5.1 ALEMTUZUMAB, solution for infusion, 10 mg/ mL, Lemtrada®, Genzyme (Sanofi-Aventis Australia Pty Ltd)

1 Purpose of Application

1.1 Authority Required listing of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis.

2 Requested listing

2.1

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
Initial treatment ALEMTUZUMAB 10mg/mL injection, 1 x 2 mL vial	5	0	[redacted]	Lemtrada®	GZ
Continuing treatment ALEMTUZUMAB 10mg/mL injection, 1 x 2 mL vial	3	0	[redacted]	Lemtrada®	GZ

Authority Required Section 100 (Highly Specialised Drugs Program)
Relapsing-remitting multiple sclerosis

2.2 Listing was sought on a cost-minimisation basis with two years of treatment with alemtuzumab compared to 2-5 years of treatment with fingolimod and natalizumab.

2.3 The submission proposed a PBS listing under a managed entry scheme (MES) using the currently available evidence for alemtuzumab with a proviso that the sponsor will provide the final results of ongoing clinical trials when available.

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

3 Background

3.1 Alemtuzumab was TGA registered on 18 December 2013 for the 'treatment of relapsing forms of multiple sclerosis for patients with active disease defined by clinical or imaging features to slow the accumulation of physical disability and reduce the frequency of clinical relapses'.

3.2 The PBAC has not previously considered alemtuzumab for multiple sclerosis.

4 Clinical place for the proposed therapy

4.1 Multiple sclerosis is a progressive, chronic disease of the central nervous system in which the myelin sheath protecting axons is damaged, resulting in distorted nerve signals and pathways. Most patients present with relapsing-remitting multiple sclerosis (RRMS), characterised by acute clinical attacks (relapses) followed by variable recovery and periods of clinical stability. Multiple sclerosis is characterised

by a complex range of symptoms including visual disturbance, fatigue, pain, reduced mobility and coordination, cognitive impairment and mood changes.

4.2 Alemtuzumab is a disease modifying therapy for multiple sclerosis. The submission positions alemtuzumab as a first-line alternative to fingolimod and natalizumab in patients with aggressive disease (rapidly evolving severe RRMS and/or highly active RRMS) as well as a second-line alternative to fingolimod and natalizumab in patients failing other disease modifying therapies.

4.3 The ESC noted that there are currently eight disease modifying drugs listed on the PBS for MS, however the listing of these items does not specify whether they are to be used as first line therapy or not. The clinical place of alemtuzumab may be unclear as there is no consensus on the sequence of treatments that patients should receive or switch between, although given its adverse effect profile, natalizumab is likely to be used as a second line therapy.

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

5 Comparator

5.1 The submission nominates fingolimod and natalizumab as the main comparators. The main argument provided in support of these comparators is that alemtuzumab, fingolimod and natalizumab are all likely to be used in the same subsets of the PBS population.

5.2 Whilst using these drugs as comparators is in line with clinician recommendations in the physician survey, the ESC considered that subcutaneous interferon beta-1a may be the appropriate main comparator, given the more robust trial data (direct comparisons) and uncertainty in the clinical management of MS patients.

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 discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease and the likely clinical place of this therapy.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (40), health care professionals (36) and organisations (8) via the Consumer Comments facility on the PBS website. The comments described a range of perceived benefits of treatment with alemtuzumab including its use in patients with aggressive forms of multiple sclerosis, and the convenience of yearly administration of alemtuzumab.

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

Clinical trials

6.3 A summary of the trials presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
Alemtuzumab vs. subcutaneous interferon beta-1a		
CAMMS223	Genzyme Corporation Clinical Study Report (2010). A Phase 2, Randomised, Open-Label, Three-Arm Study Comparing Low- and High-Dose Alemtuzumab and High-Dose Subcutaneous Interferon Beta-1a (Rebif ®) in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis	Internal study report
	Coles et al (2008). Alemtuzumab vs. interferon beta-1a in early multiple sclerosis	New England Journal of Medicine 359: 1786-1801
	Jones et al (2010). Improvement in disability after alemtuzumab treatment of multiple sclerosis is associated with neuroprotective autoimmunity	Brain 133: 2232-2247
	Coles et al (2011). Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes	Lancet Neurology 10: 338-348
	Coles et al (2012). Alemtuzumab more effective than interferon-1a at 5-year follow-up of CAMMS223 clinical trial	Neurology 78: 1069-1078
CARE MS-I	Genzyme Corporation Clinical Study Report (2012). A Phase 3 Randomized, Rater-Blinded Study Comparing Two Annual Cycles of Intravenous Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Treatment-Naïve Patients with Relapsing-Remitting Multiple Sclerosis	Internal study report
	Cohen et al (2012). Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial.	The Lancet 380: 1819-1828
CARE MS-II	Genzyme Corporation Clinical Study Report (2012). A Phase 3 Randomized, Rater- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Patients with Relapsing-Remitting Multiple Sclerosis who Have Relapsed on Therapy	Internal study report
	Coles et al (2012). Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial	The Lancet 380: 1829-1839
Trials of other disease modifying therapies		
SELECT	Giovannoni et al (2011). A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of daclizumab HYP monotherapy in relapsing-remitting multiple sclerosis: Primary results of the SELECT trial	Multiple Sclerosis 17: S508-S509.
Kappos (2008)	Kappos et al (2008). Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study	The Lancet 372: 1463-1472
CONFIRM	Fox et al (2012). Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis	New England Journal of Medicine 367: 1087-1097
DEFINE	Gold et al (2012). Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis	New England Journal of Medicine 367: 1098-1107
FREEDOMS	Kappos et al (2010). A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis	New England Journal of Medicine 362: 387-401
	Devonshire et al (2012). Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study	The Lancet Neurology 11: 420-428

	Radue et al (2012). Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis	Archives of Neurology 69: 1259-1269
FREEDOMS II	Calabresi et al (2012). Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS): Results from an additional 24-month double-blind, placebo-controlled study (FREEDOMS II study)	Neurology 79: e90-e91
	Calabresi et al (2012). Efficacy and safety of fingolimod in patients with relapsing remitting multiple sclerosis (RRMS): results from an additional 24-month double-blind, placebo-controlled study (FREEDOMS II Study)	American Academy of Neurology Meeting 2012 Poster E-002
	Calabresi et al (2012). Efficacy and safety of fingolimod versus placebo: primary outcomes from the phase 3 FREEDOMS II study in patients with relapsing–remitting multiple sclerosis	European Committee for Treatment and Research in Multiple Sclerosis Congress 2012 Abstract P491
	Vollmer et al (2012). Effect of fingolimod on severe relapses, healthcare utilisation and relapse recovery in patients with relapsing–remitting multiple sclerosis: results from the phase 3 FREEDOMS II study	European Committee for Treatment and Research in Multiple Sclerosis Congress 2012 Abstract P952
	Goodin et al (2013). Fingolimod reduces annualized relapse rate in patients with relapsing-remitting multiple sclerosis: FREEDOMS II study subgroup analysis	Neurology 80: P07.102
	Vollmer et al (2013). Long-term safety of fingolimod in patients with relapsing-remitting multiple sclerosis: Results from phase 3 FREEDOMS II extension study	Neurology 80: P01.165
TRANSFORMS	Cohen et al (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis	New England Journal of Medicine 362: 402-415
	Khatri et al (2011). Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study	The Lancet Neurology 10: 520-529
	Cohen et al (2013). Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS	Journal of Neurology 260: 2023-2032
Saida (2012)	Saida et al (2012). A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis	Multiple Sclerosis 18: 1269-1277
Kappos (2006)	Kappos et al (2006). Oral fingolimod (FTY720) for relapsing multiple sclerosis	New England Journal of Medicine 355: 1124-1140
	O'Connor et al (2009). Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study	Neurology 72: 73-79
	Comi et al (2010). Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results	Multiple Sclerosis 16: 197-207
Cohen (2007)	Cohen et al (2007). Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS	Neurology 68: 939-944
	Wynn et al (2008). Optimal Dosing of Immunomodulating Drugs: A Dose-comparison Study of GA in RRMS	Progress in Neurotherapeutics and Neuropsychopharmacology 3:137-151
FORTE	Comi et al (2011). Phase III dose-comparison study of glatiramer acetate for multiple sclerosis	Annals of Neurology 69: 75-82
BECOME	Cadavid et al (2009). Efficacy of treatment of MS with IFNβ-1b or	Neurology 72:

	glatiramer acetate by monthly brain MRI in the BECOME study	1976-1983
CombiRx	Cutter et al (2012). EDSS changes and progression in the CombiRx randomized clinical trial: 3-year results	European Committee for Treatment and Research in Multiple Sclerosis Congress 2012
	CombRx (2012). The CombiRx trial: a multi-center, double-blind, randomized study comparing the combined use of interferon beta-1a and glatiramer acetate to either agent alone in participants with relapsing remitting multiple sclerosis - clinical and MRI outcomes	American Academy of Neurology Meeting 2012
	Wolinsky et al (2012). The CombiRx trial: a multicenter, double-blind, randomized study comparing the combined use of interferon beta-1a and glatiramer acetate to either agent alone in participants with relapsing remitting multiple sclerosis - MRI outcomes	American Academy of Neurology Meeting 2012
Bornstein (1987)	Bornstein et al (1987). A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis	New England Journal of Medicine 317: 408-414
Johnson (1995)	Johnson et al (1995). Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group	Neurology 45: 1268-1276
	Johnson (1996). Management of relapsing/remitting multiple sclerosis with copolymer 1 (Copaxone)	Multiple Sclerosis 1: 325-326
	Johnson et al (1998). Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group	Neurology 50: 701-708
	Johnson et al (2000). Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years	Multiple Sclerosis 6:255-266
	Wolinsky et al (2001). United States open-label glatiramer acetate extension trial for relapsing multiple sclerosis: MRI and clinical correlates	Multiple Sclerosis 7: 33-41
	Johnson et al (2003). Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial	Multiple Sclerosis 9: 585-591
	Johnson et al (2005). Neurologic consequence of delaying glatiramer acetate therapy for multiple sclerosis: 8-year data	Acta Neurologica Scandinavica 111: 42-47
	Ford et al (2006). A prospective open-label study of glatiramer acetate: over a decade of continuous use in multiple sclerosis patients	Multiple Sclerosis 12: 309-320
Comi (2001)	Comi et al (2001). European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group	Annals of Neurology 49: 290-297
	Wolinsky et al (2002). Copaxone's effect on MRI-monitored disease in relapsing MS is reproducible and sustained	Neurology 59:1284-1286
BEYOND	O'Connor et al (2009). 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study	The Lancet Neurology 8: 889-897
Duquette (1993)	Duquette (1993). Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group	Neurology 43: 655-661
Jacobs (1996)	Jacobs et al (1996). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG)	Annals of Neurology 39: 285-294
	Simon et al (1998). Magnetic resonance studies of intramuscular	Annals of Neurology

	interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group	43: 79-87
	Rudick et al (1997). Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG)	Neurology 49: 358-363
	Bermel et al (2010). Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: A 15-year follow-up study	Multiple Sclerosis 16: 588-596
Polman (2005)	Polman et al (2005). Treatment with laquinimod reduces development of active MRI lesions in relapsing MS	Neurology 64: 987-991
Comi (2008)	Comi et al (2008). Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study	The Lancet 371: 2085-2092
BRAVO	Vollmer et al (2011). A placebo-controlled and active comparator phase III trial (BRAVO) for relapsing-remitting multiple sclerosis	Multiple Sclerosis 17: S507-S508
ALLEGRO	Comi et al (2012). Placebo-controlled trial of oral laquinimod for multiple sclerosis	New England Journal of Medicine 366: 1000-1009
AFFIRM	Polman et al (2006). A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis	New England Journal of Medicine 354: 899-910
	Balcer et al (2007). Natalizumab reduces visual loss in patients with relapsing multiple sclerosis	Neurology 68: 1299-304
	Miller et al (2007). MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS	Neurology 68: 1390-1401
	Havrdova et al (2009). Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: A retrospective analysis of the natalizumab safety and efficacy in relapsing-remitting multiple sclerosis (AFFIRM) study	The Lancet Neurology 8: 254-60
	Hutchinson et al (2009). The efficacy of natalizumab in patients with relapsing multiple sclerosis: Subgroup analyses of AFFIRM and SENTINEL	Journal of Neurology 256: 405-415
	Cree et al (2011). Efficacy of natalizumab therapy in patients of African descent with relapsing multiple sclerosis: Analysis of affirm and sentinel data	Archives of Neurology 68: 464-468
	Phillips et al (2011). Sustained improvement in expanded disability status scale as a new efficacy measure of neurological change in multiple sclerosis: Treatment effects with natalizumab in patients with relapsing multiple sclerosis	Multiple Sclerosis 17: 970-979
	Kappos et al (2013). Clinical effects of natalizumab on multiple sclerosis appear early in treatment course	Journal of Neurology 260: 1388-1395
HERMES	Hauser et al (2008). B-cell depletion with rituximab in relapsing-remitting multiple sclerosis	New England Journal of Medicine 358: 676-688
REGARD	Mikol et al (2008). Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial	The Lancet Neurology 7: 903-914
EVIDENCE	Panitch et al (2002). Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial	Neurology 59: 1496-1506
	Panitch et al (2005). Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial	Journal of Neurological Sciences 239: 67-74
	Sandberg-Wollheim et al (2005). Comparative tolerance of IFN beta-1a regimens in patients with relapsing multiple sclerosis. The EVIDENCE study	Journal of Neurology 252: 8-13

	Schwid et al (2005). Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis: the EVIDENCE Study	Archives of Neurology 62: 785-792
	Schwid et al (2007). Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis	Clinical Therapeutics 29: 2031-2048
Etamadifar (2006)	Etemadifar et al (2006). Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis	Acta Neurologica Scandinavica 113: 283-287
PRISMS	Ebers G (1998). 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	The Lancet 352: 1498-1504
TEMSO	O'Connor P et al (2011). Randomized trial of oral teriflunomide for relapsing multiple sclerosis	New England Journal of Medicine 365: 1293-1303
O'Connor (2006)	O'Connor et al (2006). A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses	Neurology 66: 894-900
TOWER	Kappos et al (2012). The efficacy and safety of teriflunomide in patients with relapsing MS: results from TOWER, a phase III, placebo-controlled study	European Committee for Treatment and Research in Multiple Sclerosis Congress 2012 Abstract 153
TENERE	Vermersch et al (2012). A multicenter, randomized, parallel-group, rater-blinded study comparing the effectiveness and safety of teriflunomide and subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis	America's Committee for Treatment and Research in Multiple Sclerosis Meeting 2012

Source: Table B.3 (p 43-50) and Attachment 6 of the submission
Note: Abstracts of studies with full publications are not presented

6.4 The ESC considered that comparative efficacy and safety against interferon beta-1a in all three direct randomised controlled trials may be more robust for informing decision making, while the mixed-treatment comparison (MTC) used for comparing alemtuzumab versus fingolimod and natalizumab is highly complex, the results of efficacy are uncertain and without direct comparison of safety.

Key features of the alemtuzumab clinical trials: direct comparison to interferon beta-1a

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Alemtuzumab vs. subcutaneous interferon beta-1a					
CAMMS223	334	MC, R, OL, PG 3 years	High	Treatment naïve RRMS patients	Relapse rates, disability progression
CARE MS-I	581	MC, R, OL, PG 2 years	High	Treatment naïve RRMS patients	Relapse rates, disability progression
CARE MS-II	840	MC, R, OL, PG 2 years	High	Treatment experienced RRMS patients	Relapse rates, disability progression

Abbreviations: MC, multi-centre; OL, open label; PG, parallel-group; R, randomised

6.5 The ESC considered that the risk of bias in these three trials was high.

- These were open-label trials with rater blinding. However, it may be difficult to blind patients and investigators given the different modes of administration.
- Relapse rates and disability progression can be subjective outcomes.

- There were differential rates of discontinuation, with higher discontinuations in the subcutaneous interferon beta-1a arm. Based on FDA documentation, the consent form states that patients would discontinue therapy if their clinical condition worsened, which may have affected reporting of changes in clinical condition.
- The majority of patients in the CARE MS-II trials had already previously failed interferon therapy (including subcutaneous interferon beta-1a).
- The initial Phase II trial had highly favourable results, which may have affected patient expectations in later trials.

6.6 The PBAC noted the assessment of the ESC that risk of bias in these trials was high, however agreed with the ESC that double blinding would have been difficult to achieve.

6.7 No head-to-head studies against fingolimod or natalizumab were available. The submission is based on a series of indirect comparisons between alemtuzumab and fingolimod and natalizumab:

- Mixed treatment comparison of alemtuzumab vs. other disease modifying therapies including published trials of fingolimod, natalizumab, teriflunomide, dimethyl fumarate, subcutaneous interferon beta-1a, intramuscular interferon beta-1a, subcutaneous interferon beta-1b, glatiramer acetate, rituximab, daclizumab, laquinimod (36 trials)
- Mixed treatment comparison of alemtuzumab vs. other disease modifying therapies limited to trials conducted exclusively in RRMS populations and published after 2000 (26 trials)
- Mixed treatment comparison using the minimum set of trials required to link alemtuzumab to fingolimod and natalizumab (14 trials)
- Multistep indirect analysis of alemtuzumab vs. fingolimod and natalizumab using subcutaneous interferon beta-1a/ teriflunomide/ placebo as bridging comparators (10 trials)
- Multistep indirect analysis of alemtuzumab vs. fingolimod and natalizumab using subcutaneous interferon beta-1a/ intramuscular interferon beta-1a/ placebo as bridging comparators (12 trials).

6.8 The submission acknowledges the inherent uncertainty of indirect comparisons. It is unclear whether the included trial populations are sufficiently exchangeable given differences in multiple sclerosis subtypes, prior therapies, diagnostic criteria, study enrolment periods, duration of randomised treatment, outcome definitions, baseline disease activity (number of recent relapses), baseline level of disability and duration of disease.

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

Comparative effectiveness

6.9 Treatment with alemtuzumab was associated with a statistically significant reduction in protocol-defined relapses compared to subcutaneous interferon beta-1a. Treatment with alemtuzumab was associated with a statistically significant increase in the proportion of relapse-free patients at 2-3 years compared to subcutaneous interferon beta-1a.

Comparison of relapse rates between alemtuzumab and subcutaneous interferon beta-1a

Trial ID	Annualised relapse rate (95% CI)		Incremental difference per 100 patients	Rate ratio (95% CI)
	Alemtuzumab	SC interferon beta-1a		

Protocol-defined relapses				
CAMMS223, treatment naive (3-year results)	0.12 (0.09, 0.17) N = 112	0.37 (0.30, 0.45) N = 111	25 fewer relapses per year	0.33 (0.20, 0.55)
CARE MS-I, treatment naive (2- year results)	0.18 (0.13, 0.23) N = 376	0.39 (0.29, 0.53) N = 187	21 fewer relapses per year	0.45 (0.32, 0.63)
CARE MS-II, treatment experienced (2-year results)	0.26 (0.21, 0.33) N = 426	0.52 (0.41, 0.66) N = 202	26 fewer relapses per year	0.51 (0.39, 0.65)
[redacted]				

Abbreviations: CI, confidence interval; NR, not reported; SC, subcutaneous

6.10 The PBAC considered that the proportion of patients remaining relapse-free may provide an informative basis for assessing durability of effect and as well as proportions of patents being re-treated if the necessary links between individual patients could be adequately demonstrated. The Committee considered Table B.27 of the submission and associated text confirming that only [redacted] of the total extension study population were relapse free at the end of Year 3. The Committee noted that these data appeared to be inconsistent with the trial data, and subsequently considered that the presentation of the data in this way may in fact be erroneous.

6.11 The PBAC noted in the Commentary:

Comparison of proportion of patients without relapse between alemtuzumab and subcutaneous interferon beta-1a

Trial ID	Proportion of patients		Incremental difference per 100 patients	Odds ratio (95% CI)
	Alemtuzumab	SC interferon beta-1a		
Proportion of relapse-free patients				
CAMMS223, treatment naive (3-year results)	0.78 (87/112)	0.58 (64/111)	20 more patients without relapse at 3 years	2.67 (1.47, 4.82)
CARE MS-I, treatment naive (2- year results)	0.78 (292/376)	0.59 (110/187)	19 more patients without relapse at 2 years	2.43 (1.64, 3.55)[a]
CARE MS-II, treatment experienced (2-year results)	0.65 (279/426)	0.47 (94/202)	18 more patients without relapse at 2 years	2.18 (1.55, 3.07)[a]
[redacted]				

[a] Calculated during evaluation based on reported proportion of relapse-free patients

6.12 The PBAC considered that, consistent with its previous considerations of medicines for relapsing-remitting multiple sclerosis, disability progression results provide an informative basis for assessing patient-relevant clinical effectiveness. The PBAC noted that these generally favoured alemtuzumab compared to subcutaneous interferon beta-1a, but were not consistently statistically significant.

Comparison of disability progression between alemtuzumab and subcutaneous interferon beta-1a

Trial ID	KM estimate of event (95%CI)		Incremental difference per 100 patients	Hazard ratio (95% CI)
	Alemtuzumab	SC interferon beta-1a		
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CARE MS-I, treatment naive (2- year results)	[redacted]	[redacted]	-	[redacted]
CARE MS-II, treatment experienced (2-year results)	[redacted]	[redacted]	-	[redacted]
[redacted]				[redacted]
6-month sustained disability				
CAMMS223, treatment naive (3-year results)	0.08 (0.04, 0.17) N = 112	0.27 (0.19, 0.38) N = 111	19 fewer patients with progression over 3 years	0.24 (0.11, 0.55)
CARE MS-I, treatment naive (2- year results)	0.08 (0.06, 0.11) N = 376	0.11 (0.07, 0.17) N = 187	-	0.70 (0.40, 1.23)
CARE MS-II, treatment experienced (2-year results)	0.13 (0.10, 0.16) N = 426	0.21 (0.16, 0.28) N = 202	8 fewer patients with progression over 2 years	0.58 (0.38, 0.87)
[redacted]				[redacted]

Abbreviations: CI, confidence interval; KM, Kaplan-Meier

6.13 Indirect comparisons (mixed treatment comparisons and multi-step indirect analyses) between alemtuzumab, fingolimod and natalizumab with respect to relapse rate and disability progression are shown below.

Indirect comparisons between alemtuzumab, fingolimod and natalizumab

Trial ID	alemtuzumab vs fingolimod	alemtuzumab vs natalizumab
Annualised relapse rate		
MTC (all trials); rate ratio (95% CrI)	[redacted]	[redacted]
MTC (post 2000 trials, all RRMS); rate ratio (95% CrI)	[redacted]	[redacted]
MTC (minimum dataset); rate ratio (95% CrI)	[redacted]	[redacted]
Indirect analysis (via teriflunomide link); rate ratio (95% CI)	[redacted]	[redacted]
Indirect analysis (via IM interferon beta-1a link); rate ratio (95% CI)	[redacted]	[redacted]
3-month sustained disability		
MTC (all trials); hazard ratio (95% CrI)	[redacted]	[redacted]
MTC (post 2000 trials, all RRMS); hazard ratio (95% CrI)	[redacted]	[redacted]
MTC (minimum dataset); hazard ratio (95% CrI)	[redacted]	[redacted]
Indirect analysis (via teriflunomide link); hazard ratio (95% CI)	[redacted]	[redacted]
Indirect analysis (via IM interferon beta-1a link); hazard ratio (95% CI)	[redacted]	[redacted]
6-month sustained disability		
MTC (all trials); hazard ratio (95% CrI)	[redacted]	[redacted]
MTC (post 2000 trials, all RRMS); hazard ratio (95% CrI)	[redacted]	[redacted]

MTC (minimum dataset); hazard ratio (95% CrI)	[redacted]	[redacted]
Indirect analysis (via teriflunomide link); hazard ratio (95% CI)	[redacted]	[redacted]
Indirect analysis (via IM interferon beta-1a link); hazard ratio (95% CI)	[redacted]	[redacted]
Proportion of relapse-free patients		
MTC (all trials); odds ratio (95% CrI)	[redacted]	[redacted]
MTC (post 2000 trials, all RRMS); odds ratio (95% CrI)	[redacted]	[redacted]
MTC (minimum dataset); odds ratio (95% CrI)	[redacted]	[redacted]
Indirect analysis (via teriflunomide link); odds ratio (95% CI)	[redacted]	[redacted]
Indirect analysis (via IM interferon beta-1a link); odds ratio (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CrI, credible interval; IM, intramuscular; MTC, mixed treatment comparison; RRMS, relapsing-remitting multiple sclerosis

6.14 The submission claims that alemtuzumab is superior to fingolimod and non-inferior compared to natalizumab in terms of efficacy based on these indirect comparisons.

6.15 The submission does not present any comparative assessment of durability of effect between alemtuzumab, natalizumab and fingolimod. The submission assumes that effects of alemtuzumab will persist after treatment using time until re-treatment as a proxy for durability of effect (average durability of effect, [redacted] years from first treatment, based on preliminary analysis of alemtuzumab re-treatment rates reported in the CARE MS-I/MS-II extension study and the assumption that re-treatments indicate loss of effect in the prior year). Re-treatment rates may not be an adequate proxy for durability of effect as they do not account for patients switching to other therapies and patients lost to follow-up. The approach used by the submission does not account for any waning of effects before re-treatment. The submission notes that fingolimod and natalizumab are ongoing therapies and therefore assumes that treatment effects will cease when therapy is stopped.

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

Comparative harms

6.16 Treatment with alemtuzumab was associated with a higher rate of adverse events and treatment-related adverse events compared to interferon beta-1a in the clinical trials. Infusion-related reactions (rash, headache, nausea, pyrexia, urticarial, pruritus, insomnia and chills), infections (nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, influenza, oral herpes, bronchitis and herpes zoster) and autoimmune disease (particularly thyroid disorders) were commonly reported with alemtuzumab treatment. Based on data from the CAMMS223 study approximately 15-20% of all treated patients required surgery and/or long-term medical treatment to manage thyroid adverse events.

6.17 Alemtuzumab requires ongoing monitoring (full blood counts, serum creatinine levels, urinalysis, thyroid function tests, pap smears) at periodic intervals for 48 months following the last treatment course of treatment. It is unclear whether patients will remain fully compliant with an extensive monitoring program up to 4 years after their last treatment. The submission assumes that all ongoing monitoring costs associated with alemtuzumab treatment will be covered by a private arrangement between the sponsor and a pathology provider ([redacted]).

6.18 The ESC noted that alemtuzumab had previously been available for the treatment of chronic lymphocytic leukaemia. The ESC considered that this experience of clinical use of alemtuzumab may provide additional information about the safety of the product. The ESC noted that adverse events reported with higher dose alemtuzumab include autoimmune disease (e.g. cytopenias, nephropathies, thyroid disorders),

infusion-related reactions (e.g. respiratory distress, acute cardiac events, anaphylactic shock), infections and infestations (e.g. reactivation of latent infections, progressive multifocal leucoencephalopathy), blood and lymphatic system disorders (e.g. severe bleeding), cardiac disorders (e.g. congestive heart failure, cardiomyopathy) and Epstein-Barr Virus-associated lymphoproliferative disorders.

6.19 A summary of the comparative harms for alemtuzumab versus subcutaneous interferon beta-1a is presented in the table below.

Summary of comparative harms for alemtuzumab and subcutaneous interferon beta-1a

Trial ID	Alemtuzumab	SC interferon beta-1a	Relative difference	Incremental difference per 100 patients[a]
Infection, proportion of patients with adverse events [event rate per person year]				
CAMMS223, treatment naive (3-year results)	71/108 (65.7%) [0.67]	48/107 (44.9%) [0.38]	NE	29 more infections per year
CARE MS-I, treatment naive (2- year results)	253/376 (67.3%) [1.18]	85/187 (45.5%) [0.51]	NE	67 more infections per year
CARE MS-II, treatment experienced (2-year results)	334/435 (76.8%) [1.43]	134/202 (66.3%) [0.94]	NE	49 more infections per year
Thyroid disorders, proportion of patients with adverse events [event rate per person year]				
CAMMS223, treatment naive (3-year results)	27/108 (25.0%) [0.10]	2/107 (1.9%) [0.01]	NE	9 more thyroid disorders per year
CARE MS-I, treatment naive (2- year results)	68/376 (18.1%) [0.15]	12/187 (6.4%) [0.04]	NE	11 more thyroid disorders per year
CARE MS-II, treatment experienced (2-year results)	69/435 (15.9%) [0.10]	10/202 (5.0%) [0.03]	NE	7 more thyroid disorders per year
Immune thrombocytopenic purpura, proportion of patients with adverse events [event rate per person year]				
CAMMS223, treatment naive (3-year results)	1/108 (0.9%) [<0.01]	1/107 (0.9%) [<0.01]	NE	Not estimated. Rare adverse event
CARE MS-I, treatment naive (2- year results)	3/376 (0.8%) [0.01]	1/187 (0.5%) [<0.01]	NE	Not estimated. Rare adverse event
CARE MS-II, treatment experienced (2-year results)	4/435 (0.9%) [0.01]	0/202 (0%) [<0.01]	NE	Not estimated. Rare adverse event

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimated; NR, not reported; SC, subcutaneous
[a] Estimated post-hoc during the evaluation. Assumes constant risk over time

6.20 The submission does not present any comparative assessment of harms between alemtuzumab, natalizumab and fingolimod.

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

Clinical claim

6.21 The submission describes alemtuzumab as superior compared to fingolimod and non-inferior compared to natalizumab in terms of comparative short-term effectiveness. The Commentary noted that claim of superiority is not justified based on the available data, however a claim of non-inferiority against both fingolimod and natalizumab may be considered reasonable.

6.22 The submission describes alemtuzumab as superior compared to fingolimod and natalizumab in terms of comparative long-term durability of effect.

6.23 The submission makes no specific claim in terms of comparative safety. The Commentary noted that alemtuzumab may be inferior to fingolimod and natalizumab based on the limited available information.

6.24 The ESC considered that alemtuzumab is superior compared to subcutaneous interferon beta-1a in terms of comparative effectiveness and inferior to subcutaneous interferon beta-1a in terms of comparative safety.

6.25 The PBAC considered that the claim of superior comparative effectiveness to fingolimod was not adequately supported by the data and that a claim of non-inferior comparative effectiveness to fingolimod or natalizumab was appropriate. The PBAC recalled that both relapse rate and disability progression were relevant patient outcomes in the consideration of other disease modifying drugs for MS. Though the comparative effectiveness was uncertain due to the high risk of bias associated with the nature of the indirect mixed treatment comparisons and limited exchangeability of the trials, the PBAC considered that the available relapse rate and disability progression data supported the claim that alemtuzumab was non-inferior to both natalizumab and fingolimod in terms of comparative effectiveness.

6.26 The PBAC considered that there were no adequate data provided in the submission to support any claim of comparative safety to fingolimod or natalizumab. The PBAC noted that there was no comparative assessment of harms of alemtuzumab, natalizumab and fingolimod, though each drug has a different safety profile. The PBAC noted in the direct randomised controlled trials against interferon beta-1a treatment, that patients treated with alemtuzumab had a higher rate of infections and required prophylactic treatment with methylprednisolone and aciclovir.

Economic analysis

6.27 The submission presents a cost-minimisation analysis comparing two years of treatment with alemtuzumab to 2-5 years of treatment with fingolimod and natalizumab (average [redacted] years) based on the claim of superior durability of effect. The analysis includes drug costs, prophylactic treatment costs and administration costs. The key source of uncertainty is the claimed durability of effect associated with alemtuzumab treatment.

Alemtuzumab price based on cost-minimisation analysis: base case and sensitivity analyses

Analysis	Ex-man cost per vial
Base case	[redacted]
2 year treatment durability, all patients	[redacted]
3 year treatment durability, all patients	[redacted]
4 year treatment durability, all patients	[redacted]
5 year treatment durability, all patients	[redacted]

Source: Constructed during the evaluation using the Alemtuzumab Section D excel spreadsheet

6.28 Additionally, the cost-minimisation does not include adverse events costs, drug monitoring costs (fully funded by sponsor) and costs associated with healthcare professional attendances. The analysis does not account for alemtuzumab re-treatments beyond the standard two course of therapy.

6.29 The ESC agreed with the Commentary that a modelled cost-utility analysis may be more appropriate to better account for the differences in the risk/benefit profile (both short-term and long-term) between treatments.

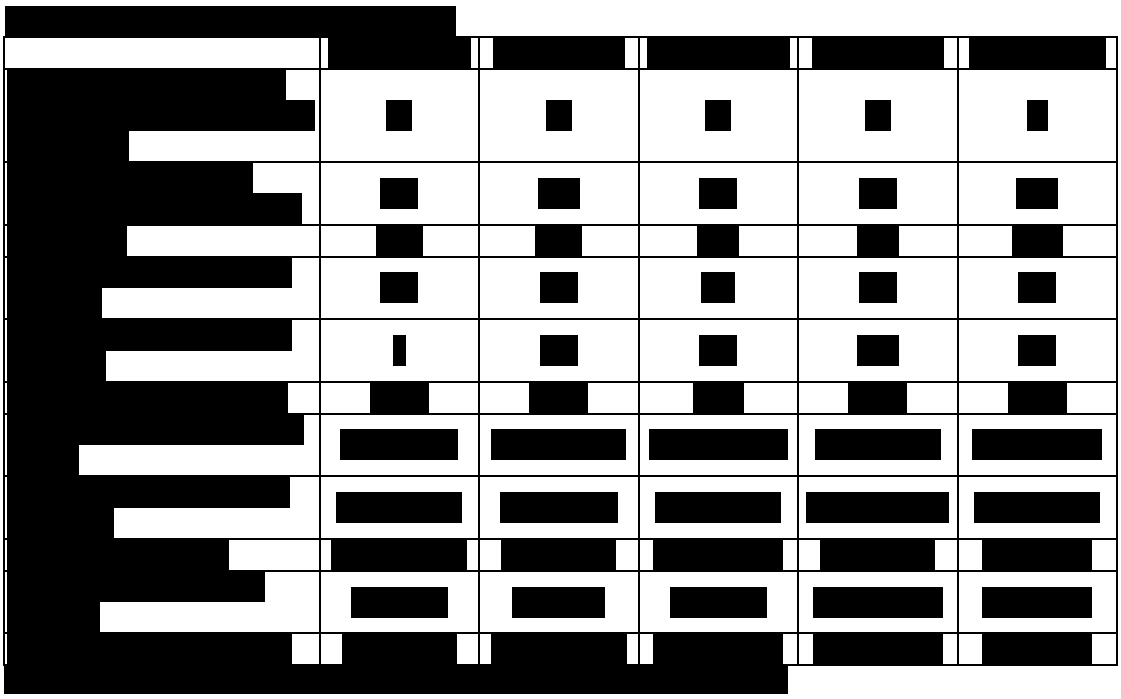
6.30 With the evidence provided, the PBAC did not accept the submission's claim of durability of effect, and so considered it was inappropriate to compare two years treatment with alemtuzumab with 2-5 (average of [redacted]) years duration of treatment with fingolimod or natalizumab. The PBAC considered that cost-minimisation based on two years of treatment with fingolimod or natalizumab was supported by the available data. This duration of two years is based on the follow-up of the CARE randomised trials, not the interim results of the CARE MS extension studies. The PBAC considered that any price advantage for fingolimod accounting for its oral form should not apply in the cost-minimisation analysis. The PBAC also agreed that, given the adverse effect profile of alemtuzumab that offsets for infection management as well as prophylaxis should be accounted for in the cost comparison with fingolimod. The PBAC noted the submission, based on a clinician survey, stated that the relative proportion of use from replacement of natalizumab and fingolimod is [redacted] respectively. The PBAC considered given the uncertainty of how alemtuzumab would be used in clinical practice, that a weighting of 50:50 would be more appropriate.

Drug cost/patient/course (over 2 years)

6.31 In the submission, based on the proposed ex-manufacturer list price and cost-minimisation approach, alemtuzumab will cost [redacted] for the standard two courses of therapy (one course per year for two years). The annual ex-manufacturer list price is $28,243 for fingolimod and $26,500 for natalizumab.

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC. The estimated PBS usage and financial implications presented in the submission are shown below.



The submission appears to substantially underestimate the costs associated with alemtuzumab and to substantially overestimate the cost-offsets associated with comparator therapies. The Commentary reported:

- Alemtuzumab may grow the market for multiple sclerosis therapies by providing another line of therapy. The submission argues against this on the basis that

there are already several other PBS-listed treatment options that would be used if alemtuzumab was not available. The submission also suggests that patients are unlikely to be prescribed another disease modifying therapy after alemtuzumab. This assumption is unjustified.

- The estimates implicitly assume that patients prematurely discontinuing alemtuzumab treatment after one course of therapy will have the same level of substitutions as patients who undergo the standard two courses of therapy. This assumption is unjustified.
- The submission does not include re-treatment dosing with alemtuzumab beyond the standard two courses in the utilisation/financial estimates. This is inappropriate as the available study data indicate that some patients will require re-treatments within this timeframe.
- Comparator utilisation is based on the number of scripts/packs needed to cover the forecast period (2015-2020) at the recommended dose with adjustments for treatment adherence (discontinuation rates reported from clinical trials and compliance rates reported from the 10% Medicare sample). There are a number of issues associated with the predicted estimates:
  - The calculation of compliance rates is not adequately justified in the submission and appears high for all treatments [redacted] compliance). There is limited documentation describing the methodology used in the calculation, the analysis uses immature utilisation data for fingolimod (11 months), the submission assumes compliance for other oral treatments based on fingolimod, and the submission does not assess the sensitivity of changing assumptions regarding the definition of a 'medicated' patient and an 'active' patient in the analysis of the 10% Medicare sample.
  - The discontinuation rates reported from clinical trials are substantially lower than those estimated in the Australian PBS population (for example, natalizumab and fingolimod, 2.39-6.21% in trials and [redacted] in PBS population) indicating that the submission substantially overestimates adherence to comparator therapies.
- The financial estimates do not account for any differences in prophylactic treatment, adverse events, drug monitoring (assumed to be covered by a private arrangement between the sponsor and a pathology provider) and healthcare professional attendance costs between therapies.
- The submission assumes a cost-saving associated with a reduced number of infusions with alemtuzumab compared to natalizumab. This saving may not be reasonable as it assumes that the cost per infusion is the same for both treatments despite differences in administration times between alemtuzumab (4 hour infusion, 2 hour post-observation) and natalizumab (1 hour infusion, 1 hour post-observation).

6.33 The submission proposes a PBS listing under a managed entry scheme (MES) using the currently available evidence for alemtuzumab with a proviso that the sponsor will provide the final results of the CARE MS extension study when available. The ESC noted that the full five year results are due to be reported in the 2nd quarter of 2015.

6.34 The submission claims that the current evidence base is sufficient to justify the requested price and that the final results from the CARE MS extension study are for confirmative purposes only and are not necessary to establish the magnitude of benefit associated with alemtuzumab treatment. The ESC Advice noted in regards to the MES, based on the proposal in the submission, it may be more appropriate to base the price of alemtuzumab on 2 years of therapy with fingolimod and natalizumab with future price increases dependent on further evidence of durability of effect. Alternatively, the basis of MES may be constructed from the direct clinical

evidence with interferon beta-1a, given the clinical uncertainties of alemtuzumab, including the place in the treatment algorithm, comparative efficacy and safety with other treatment for MS in terms of magnitude and duration, and requirements for the treatment of adverse effects.

6.35 The submission states that confirmation of durability of effect will be based on re-treatment rates reported over five years. Longer-term results of the CARE MS extension study may reduce some but not all of the uncertainty associated with durability of effect. The ESC Advice noted that results would need to include efficacy and safety outcomes in addition to re-treatment rates. Final results are likely to be subject to many of the same limitations as the preliminary data: re-treatment rates do not account for patients switching to other therapies and patients lost to follow-up; waning of effects before re-treatment are not accounted for; it is unclear whether the re-treatment criteria used in the CARE MS extension studies are likely to be representative of clinical practice.

6.36 Fingolimod and natalizumab are subject to special pricing arrangements. The sponsor proposes a similar arrangement for alemtuzumab.

6.37 The PBAC considered, among other matters, that the measures below should be implemented to contain risks associated with the cost of the alemtuzumab to the PBS:

- A Risk Share Agreement (RSA) between the sponsor and the Government
- The RSA should include a rebate during the treatment period for other treatments for MS used by patients including re-treatment beyond the standard two doses of alemtuzumab.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required Section 100 (Highly Specialised Drugs Program) listing of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis, on the basis of non-inferior effectiveness and a different safety profile to fingolimod and natalizumab.

7.2 The PBAC noted that the clinician at the hearing reaffirmed the proposed clinical place for alemtuzumab as: a first-line therapy in patients with poor prognostic signs; and as escalation therapy in treatment experienced patients with ongoing disease activity. The PBAC recognised that there may be a clinical need for the drug in patients with high disease activity, noting the consumer comments. The PBAC considered that this clinical place was uncertain, particularly in the early stages of the disease, where there is pressure to decide which treatment to initiate before poor prognostic signs manifest. Over time, should confidence with this medicine grow in the absence of any emerging but unexpected safety concerns, this is likely to result in earlier treatment in patients with better prognosis.

7.3 The PBAC considered the submission's main comparators, fingolimod and natalizumab, were acceptable. The PBAC noted the ESC advice that subcutaneous interferon beta-1a may be a more appropriate comparator, given the available randomised data. However, the PBAC agreed with the submission and the hearing that fingolimod and natalizumab are the therapies that would be replaced by alemtuzumab in practice, particularly in the period immediately after listing, and therefore could also be considered appropriate comparators.

7.4 The PBAC considered that the claim of clinical durability of alemtuzumab compared to fingolimod and natalizumab had not been supported in the submission. The PBAC noted that the claim of durability was informed by the interim results of the CARE-MS extension study, and that the duration of the clinical effect compared to fingolimod and natalizumab remains uncertain. The PBAC did not accept that in-trial re-treatment rates were justified to be an adequate proxy for durability of effect as they do not account for patients switching to other therapies and patients lost to follow-up. Further, the basis of the clinician's decision to re-treat with alemtuzumab (as opposed to another disease modifying therapy) is not clearly linked to monitoring of any particular aspect of effect. The PBAC noted that the approach used by the submission does not account for any waning of effects before re-treatment. The PBAC considered that the criteria for a patient to seek re-treatment was unclear and that it was uncertain how any such criteria may be interpreted by clinicians. The PBAC considered that once the final results of the extension study are known, and if they support durability of effect, the sponsor is welcome to lodge a submission to the PBAC providing this evidence. The PBAC also agreed with the ESC that a modelled cost-utility analysis may be an alternate way to value alemtuzumab to better account for the differences in the risk/benefit profile (both short-term and long-term) between treatments.

7.5 The PBAC considered the submission's proposed MES, but was concerned that the CARE MS extension studies would not further address the uncertainty of the treatment duration for patient relevant outcomes and that the sponsor had not presented a proposal for what action should be taken if the final results from the CARE MS extension study do not confirm the treatment duration claimed in the submission. The PBAC recommended a RSA between the sponsor and the Government.

7.6 The PBAC noted that, although based on a cost-minimisation approach, the submission estimates a substantial net cost to the PBS of [redacted] over 5 years.

7.7 The PBAC advised that alemtuzumab is not suitable for prescribing by nurse practitioners as it is a Section 100 medicine.

7.8 The PBAC recommended that the Safety Net 20 Day Rule should not apply to alemtuzumab, as it does not apply to items supplied under Section 100.

7.9 The PBAC advised under Section 101(3BA) that it did not consider there were any other PBS listed drugs that are interchangeable with alemtuzumab on an individual patient basis.

7.10 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:
Recommended.

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ALEMTUZUMAB Injection, 10 mg/ mL, 1x 1.2 mL vial	5	0	Lemtrada	Sanofi-Aventis Australia

Category/Program	Section 100 Highly Specialised Drugs Program
Condition:	Multiple sclerosis
Treatment phase:	Initial
Restriction:	Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Treatment criteria:	The treatment must be as monotherapy AND Must be treated by a neurologist AND Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding 2 years AND Patient must be ambulatory (without assistance or support)
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.
Prescriber instructions	Where applicable, the date of the magnetic resonance imaging scan must be provided with the authority application. Neurologists prescribing PBS subsidised alemtuzumab must be registered with the [redacted]
Administrative Advice	Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ALEMTUZUMAB Injection, 10 mg/ mL, 1x 1.2 mL vial	3	0	Lemtrada	Sanofi-Aventis Australia

Category/Program	Section 100 Highly Specialised Drugs Program
Condition:	Multiple sclerosis
Treatment phase:	Continuing
Restriction:	Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Treatment criteria:	The treatment must be as monotherapy AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy AND Must be treated by a neurologist
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug. AND Patient must not show continuing progression of disability while on treatment with this drug AND Patient must not receive more than one PBS-subsidised treatment per year.
Administrative Advice	Neurologists prescribing PBS subsidised alemtuzumab must be registered with the [redacted] Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.