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

1 Purpose of Application

1.1 Amend the July 2014 PBAC recommendation to list alemtuzumab on a cost-minimisation basis with natalizumab and fingolimod with regards to the claimed dosing durability.

2 Requested listing

2.1 The re-submission presented the restriction as recommended by the PBAC at the July 2014 meeting.

3 Background

3.1 Alemtuzumab was TGA registered on 18 December 2013 for the treatment of relapsing-remitting MS (RRMS).

3.2 A major submission for alemtuzumab for the treatment of relapsing-remitting multiple sclerosis was considered and recommended by the PBAC at its July 2014 meeting. Listing was recommended on a cost-minimisation basis against [redacted] years of treatment with fingolimod (50%) and natalizumab (50%) and with (a) any price advantage for fingolimod accounting for its oral form not applying and (b) cost-offsets for infection management and prophylaxis for alemtuzumab.

3.3 In making this recommendation:
"The PBAC considered that the claim of clinical durability of alemtuzumab [2 years] compared to fingolimod and natalizumab [4.059 years] 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."

3.4 The key difference in this re-submission compared to the base case recommended by PBAC in July 2014 is that a cost-minimisation analysis based on [redacted] years of treatment with fingolimod and natalizumab is proposed – the base case recommended by PBAC is a cost-minimisation based on [redacted] years of treatment with the later medicines.

Summary of the changes between the previous submission and current re-submission

	Alemtuzumab July 2014	Current re-submission
Cost-minimisation	Authority required listing of alemtuzumab was sought on a cost-minimisation basis with [redacted] years of treatment with alemtuzumab compared to 2-5 years (4.059) of treatment with fingolimod and natalizumab. **PBAC Comment:** The PBAC considered a cost-minimisation based on [redacted] years of treatment with fingolimod and natalizumab is more appropriate.	Proposes a revised cost minimisation analysis based on [redacted] years of treatment with fingolimod and natalizumab.
Comparator weighting	Submission noted that based on a clinician survey the relative proportion of alemtuzumab use from replacement of natalizumab and fingolimod is 71% and 29% respectively. **PBAC Comment:** 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.	Adopts the requested changes to comparator weighting of 50:50.
Cost offsets	Submission includes prophylactic treatment costs and administration costs. **PBAC Comment:** Should include cost-offsets for infusion and for prophylaxis and treatment of adverse events.	The re-submission does not account for infusion cost unlike previous submission and the prices used for prophylaxis are not consistent with current PBS prices. Submission does not include costs for treating adverse events.
Utilisation/ Financial Estimates	Submission assumes no re-treatment dosing with alemtuzumab beyond the standard two courses **PBAC Comment:** This is inappropriate as the available study data indicate that some patients will require re-treatments within this timeframe.	Submission appears to continue to assume two treatments per patient.

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 At the July 2014 meeting, 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.

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

5 Comparator

5.1 The re-submission nominated fingolimod and natalizumab as the main comparators, which were previously accepted by the PBAC at the July 2014 meeting.

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 as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (2) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described a range of perceived benefits of treatment with alemtuzumab including efficacy with respect to relapses and progression, durability of the treatment which may obviate need for future treatment and compliance benefits of the drug.

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

Clinical trials

6.3 No new data was provided in the re-submission. The resubmission relies on data present in the July 2014 submission, including from the extension study of the CARE MS-I and CARE MS-II trials.

Trial ID	Protocol title/ Publication title	Publication citation
Alemtuzumab vs. subcutaneous interferon beta-1a		
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
CAMMS03409	Patients from CARE-MS I and CARE-MS II enrolled in extension	

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

Clinical claim

6.4 The re-submission presented an analysis for the duration of treatment based on approximately three years treatment of natalizumab and fingolimod compared to the base case recommended by PBAC – cost-minimisation based on [redacted] years treatment. This results in an ex-manufacturer price per vial that is [redacted] higher than that recommended by PBAC.

6.5 The resubmission relies on data included in the major submission considered at the July 2014 PBAC meeting to justify the proposed three year cost-minimisation approach, arguing that trial re-treatment rates are an adequate proxy for durability of effect because *"In years 2 and 3, a total of approximately 19% of patient experienced relapse (9% in year 2 and 10% in year 3), compared with 19.3% of patients who received re-treatment in year 3 This alignment in the results indicates that re-treatment rates do represent an accurate proxy for relapse, and therefore supports the pricing assumptions made in the submission. Data presented in the major submission (page 106) also demonstrated that, at year 3, improvements with respect to progression of disability observed during the main studies was also maintained during year 3, with 84% of patients enrolled into the extension study shown to be free of progression of disability at the end of year 3".*

6.6 However, the criteria for re-treatment in the extension trials, CARE MS-I and CARE MS-II trials, were that patients could receive alemtuzumab re-treatments if they had:

- At least one protocol-defined relapse;
- or At least two new or enlarging T2 and/or Gd-enhancing brain or spinal lesions on MRI.

6.7 The PBAC did consider the [redacted] results from CARE MS-I and CARE MS-II in its July deliberations and:

- 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,
- noted it is unclear whether the re-treatment criteria used in the CARE MS extension studies are likely to be representative of clinical practice and that the criteria for a patient to seek re-treatment were unclear and that it was uncertain how any such criteria may be interpreted by clinicians, and
- noted that the approach used by the submission does not account for any waning of effects before re-treatment.

6.8 Additionally, the July PBAC minutes stated,

”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 15% 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.”

The minor resubmission appears to present no data or arguments that address these concerns.

Economic analysis

6.9 The resubmission presents an updated cost-minimisation analysis comparing [redacted] years of treatment with alemtuzumab to [redacted] years of treatment with fingolimod and natalizumab.

6.10 The resubmission presents cost offsets in the cost-minimisation analysis.

6.11 The resubmission presents the total infusion cost incurred over two-courses of alemtuzumab treatment ($97.95 x 8 = $783.60), but does not include these in its calculation of the price of alemtuzumab.

6.12 The resubmission did not use the current PBS Schedule price to calculate the cost of pre-treatment and prophylaxis for two-courses of alemtuzumab treatment.

6.13 In the pre-PBAC response, the sponsor agreed to the re-calculated price based on the updated cost of pre-treatment and prophylaxis and inclusion of infusion costs.

6.14 The table below provides a corrected resubmission price for alemtuzumab and compares these to the “[redacted] cost-minimisation” price. The resubmission does not account for the costs of treating adverse effects with alemtuzumab. Neither price includes a cost offset for treating adverse events.

Effective ex-manufacturer cost per vial of alemtuzumab

Assumed length of treatment benefit (years)	Cost per patient (including administration and prophylaxis costs but not costs for treatment of adverse events)	Cost per vial (effective Ex-manufacturer)
[redacted]	[redacted]	[redacted]

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

Drug cost/patient/ course (over 2 years)

6.15 Based on the proposed ex-manufacturer list price and revised cost-minimisation approach, alemtuzumab will cost [redacted] for the standard two courses of therapy (one course per year for two years). A cost of [redacted] was recommended by the PBAC at the July 2014 meeting.

Estimated PBS usage & financial implications

6.16 The re-submission provides updated financial estimates based on the proposed effective price for alemtuzumab and the effective prices for natalizumab and fingolimod. Based on these updated calculations, the overall net cost of the listing of alemtuzumab on the PBS is estimated to be approximately [redacted] in year one, decreasing to approximately [redacted] in year 5. The updated financial estimates do not appear to have taken account of the potential for patients to require re-treatment beyond the standard two courses.

7 PBAC Outcome

7.1 The PBAC reiterated its previous recommendation for the Authority Required Section 100 (Highly Specialised Drugs Program) listing of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. The PBAC rejected the re-submission to amend the basis of the July 2014 PBAC recommendation to list alemtuzumab.

7.2 The PBAC noted that no new information was provided about the clinical place of alemtuzumab and recalled that the committee recognised that there may be a clinical need for the drug in patients with high disease activity but considered that this clinical place was uncertain. The PBAC noted the consumer comments submitted with this submission.

7.3 The PBAC noted that the re-submission nominated the previously accepted fingolimod and natalizumab as the main comparators.

7.4 The PBAC noted that no new data was presented in the submission to justify revising the dosing durability compared to the comparators. The resubmission relied on the same trials as presented in the July 2014 submission, namely CARE-MSI, CARE-

MSII and the extension study, CAMMS03409. The PBAC recalled its concern regarding a high risk of bias in the pivotal trials.

7.5 The PBAC reiterated its view from July 2014 of substantial concern regarding use of the extension study (CAMMS03409) to establish the durability of the effect of alemtuzumab. 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.

7.6 The PBAC recalled that it 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 again considered Table B.27 of the July 2014 submission and associated text confirming that only 15% of the total extension study population were relapse free at the end of Year 3. The Committee again noted that these data appeared to be inconsistent with the trial data, and was again concerned that the presentation of the data in this way may in fact be erroneous. The PBAC noted that the submission did not address this issue.

7.7 The PBAC noted the sponsor-funded Lemtrada safety monitoring program.

7.8 The PBAC recalled that it had considered 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.

7.9 The PBAC again noted that, although based on a cost-minimisation approach, the submission estimated a net cost to the PBS, though lower than the net cost estimated in the previous submission.

7.10 The PBAC did not recommend any changes to the listing recommended at the July 2014 meeting.

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

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

Genzyme (a Sanofi company) remains committed to working with the Department towards achieving the PBS listing of Lemtrada for patients with relapsing-remitting multiple sclerosis.