- ⁵ 40,000 to < 50,000
- ⁶ 50,000 to < 60,000
- ⁷ 60,000 to < 70,000
- ⁸ \$20 million to < \$30 million
- ⁹ \$30 million to < \$40 million
- ¹⁰ \$50 million to < \$60 million
- ¹¹ \$70 million to < \$80 million
- ¹² \$80 million to < \$90 million
- ¹³ \$90 million to < \$100 million
- ¹⁴ \$10 million to < \$20 million
- ¹⁵ \$40 million to < \$50 million
- ¹⁶ \$60 million to < \$70 million
- ¹⁷ \$0 to < \$10 million

- 6.67 The submission estimated a total net cost to the Government health budget of \$0 to \$10M in Year 1, increasing to \$0 to < \$10M in year 6, for a total of \$30M to < \$40M over the first 6 years of listing.
- 6.68 The submission considered that the increased net cost associated with listing ofatumumab was due to the replacing of lower cost therapies such as ABCR (Avonex [IM Interferon-beta-1a], Betaferon [Interferon-beta-1b], Copaxone [glatiramer acetate] and Rebif [SC Interferon-beta-1a]), teriflunomide, and dimethyl fumarate. The submission noted that in practice this incremental cost would be incurred through any patient switching from low cost drugs to PBS-listed high efficacy DMTs. The ESC considered this was reasonable and consistent with the financial impacts of nominated comparators of the high efficacy DMTs (ocrelizumab, fingolimod, cladribine, natalizumab) that were previously considered by the PBAC.
- 6.69 The submission presented an analysis which removed substitution from ABCR and other low cost therapies. This analysis resulted in a financial impact to Government that is almost cost-neutral (at effective prices). The net financial impact decreases by approximately \$0 to < \$10M in Year 1 up to \$0 to < \$ 10M in Year 6 compared to the base case. The results of this analysis is presented in the table below.

Table 16: Impact of removing uptake of ABCR and other low cost therapies (effective prices net of copayments)

Ofatumumab	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Scripts	█ ¹	█ ²	█ ³	█ ⁴	█ ⁵	█ ⁵
Financial impact to PBS/RPBS	\$█ ⁶	\$█ ⁷	\$█ ⁸	\$█ ⁹	\$█ ¹⁰	\$█ ¹¹
Treatments displaced						
Scripts displaced	-█ ¹	-█ ¹	-█ ²	-█ ²	-█ ³	-█ ³
Financial impact to PBS/RPBS	-\$█ ⁶	-\$█ ⁷	-\$█ ⁸	-\$█ ⁹	-\$█ ¹⁰	-\$█ ¹¹
Net financial impact to PBS/RPBS	\$█ ¹²	\$█ ¹²	\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²
Cost to MBS	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²
Net cost to Government	\$█ ¹²	\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²
Difference to base case	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²	-\$█ ¹²

Source: Table 4.34 of the submission. ABCR = Avonex (Interferon-beta-1a), Betaseron (Interferon-beta-1b), Copaxone (glatiramer acetate) and Rebif (Interferon-beta-1a); MBS, Medical benefits Scheme; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

Low cost therapies includes dimethyl fumarate and teriflunomide

The redacted values correspond to the following ranges:

- ¹ 5,000 to < 10,000
- ² 10,000 to < 20,000
- ³ 20,000 to < 30,000
- ⁴ 30,000 to < 40,000
- ⁵ 40,000 to < 50,000
- ⁶ \$10 million to < \$20 million
- ⁷ \$20 million to < \$30 million
- ⁸ \$30 million to < \$40 million
- ⁹ \$50 million to < \$60 million
- ¹⁰ \$60 million to < \$70 million
- ¹¹ \$70 million to < \$80 million
- ¹² \$0 to < \$10 million

Quality Use of Medicines

- 6.70 The submission stated that injection site reaction (local) symptoms observed in clinical studies included erythema, swelling, itching and pain. Systemic injection-related reactions observed in clinical studies occurred predominantly with the first injection. Symptoms observed include fever, headache, myalgia, chills and fatigue and were predominantly (99.7%) non-serious and mild to moderate in severity.
- 6.71 The submission noted that the first injection of ofatumumab should be performed under the guidance of an appropriately trained healthcare professional. Only limited benefit of premedication with steroids, antihistamines, or paracetamol was seen in RMS clinical studies, therefore, use of premedication is not required.
- 6.72 No other quality use of medicines issues were identified in the submission.

Financial Management – Risk Sharing Arrangements

- 6.73 The submission stated that if the PBAC feels that the degree of uncertainty in these estimates warrants a Risk Sharing Arrangement, Novartis will discuss this with the Department of Health once other aspects of the submission have been agreed on.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of ofatumumab for the treatment or relapsing-remitting multiple sclerosis (RRMS). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of ofatumumab would be acceptable if it were cost minimised to the least costly therapy of either fingolimod, natalizumab, alemtuzumab, ocrelizumab, cladribine or ozanimod (the higher tier agents).
- 7.2 The PBAC considered the nominated comparator of fingolimod was reasonable, however also considered ofatumumab may substitute for a number of other RRMS therapies currently listed on the PBS.
- 7.3 Based on the results of two direct, randomised head-to-head trials (ASCLEPIOS I and ASCLEPIOS II) of ofatumumab and teriflunomide, the PBAC was satisfied that ofatumumab provides, for some patients, a significant improvement in effectiveness over teriflunomide for the purposes of Section 101 (3B) of the *National Health Act 1953*. Based on the previously determined relativities, the PBAC also considered ofatumumab provides, for some patients, a significant improvement in effectiveness over the other lower tier therapies: interferon beta-1a/1b (SC and IM presentations), peginterferon beta-1a, glatiramer acetate and dimethyl fumarate.
- 7.4 The PBAC noted fingolimod and natalizumab were recommended based on cost-effectiveness to interferon beta-1a/1bs. The PBAC further noted alemtuzumab, cladribine, ocrelizumab and ozanimod were recommended for listing on a cost minimisation basis compared to fingolimod and could also be considered alternative therapies to ofatumumab. The PBAC considered that, as no evidence was provided to demonstrate ofatumumab provided a significant improvement in efficacy and/or reduction of toxicity over these alternative therapies, it should not be more costly.
- 7.5 The PBAC considered that the equi-effective doses should be based on the dosage regimen of ofatumumab used in the clinical trials and established equi-effective doses outlined in previous PBAC decisions. The cost minimisation analysis should be conducted over two years using approved ex-manufacturer prices.
- 7.6 The PBAC noted there are numerous therapies for RRMS available on the PBS, however also noted the advice from MS Australia and the Australian and New Zealand Association of Neurologists (ANZAN) that there are no subcutaneous injectable

therapies available in the higher efficacy tier. The PBAC agreed a self-administered injectable therapy with a similar mechanism of action to ocrelizumab may be useful for some patients, particularly those in regional and remote areas who may have difficulty attending an infusion clinic.

- 7.7 The PBAC considered the requested listing should be aligned with other RRMS listings and include a grandfather restriction, which should remain in place for 12 months.
- 7.8 The PBAC noted the ASCLEPIOS I and II trials comparing ofatumumab and teriflunomide had a low risk of bias, however the comparisons with the nominated comparators relied on multi-step indirect comparisons. The comparisons with fingolimod, cladribine and natalizumab included the TEMSO and TOWER teriflunomide versus placebo trials which were older and had a high risk of bias. The comparison with ocrelizumab relied on the assumption that that IM interferon beta-1a and SC interferon beta-1a results were exchangeable. The PBAC considered that while there were uncertainties with the multi-step indirect comparison of ofatumumab to the nominated alternative therapies, that overall the plurality of analyses and included network meta-analysis supported a conclusion that ofatumumab is of non-inferior comparative efficacy compared to any of the other higher tier agents.
- 7.9 The PBAC noted that whilst it was difficult to evaluate the comparative safety of ofatumumab and the comparators due to the differences in the overall safety profiles, mechanisms of action, treatment regimens, routes of administration and other factors, the Committee considered the overall adverse event profile was likely non-inferior to ocrelizumab and comparable to that of any of the other higher tier agents and that there were no specific signals which would indicate ofatumumab is of inferior safety to these therapies.
- 7.10 The PBAC considered that the equi-effective doses should be based on the dosage regimen of ofatumumab used in the clinical trials. The cost minimisation analysis should be conducted over two years using approved ex-manufacturer prices, applying the following dosage regimen for ofatumumab and fingolimod:
- One injection of OFA 200mg at weeks 0, 1, 2 and 4 (loading period) with a maintenance dose of one injection every four weeks after; and
 - Fingolimod 500 mcg once daily.
- 7.11 The PBAC noted equi-effective doses for cladribine, ocrelizumab and ozanimod relative to fingolimod 500 mcg once daily have been previously established and could be used to determine if any of these therapies are less costly than fingolimod. Similarly, the cost minimisation basis for listing alemtuzumab versus fingolimod (and natalizumab) could be used to determine if alemtuzumab is less costly than fingolimod.
- 7.12 The PBAC considered the market share approach used in the submission and noted that the utilisation and financial expenditure of ofatumumab will be primarily

determined by the alternative RRMS therapies substituted in practice. The PBAC noted that the base case resulted in a net cost due to the substitution of lower efficacy tier treatments that are less costly, however also noted the supplementary analysis that included only substitution of higher efficacy tier medicines resulted in a net save to the PBS. On balance, the PBAC considered the listing of ofatumumab is unlikely to increase the rate of switch from lower tier to higher tier treatments and thus the financial implications of the listing of ofatumumab were likely to be minimal.

- 7.13 The PBAC advised that, under section 101(3BA) of the *National Health Act 1953* ofatumumab should be treated as interchangeable with ocrelizumab, fingolimod, ozanimod, cladribine and alemtuzumab.
- 7.14 The PBAC advised that ofatumumab is not suitable for prescribing by nurse practitioners, consistent with other RRMS DMT listings.
- 7.15 The PBAC recommended that the Early Supply Rule should apply.
- 7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ofatumumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, any of the higher efficacy tier RRMS therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new medicinal product (ofatumumab) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OFATUMUMAB					
ofatumumab 20 mg/0.4mL injection, 0.4 mL pen device	NEW	3	3	0	Kesimpta
		Max.Qty multiplier = 1; Repeat increases: nil			
Restriction Summary 10987 / Treatment of Concept: 10162 (as at 1 March 2021; based on fingolimod 5262Y)					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [10162]					
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 a 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).					
Prescribing Instructions:					
Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical record.					
Administrative advice:					
The intent of this listing is to provide doses at weeks 0, 1 and 2. For treatment at week 4 and beyond, see the 'Continuing treatment' listing.					

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OFATUMUMAB					
ofatumumab 20 mg/0.4mL injection, 0.4 mL pen device	NEW	1	1	5	Kesimpta
		Max.Qty multiplier = 1; Repeat increases: nil			
Restriction Summary 10172 / Treatment of Concept: 10172 (as at 1 March 2021; based on fingolimod 5262Y)					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [10172]				
	Indication: Multiple sclerosis				
	Treatment Phase: Continuing treatment				
	Clinical criteria:				
	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis,				
	AND				
	Clinical criteria:				
	The treatment must be the a sole PBS-subsidised disease modifying therapy for this condition,				
	AND				
	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:				
	Patient must have demonstrated compliance with, and an ability to tolerate this therapy.				
Restriction Summary [new 1]/ Treatment of Concept: [new 2]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [New 2]				
	Indication: Multiple sclerosis				
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – ‘Grandfather’ arrangements				
	Clinical criteria:				
	The condition must have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of at least one of the brain/spinal cord prior to initiating non-PBS-subsidised treatment with this drug for this condition; OR				
	The condition must have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis supported by written certification, which is documented in the patient’s medical records, from a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient prior to initiating non-PBS-subsidised treatment with this drug 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 prior to initiation of this drug,				
	AND				
	Clinical criteria:				
	Patient must have been ambulatory (without assistance or support) prior to having initiated treatment with this drug for this condition,				
	AND				
	Clinical criteria:				

	Patient must have been receiving treatment with this drug for this condition prior to [PBS listing date].
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised disease modifying therapy for this condition,
	AND
	Clinical criteria:
	Patient must not show continuing progression of disability while on treatment with this drug.
	AND
	Clinical criteria:
	Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
	Prescribing Instructions:
	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical record.
	Administrative advice:
	Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative advice:
	This grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria.

This restriction 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

Novartis welcomes the decision by the PBAC to recommend the PBS listing of ofatumumab (Kesimpta) and are committed to make this treatment available to Australian patients with multiple sclerosis.