

## 6.01 ALEMTUZUMAB, Solution concentrate for I.V. infusion, 12 mg in 1.2 mL vial, Lemtrada<sup>®</sup>, Sanofi Aventis Australia.

### 1 Purpose of Application

- 1.1 Two initial courses of alemtuzumab are currently listed on Section 100 of the PBS for the treatment of relapsing remitting multiple sclerosis (RRMS). The resubmission is seeking:
- An increase in the price per vial based on a claim of extended clinical benefit from two years to six years; and
  - Reimbursement of up to two additional courses of treatment for patients who meet the proposed re-treatment criteria.
- 1.2 The first submission of alemtuzumab for RRMS was in July 2014. Alemtuzumab was recommended for listing on the basis of non-inferiority to fingolimod and natalizumab over two years. A second minor submission was presented in November 2014 with the same trial data and interim CARE-MS extension trial data, requesting a price increase on the basis of greater durability of effect compared to natalizumab and fingolimod.

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

Component	Description
Population	Adult patients with relapsing remitting multiple sclerosis. There are two subpopulations of interest: 1. Those who do NOT experience one or more relapses OR two or more new or enlarging brain or spinal cord lesions (with no continuing progression while on treatment) following two courses of PBS-subsidised alemtuzumab; and 2. Those who experience one or more relapses OR two or more new or enlarging brain or spinal cord lesions (with no continuing progression while on treatment) following two courses of PBS-subsidised alemtuzumab.
Intervention	Consistent with the two subpopulations, two treatment regimens are relevant: 1. Alemtuzumab 12 mg/day administered by IV infusion for 2 courses, with no further treatment; and 2. Alemtuzumab 12 mg/day administered by IV infusion for 2 courses with additional (up to four), as-needed, treatment courses given upon documented evidence of MS disease activity (relapse or MRI) at least 12 months after prior treatment
Comparator	The resubmission nominated current standard of care, defined as two courses of alemtuzumab for all patients up to two additional courses in a minority of patients as-needed. <sup>a</sup>
Outcomes	Comparison of outcomes at two years versus outcomes at six years following an initial course of alemtuzumab treatment (sustained accumulation of disability, annualised relapse rate, proportion of subjects remaining free from relapses, subclinical measures of progression based on MRI).
Clinical claim	For a majority of patients, the clinical benefits in terms of annual rate of relapse and rate of accumulation of disability observed after two years of follow-up is maintained for a minimum of six years with no additional courses of treatment. For a small subset of patients, one or two additional courses of treatment are required to maintain the clinical benefit.

Source: Table 1.1.1, p2 of the resubmission.

<sup>a</sup> Two additional courses included in definition of standard of care on the basis that the third and fourth courses are currently supplied by the sponsor under a compassionate supply arrangement.

## 2 Requested listing

2.1 The table below presents the requested restriction. Underlined text represents criteria that is new to the requested restriction and that differs from the current alemtuzumab restriction for continuing treatment.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ALEMTUZUMAB SOLUTION FOR INFUSION, 10 MG/ML; 2ML VIAL	3	0	Effective: \$ Published: \$	Lemtrada Sanofi Aventis Australia

Category Program	/	Section 100 – Highly Specialised Drugs Program
Prescriber type:		<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:		Multiple Sclerosis
PBS Indication:		Multiple Sclerosis
Treatment phase:		Continuing
Restriction Level / Method:		<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:		Must be treated by a neurologist
Clinical criteria:		<u>Patient must have previously received at least two courses of PBS-subsidised treatment with this drug for this condition (at least 12 months prior).</u> AND <u>Patient must have had one or more relapses OR two or more new or enlarging brain or spinal cord lesions</u> 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 AND The treatment must be a sole PBS-subsidised modifying therapy for this condition AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy

Source: Table 1.4.2, p11 of the resubmission. PBS = Pharmaceutical Benefits Scheme

2.2 The resubmission stated that under current reimbursement conditions, alemtuzumab is listed on the PBS with a special pricing arrangement (SPA: % rebate) and stated that the sponsor's intention was to retain this SPA following the requested changes to the current reimbursement.

- 2.3 Compared to the previous submissions, the current resubmission is for the same population. However, up to two additional as-needed treatment courses are requested for listing for patients who have:
- had one or more relapses; or
  - two or more new enlarging brain or spinal cord lesions.

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

### 3 Background

#### **Registration status**

- 3.1 Alemtuzumab was initially listed on the Australian Register of Therapeutic Goods (ARTG) for the treatment of RRMS on 18 December 2013 for two courses of treatment.
- 3.2 The PBAC noted that a submission to the TGA requesting an update to the PI to allow for two additional treatment courses for patients experiencing a resumption of disease activity following the initial two courses of treatment was approved on 1 May 2018.

#### **Previous PBAC consideration**

- 3.3 Table 2 presents a summary of outstanding matters of concern from the November 2014 minor resubmission of alemtuzumab.

**Table 2: Summary of outstanding matters of concern**

Component	Matter of concern (November 2014 PSD)	How the resubmission addresses it
Clinical place of alemtuzumab	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 (paragraph 7.2).	Not explicitly addressed. The resubmission considered the place of alemtuzumab therapy in terms of the two additional courses of as-needed therapy.
Clinical evidence	The PBAC noted that no new data was presented in the submission to justify revising the dosing durability compared to the comparators... The PBAC recalled its concern regarding a high risk of bias in the pivotal trials (paragraph 7.4).	The current resubmission included final results (six years) of the CARE-MS extension study to justify the dosing durability compared to itself rather than to previous comparators.
	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 (paragraph 7.5).	The resubmission’s cost analysis attempted to explicitly address assumptions regarding re-treatment rates and patients switching to other therapies. The cost analysis did not address waning effects before re-treatment, and whether re-treatment criteria used in CARE-MS extension would be representative of clinical practice.
	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 (paragraph 7.6).	The resubmission mostly based its clinical claim on annualised relapse rates rather than patients remaining relapse-free over the time period. It did not appear that the necessary links between individual patients were demonstrated.

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<b>Component</b>	<b>Matter of concern (November 2014 PSD)</b>	<b>How the resubmission addresses it</b>
Economic evaluation	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 (paragraph 7.8).	No cost-utility analysis was presented

Source: Alemtuzumab November 2014 PSD

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

## **4 Population and disease**

- 4.1 Multiple sclerosis (MS) is an acquired, immune-mediated disorder of the central nervous system (CNS) characterised by inflammation, demyelination and axonal degeneration. The disease is progressive and eventually results in permanent CNS damage and chronic neurological disability. The cause of MS is not known.
- 4.2 The clinical course of MS is varied. Without treatment, more than 30% of patients with MS develop significant physical disability within 15-20 years of onset, with a shortened life expectancy directly related to the level of neurological disability. Clinical manifestations of the disease including sensory disturbances, fatigue and limb weakness, bladder and bowel symptoms and restrictions to mobility progressively reduce the quality of life for people with MS.
- 4.3 The PBAC noted that alemtuzumab is positioned as a first-line treatment in patients with aggressive disease, as well as a second-line treatment in patients failing other disease modifying therapies. Alemtuzumab may be considered as a ‘high potency’ (those therapies listed on a cost-effectiveness basis to interferon beta, or subsequently cost-minimised to one of these) disease modifying treatment (DMT) in RRMS. Other PBS-listed ‘high potency’ DMTs include fingolimod, natalizumab and ocrelizumab. The resubmission’s requested two additional courses of treatment as-needed would be for patients with at least one relapse or at least two new enlarging brain or spinal cord lesions after a previous course of alemtuzumab.

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

## **5 Comparator**

- 5.1 The resubmission nominated current standard of care, which includes two courses of PBS-funded alemtuzumab for the majority of patients and up to two additional courses of treatment as currently supplied by the sponsor as the main comparator. The PBAC considered that the nominated comparator was inappropriate as the treatment described was the intervention for which listing was sought in the resubmission.
- 5.2 The resubmission acknowledged that while the PBAC has previously accepted fingolimod and natalizumab as the comparators for alemtuzumab (Alemtuzumab July 2014 PSD, paragraph 7.3) the sponsor considered these two therapies not to be relevant primary comparators when considering the long-term efficacy of alemtuzumab as neither therapy currently substitute for extended use of

alemtuzumab (beyond the second course of therapy), and therefore both therapies would not be replaced by listing a third and fourth course of alemtuzumab on the PBS. The PBAC noted that based on the algorithm presented in the resubmission and the relevant PBS restrictions, patients should be able to be treated with another PBS-listed disease modifying therapy (DMT; e.g. fingolimod, natalizumab, or ocrelizumab; and cladribine with its positive recommendation for PBS-listing at the July 2018 PBAC meeting) after a second course of alemtuzumab and therefore considered other DMTs are valid comparators.

- 5.3 The ESC noted that if treatment with alemtuzumab is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend alemtuzumab if it is satisfied that alemtuzumab provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The alternative therapies in this case may include fingolimod, natalizumab, ocrelizumab, cladribine or any other DMT PBS-listed for RRMS. The pre-PBAC response (p1) argued that the requested price increase did not represent a price premium over other high potency DMTs. The pre-PBAC response (p1) instead argued that the current price of the two courses of alemtuzumab was based on cost-minimisation to 2 years of ongoing treatment with fingolimod or natalizumab. Hence, the pre-PBAC response (p1) argued that the price increase represented a price consistent with ongoing treatment with these alternative DMTs over the period of clinical benefit achieved. The PBAC considered that an assessment of the claim of extended benefit put forward by the resubmission would require data against the comparison of interest outlined in paragraph 5.4.
- 5.4 The resubmission asserted that two courses of alemtuzumab are sufficient for six years of therapy in a majority of patients. In its cost analysis, the resubmission assumes that the cost of these two courses of alemtuzumab should be equivalent to six years of continuous use of fingolimod or natalizumab (ocrelizumab and cladribine have also become relevant comparators). Thus, for patients not requiring further treatment following two courses of PBS-subsidised alemtuzumab, the relevant comparison to support the approach to the cost-minimisation analysis, predicated on the demonstration of non-inferior effectiveness and safety, would be that described in Table 3.

**Table 3: Comparison of interest for those who do not experience one or more relapses OR two or more new or enlarging brain or spinal cord lesions (with no continuing progression while on treatment) following two courses of PBS-subsidised alemtuzumab**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Alemtuzumab	Course 1	Course 2	No further treatment			
versus						
Fingolimod, natalizumab (and ocrelizumab, cladribine)	Continuous treatment					

- 5.5 The requested restriction for the third and fourth courses of alemtuzumab is for those who “had one or more relapses OR two or more new or enlarging brain or spinal cord lesions (with no continuing progression while on treatment)”, with the third and fourth courses being administered at least 12 months after the last (e.g. the third (and

subsequently fourth) course could be administered in Year 3 or later). Patients experiencing relapses and the accumulation of new lesions may generally signal that patients should be switching therapy. There are no preclusions or special requirements for treatment switching with RRMS medicines, however there are preclusions to concomitant use of some therapies on the PBS (the dimethyl fumarate, teriflunomide, natalizumab, fingolimod, alemtuzumab and ocrelizumab PBS listings each specify that the therapy is the “sole PBS-subsidised disease modifying therapy for this condition”). Thus, for patients experiencing relapses or accumulation of new lesions, the relevant comparison to determine the comparative effectiveness and safety and cost-effectiveness would be that described in Table 4.

**Table 4: Comparison of interest for those who experience one or more relapses OR two or more new or enlarging brain or spinal cord lesions (with no continuing progression while on treatment) following two courses of PBS-subsidised alemtuzumab**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year ∞
Alemtuzumab	Course 1	Course 2	Course 3				
and							
Alemtuzumab	Course 1	Course 2	Courses 3 and 4				
versus							
Alemtuzumab	Course 1	Course 2	Switch to alternative RRMS medicine <sup>a</sup> or no further treatment				

<sup>a</sup> may be a preference for other ‘high potency’ treatments (fingolimod, natalizumab, ocrelizumab, cladribine) but all PBS-listed therapies for RRMS are relevant, or possibly other ‘third line’ agents such as mitoxantrone or cyclophosphamide. This should include those who switch to an alternative therapy within 12 months of the second course of alemtuzumab.

- 5.6 The PSCR (p1) argued that for the proportion of patients who do relapse following two courses of alemtuzumab, an alternative DMT would be an unlikely treatment option noting that in the extension study only █% of patients were treated with other DMTs and that investigators in the study made this decision independently. The PBAC disagreed with the sponsor and advised that an assessment of any incremental benefit provided by the administration of up to two additional courses of alemtuzumab would require comparison with an alternative RMMS medicine or no further treatment after the initial two courses of alemtuzumab.
- 5.7 The ESC considered that the comparison of up to two additional courses of treatment with the currently reimbursed two courses of treatment was not a sufficient basis upon which to request a price increase. The PBAC agreed with the ESC that it was unreasonable to conflate the requested price increase which is based on the assumption of the same level of benefit being maintained in all patients, with the request for up to two additional courses of treatment as the requirement for additional courses of treatment indicates that the extent of sustained treatment benefit is not equivalent for all patients.

*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 the organisation MS Research Australia via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with alemtuzumab including stabilising or improving disabilities (as demonstrated by EDSS scores) and its impact on conversion from RRMS to secondary progressive MS reported in the CARE-MS I and II trials. The comments supported the inclusion of the additional dosage of alemtuzumab on the PBS to maximise the treatment options for people with this condition stating that reducing the frequency of disabling responses will improve quality of life for people with MS and their families.

### ***Clinical trials***

6.3 The resubmission was based on an extension study to the core CARE-MS I and II trials comparing immediate alemtuzumab treatment to delayed alemtuzumab treatment (n=1,314) as well as the core CARE-MS I and II trials. All of this evidence had previously been presented in the July and November 2014 alemtuzumab submissions. However, the current resubmission presented final results from CARE-MS extensions that were not available for the previous submissions.

6.4 Details of the trials presented in the resubmission are provided in Table 5.

**Table 5: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
CAMMS323 (CARE-MS-I)	Clinical Study Report: A Phase 3 randomised rater blinded study comparing two annual cycles of intravenous alemtuzumab to three-times weekly subcutaneous interferon beta-1a (Rebif®) in treatment naïve patients with relapse-remitting multiple sclerosis (CARE-MS I)  Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial.	2012  <i>Lancet.</i> 2012; 380(9856):1819-28
CAMMS324 (CARE-MS-II)	Clinical study report: A Phase 3 randomised 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 (CARE-MS II)  Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial.	2012  <i>Lancet.</i> 2012; 380(9856):1829-39
<b>Extension studies</b>		
CAMMS(03409) CARE-MS extension	Clinical Study Report: An extension protocol for multiple sclerosis patients who participated in Genzyme-sponsored studies of alemtuzumab.  Havrdova E et al. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. Coles AJ et al. Alemtuzumab CARE-MS II 5-year follow-up: Efficacy and safety findings.	2017  <i>Neurology.</i> 2017; 89(11):1107-16. <i>Neurology.</i> 2017; 89(11):1117-26.

Source: Source: Table 2.2.1, p16 of the resubmission.

6.5 The resubmission stated that a statistically robust indirect comparison of the long-term efficacy and safety of alemtuzumab versus fingolimod or natalizumab was hampered by lack of comparators, lack of data, and differences in trial design, patient cohorts and lengths of follow up. The resubmission stated that a naïve indirect comparison of the efficacy and safety over an extended time period with alemtuzumab compared to continuous fingolimod or natalizumab was presented in an Attachment to the resubmission. The resubmission provided the results of literature searches however a formal indirect comparison was not provided. The PBAC noted that a matched cohort study comparing interferon beta, fingolimod, natalizumab and alemtuzumab in patients with RRMS for up to 4 years (Kalincik et al 2017<sup>1</sup>) was identified during the evaluation.

6.6 The key features of the direct randomised trials and extension study are summarised in Table 6.

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<sup>1</sup> Kalincik et al. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. *Lancet Neurol.* 2017 Apr;16(4):271-281. doi: 10.1016/S1474-4422(17)30007-8. Epub 2017 Feb 11

**Table 6: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in cost analysis
<b>Alemtuzumab versus interferon beta</b>						
CARE-MS I	581	OL 2 years	High	Treatment Naive RRMS	ARR, SAD, re-treatment rates	Not used
CARE-MS II	840	OL 2 years	High	Treatment experienced RRMS		Not used
<b>Alemtuzumab</b>						
CARE-MS extension	1,314	OL 6 years	High	Patients enrolled in core CARE-MS trials		Re-treatment rates

Source: pp17-22 of the resubmission.

ARR=annualised relapse rate; DB=double blind; MC=multi-centre; OL=open label; SAD= sustained accumulation of disability

- 6.7 The comparison of alemtuzumab over two years versus over six years was conducted post-hoc, was descriptive with no statistical testing and based on the unblinded, single intervention CARE-MS extension study, which made it susceptible to bias. The PSCR (p1) stated that the extension study was analysed according to a pre-planned statistical analysis plan and therefore was not post-hoc. The ESC noted the specific comparison of results at two and six years was not presented in the Clinical Study Report and appeared to be post-hoc. The PBAC considered that because it was a single arm study the efficacy and safety of the additional courses of alemtuzumab versus no additional treatment or switching to an alternative treatment could not be assessed.
- 6.8 The resubmission’s choice of analysis sets from the CARE-MS extension was inconsistent and not clearly discussed. The resubmission described the full analysis set (FAS) as including all patients who received at least one intervention in the core CARE-MS trials. However, the resubmission presented most of the re-treatment rate comparisons from the immediate alemtuzumab treatment (IAT) subgroup (those treated with alemtuzumab in the core trials and enrolled in the extension for possible treatment with a third to sixth course). The delayed alemtuzumab treatment (DAT) subgroup were those treated with interferon beta in the core trials and enrolled in the extension study for possible treatment with a first to fourth course of alemtuzumab. The IAT and DAT subgroups appeared to be based on the set of patients who enrolled in the CARE-MS extension study only. The PSCR stated ‘█ patients who completed the study did not enrol in the extension study’. The ESC noted of the 822 patients randomised to receive 12 mg alemtuzumab in the IAT subgroup of the CARE-MS trials, █ enrolled in the extension study (MS-CARE extension study CSR, Table 10). Thus, █% of patients may have derived less than 2 years of benefit.
- 6.9 The PBAC considered that given the differences in inclusion criteria and the baseline characteristics of the patients recruited in CARE-MS I and CARE-MS II, it may not be reasonable to pool the results of the two patient groups. Patients in CARE-MS I were younger, had less severe disease (measured by baseline EDSS), a more recent diagnosis and reported a lower re-treatment rate than patients in CARE-MS II (33.0% vs 40.9%), which the resubmission has pooled together with no weighting. Should the relative patient mix in the proposed PBS population be different to the relative patient mix in CARE-MS I compared to CARE-MS II, the re-treatment rate in the proposed PBS population would be different to that reported in CARE-MS extension.

### Comparative effectiveness

- 6.10 The resubmission presented a comparison of outcomes at two years versus outcomes after 3-6 years among patients enrolled in the CARE-MS (CAMMS03409) extension study who were treated with two to six courses of alemtuzumab. The PBAC has previously expressed concern in using the CARE-MS (CAMMS03409) extension study in assessing sustained benefit due to the risk of bias (Alemtuzumab November 2014 PSD, paragraph 7.5). Additionally, the comparison of re-treatment rates without annualising the rates presented challenges in interpreting key outcomes (relapse and disability progression) over time specifically in light of the fact that the PBAC has previously stated its preference for the outcome of proportion of patients remaining relapse-free (Alemtuzumab July 2014 PSD, paragraph 6.10, Alemtuzumab November 2014 PSD, paragraph 7.6) as an outcome of sustained benefit.
- 6.11 Only data from patients in the “immediate alemtuzumab treatment” (IAT) group, which consisted of patients who had received treatment with two courses of alemtuzumab 12 mg in the phase III RCTs, were included in the resubmission.
- 6.12 The proportion of patients remaining relapse-free (patients were considered relapse-free if they did not experience a relapse in the relevant time period) are presented in Table 7.

**Table 7: Proportion of patients relapse-free, IAT subgroup from CARE-MS I and CARE-MS II populations**

Time period	Outcome	CARE-MS I IAT N=376	CARE-MS II IAT N=426	IAT N=802
Year 0-2	Patient with event, n	82	147	NA
	KM estimate of event (95% CI)	NR	NR	
	KM no event (95% CI)	77.6 (72.9, 81.6)	65.4 (60.7, 69.7)	
Year 0-4	Patient with event, n	■	■	■
	KM estimate of event (95% CI)	■	■	■
	KM no event (95% CI)	■	■	■
Year 0-6	Patient with event, n	■	■	■
	KM estimate of event (95% CI)	■	■	■
	KM no event (95% CI)	■	■	■

Source: Table 2.5.6, p43 of the resubmission.

CI = confidence interval; IAT = immediate alemtuzumab group; KM = Kaplan Meier; NA = not available; NR=not reported.

- 6.13 Around ■ of all patients who remained relapse-free over two years (77.6% in CARE-MS I and 65.4% in CARE-MS II) remained relapse-free over six years (■% in CARE-MS I and ■% in CARE-MS II). This indicated that while rates of relapse may have been consistent, in the aggregate, the benefit was not maintained from two to six years. This was to be expected given the natural history of MS, but it is important as the cost-analysis assumed that efficacy is maintained for six years. Moreover, there appears to be tangible differences between patients enrolled in CARE-MS I and CARE-MS II, with a larger proportion of patients enrolled in CARE-MS I reporting no event at 6 years than patients enrolled in CARE-MS II. The ESC considered that the data presented suggested that a proportion of patients may receive some benefit from

treatment with alemtuzumab beyond two years. However, a substantial proportion of patients (22-35%) had a relapse event within the first 2 years of treatment. The PBAC reaffirmed its July 2014 and November 2014 advice regarding its preference for the outcome of proportion of patients remaining relapse free as the basis for assessing durability of effect. The PBAC noted that the proportion of patients remaining free of accumulated disability (or free of relapse) in CARE-MS extension decreased over time (77.6%/65.4% at Year 2, ██████% at Year 4 and ██████% at Year 6). The PBAC considered that this was inconsistent with a claim of sustained benefit.

6.14 Table 8 presents re-treatment rates from the extension study as well as re-treatment rates recalculated during the evaluation.

**Table 8: Re-treatment rates (safety IAT; n = 802) as per re-treatment memo and CSR (and revised in PSCR)**

Trial cohort	Course	Over 3 years	Over 4 years	Over 5 years	Over 6 years
<b>As per re-treatment memo</b>					
CARE-MS I	3rd	██████	██████	██████	██████
	4th	█	████	████	████
	5th	█	█	████	████
	6th	█	█	█	████
	Total re-treatment				██████
CARE-MS II	3rd	██████	██████ ██████	██████ ██████	██████ ██████
	4th	█	██████	████	████
	5th	█	█	████	████
	6th	█	█	█	████
	Total re-treatment				██████
Pooled	3rd	██████ ██████	██████ ██████	██████ ██████	██████ ██████
	4th	█	████	████	████
	5th	█	█	████	████
	6th	█	█	█	████
	Total re-treatment				██████
<b>Re-treatment as per CSR</b>					
Pooled IAT	Patients who complete course n (%) N=742		Reconstructing memo methodology: N=802; subtracting subsequent courses		
	Course 3	██████		████	
	Course 4	██████		████	
	Course 5	██████		████	
	Course 6	██████		████	

Source: Table 2.5.1, p32-33 of the resubmission. Table 25, p 127 of the CARE-MS extension CSR. IAT = immediate alemtuzumab group. CSR = clinical study report

Note: The resubmission noted that in order to calculate the number of patients receiving only a third course over each year, the fourth, fifth and sixth course (as required) have to be subtracted from the total of patients that received three courses to avoid double counting; to calculate the number of patients receiving only a fourth course over each year, the number of patients receiving the fifth and sixth course (as required) have to be subtracted from the total patients that received four courses to avoid double counting; and in order to calculate the number of patients receiving only a fifth course over each year, the number of patients receiving sixth course (as required) have to be subtracted from the total of patients that received five courses to avoid double counting. <sup>a</sup> revised in PSCR (Table 1, p6)

- 6.15 Re-treatment rates were based on a sponsor 're-treatment memo.' The resubmission stated that some results may differ from what was presented in the CARE-MS extension clinical study report but the re-treatment rates presented in the resubmission should be considered final. Review of the CARE-MS extension CSR indicated that the results in the CSR were final and included results after the database lock. Consequently, discrepancies between the pre-specified protocol defined analyses of re-treatment in the CSR and the post-hoc update in the re-treatment memo were not adequately accounted for. The resubmission and the re-treatment memo included very little information regarding the methodology for recalculating the re-treatment rates, nor any data except for percentages. The PSCR (p5-6) provided a table detailing the calculation of retreatment rates in the re-treatment memo. The treatment percentages for each course in each year was calculated by dividing the number of patients initiating the relevant course in the corresponding year by the total number of participants from CARE MS I/II in the CARE-MS extension trial. A number of the retreatment rates reported in the PSCR differed slightly to those presented in the resubmission (see Table 8).
- 6.16 The re-treatment memo assumed a total of 802 patients to calculate re-treatment, reflective of the total patients who received an intervention in one of the core CARE-MS studies. This, however, was inconsistent with the use of the IAT group in calculating the proportion of patients remaining relapse-free, 6 month sustained accumulation of disability and annualised relapse rate as the IAT subgroup was defined on the basis of patients who enrolled in the extension studies (N=742). While it would be reasonable to assume that many of the patients who did not enrol in the extension study would not have been re-treated, it may also be reasonable to assume that many of those patients were lost to follow up for many reasons including lack of benefit, and thus may not be reasonable to include in the analysis. Using only patients enrolled in the CARE-MS extension, results in significantly higher re-treatment rates. The PBAC considered that inconsistency in applying a methodology for calculating re-treatment percentages suggested that outcomes sourced from the re-treatment memo may be at increased risk of bias.
- 6.17 The PBAC noted that the alemtuzumab re-treatment percentages were based on number of patients who received an intervention in one of the core CARE-MS trials, patients who discontinued or were lost to follow-up without being re-treated were assumed to not require alemtuzumab re-treatment.
- 6.18 The PBAC also noted that according to the re-treatment memo █████% of patients in the CARE-MS extension trial required one or two additional courses of alemtuzumab to maintain clinical benefit.
- 6.19 The resubmission included proportions of patients receiving alternative DMTs from the re-treatment memo. The resubmission's re-treatment memo considered that approximately █████% of patients switched to an alternative DMT during the extension. The CSR included data on concomitant DMT use, but no information was given regarding when a switch occurred. The resubmission did not address whether the

CARE-MS extension would provide estimates of DMT use applicable to the current Australian setting. It could be reasonable to assume that treatment switch was lower in an open-label extension study designed specifically to study long term efficacy of alemtuzumab than in the Australian population. Additionally, the CARE-MS extension estimates would not account for possible increases in switching due to more recently recommended treatments such as ocrelizumab or cladribine. The ESC agreed with the evaluation that the proportion of patients that would switch to alternative DMTs in clinical practice was uncertain as retreatment rates were derived from an extension study investigating the long term efficacy of alemtuzumab. Further, the possibility of additional patients switching to newer treatments such as ocrelizumab or cladribine has not been considered.

6.20 Details of the six-month sustained accumulated disability results presented in the resubmission are provided in Table 9.

**Table 9: Six-month sustained accumulated disability (SAD), IAT subgroup from CARE-MS extension**

Time period	Outcome	CARE-MS I IAT N=376	CARE-MS II IAT N=426	IAT N=802
Year 0-2	Patient with event, n	30	54	NA
	KM estimate of event (95% CI)	8.00 (5.66, 11.24)	12.71 (9.89, 16.27)	
	KM no event (95%CI)	██████████	██████████	
	Annual rate of SAD	██	██	
Year 0-4	Patient with event, n	██	██	██
	KM estimate of event (95% CI)	██████████	██████████	██████████
	KM no event (95%CI)	██████████	██████████	██████████
	Annual rate of SAD	██	██	██
Year 0-6	Patient with event, n	██	██	██
	KM estimate of event (95% CI)	██████████	██████████	██████████
	KM no event (95%CI)	██████████	██████████	██████████
	Annual rate of SAD	██	██	██

Source: Table 2.5.3, p34 of the resubmission. CI = confidence interval; IAT = immediate alemtuzumab group; KM = Kaplan Meier; NA = not available; SAD =sustained accumulation of disability.

6.21 Table 10 presents annualised relapse rates in the IAT subgroup of CARE-MS extension.

Table 10: Annualised relapse rate, IAT subgroup from CARE-MS extension

Time period	Outcome	CARE-MS I IAT N=376	CARE-MS II IAT N=426	IAT N=802
Year 0-2	Patient with any event, n	25	147	NA
	Total number of events	38	236	
	Annualised rate (95%CI)	0.18 (0.13, 0.23)	0.26 (0.21, 0.33)	
Year 0-4	Patient with any event, n	█	█	█
	Total number of events	█	█	█
	Annualised rate (95%CI)	██████████	██████████	██████████
Year 0-6	Patient with any event, n	█	█	█
	Total number of events	█	█	█
	Annualised rate (95%CI)	██████████	██████████	██████████

Source: Table 2.5.5, p41 of the resubmission. CI = confidence interval; IAT = immediate alemtuzumab treatment group; NA = not available

6.22 Overall, these results show that disease progression continues over the 6 year period, though the resubmission claimed that the rate of disease progression was low. However, without an appropriate comparator this is impossible to verify.

6.23 Overall, based on the CARE-MS extension efficacy data presented in the resubmission, the PBAC considered the following may be reasonably concluded:

- patients will continue to progress over time at a reasonably steady rate;
- a significant proportion of patients (█%) would require at least one additional course of alemtuzumab or an alternative DMT; and
- older patients who have more severe disease (represented by patients enrolled in CARE-MS II) potentially respond differently to younger patients with less severe disease (represented by patients enrolled in CARE-MS I).

6.24 Based on the results presented in the resubmission, the following are still unknown:

- the disease progression of patients without the third and fourth course of alemtuzumab (i.e. the current PBS-subsidised population) and whether the third and fourth courses of alemtuzumab provided any incremental benefit; and
- how the response rate over time for alemtuzumab compares to other medications in the same place of the algorithm (i.e. fingolimod, natalizumab, ocrelizumab or cladribine).

The ESC considered that comparative data against either two courses of alemtuzumab or other DMTs to support the claimed durability of benefit with up to two additional courses of alemtuzumab would be informative. Without this, the response rate for alemtuzumab over time compared to other DMTs and the progression of patients who would not have received any additional courses of alemtuzumab beyond the initial two doses are unknown.

6.25 Kalincik et al 2017, identified during the evaluation, reported results from an international cohort study (21 countries, including Australia) using longitudinal data from propensity-matched patients with RRMS. Patients must have been treated with one of alemtuzumab (n=189), interferon beta (n=2155), fingolimod (n=828) or

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natalizumab (n=1160), aged 65 years or younger with EDSS score of 6.5 or lower. The results from Kalincik et al 2017 are summarised in Table 11. The number of patients treated with alemtuzumab differed in each comparison as patients were matched based on a propensity score calculated via a multivariate logistic regression including sex, age, time from first multiple sclerosis symptom, EDSS, number of relapses in the previous 12 months, number of previous courses of treatment for multiple sclerosis, and the most effective previous treatment for multiple sclerosis as variables.

Table 11: Summary of results from Kalincik et al 2017

Comparison	Alemtuzumab	Comparator	Comparative statistics
<b>Overall annualised relapse rate</b>			
Alemtuzumab (n=156) vs interferon beta (n=282) (mean, over 5 yrs)	<b>0.19 (0.14, 0.23)</b>	<b>0.53 (0.46, 0.61)</b>	<b>p&lt;0.0001</b>
Alemtuzumab (n=114) vs fingolimod (n=195) (mean, over 3 yrs)	<b>0.15 (0.10, 0.20)</b>	<b>0.34 (0.26,0.41)</b>	<b>p&lt;0.0001</b>
Alemtuzumab (n=138) vs natalizumab (n=223) (mean, over 4 yrs)	0.20 (0.14, 0.26)	0.19 (0.15, 0.23)	p=0.78
<b>Probability of remaining free from relapse</b>			
Alemtuzumab vs interferon beta	2 years: 80% 5 years: 74%	2 years: 40% 5 years: 31%	NR <sup>a</sup>
Alemtuzumab vs fingolimod	2 years: 82% 3 years: 81%	2 years: 67% 3 years: 65%	p=0.59 <sup>a</sup>
Alemtuzumab vs natalizumab	2 years: 81% 4 years: 78%	2 years: 78% 4 years: 70%	p=0.65 <sup>a</sup>
<b>Probability of 6 month disability accumulation</b>			
Alemtuzumab vs interferon beta	NR	NR	HR=0.66 (0.36, 1.22)
Alemtuzumab vs fingolimod	NR	NR	HR=1.27 (0.60, 2.70)
Alemtuzumab vs natalizumab	NR	NR	HR=0.81 (0.47, 1.39)
<b>Probability of 6 month disability improvement</b>			
Alemtuzumab vs interferon beta	NR	NR	HR=0.98 (0.65,1.49)
Alemtuzumab vs fingolimod	NR	NR	HR=0.50 (0.25, 1.01)
Alemtuzumab vs natalizumab	NR	NR	<b>HR=0.35</b> <b>(0.20, 0.59)</b>

<sup>a</sup> Publication states reported in appendix but appendix to publication could not be located during evaluation.

NR = not reported, HR = hazard ratio

Values in bold indicate statistically significant differences, text in italics indicate information compiled during evaluation

Source: Compiled during evaluation using information from Kalincik et al 2017.

6.26 Of the 189 patients treated with alemtuzumab, 84 (44%) required additional treatment cycles (time period not reported), a rate similar to that reported in CARE-MS extension. The authors also noted that analysis of propensity scores calculated with logistic models showed that patients started alemtuzumab treatment at earlier stages of disease, at a younger age, and had higher EDSS scores and pre-baseline relapse activity than patients given interferon beta, fingolimod, or natalizumab.

6.27 The probability of patients treated with alemtuzumab remaining relapse-free in Kalincik et al 2017 appears to be higher than that reported in CARE-MS extension (using the proportion who remained relapse-free as a proxy for probability, see Table 7), although the time periods analysed are not comparable. From the results reported in Kalincik et al 2017, it appears that treatment with alemtuzumab:

- is likely to be superior to interferon beta;
- is possibly superior to fingolimod in annualised relapse rate, noting that no MCID was specified and a confidence interval around the difference was not presented, and not statistically different in disability outcomes;
- is similar to natalizumab in annualised relapse rate, but statistically significantly worse in probability of six month disability improvement (HR=0.35, 95% CI: 0.20, 0.59).

However, as this was not a randomised controlled trial, the results should be interpreted with caution. The ESC noted results from Kalincik et al 2017 indicated that alemtuzumab may be inferior to natalizumab. The ESC noted that natalizumab is only used in RRMS patients who are JC virus antibody negative.

### Comparative harms

6.28 Table 12 presents a summary of key adverse events (AEs) by the number of treatment courses in the CARE-MS extension.

**Table 12: Summary of key adverse events by treatment course in CARE-MS extension**

Annualised rate of AE	Overall	Course 1	Course 2	Course 3	Course 4	Course 5	Course 6
Any AE event							
IAT patients at risk	■	■	■	■	■	■	■
Total person years	■	■	■	■	■	■	■
Events (rate)	■	■	■	■	■	■	■
Total patients at risk	■	■	■	■	■	■	■
Total person years	■	■	■	■	■	■	■
Events (rate)	■	■	■	■	■	■	■
Treatment emergent SAE							
Total patients at risk	■	■	■	■	■	■	■
Total person years	■	■	■	■	■	■	■
Events (rate)	■	■	■	■	■	■	■
Treatment emergent infections							
Total patients at risk	■	■	■	■	■	■	■
Total person years	■	■	■	■	■	■	■
Events (rate)	■	■	■	■	■	■	■

Source: Table 2.5.15, p57 of the resubmission; Table 33, p145 and Table 44, p 164 of the CARE-MS extension CSR.

Note: for course 1 and course 2, the events were sourced from the core CARE-MS trials

AE = adverse events, SAE = serious adverse events

6.29 Overall, it appeared that both AEs and treatment emergent serious adverse events (SAEs) have an initial high risk of events at course one, with a subsequent decrease at

course two followed by a slight increase for every course through course four. Though no statistical comparison was made, the point estimates indicated that with the exception of the second course, the risk per-person year of an AE or a treatment emergent serious AE increased slightly after every additional treatment course through the fourth course.

- 6.30 The adverse event profile for alemtuzumab in CARE-MS extension was similar to the two year CARE-MS I and CARE-MS II 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. The ESC noted that the toxicity of the high potency DMTs is greater than that for the lower potency DMTs, with pneumonitis and listeriosis having been adjudicated as important identified risks with alemtuzumab treatment. The ESC noted the comparative safety of alemtuzumab over six years compared to other DMTs is not known.

### **Clinical claim**

- 6.31 The resubmission claimed that for the majority of patients, the clinical benefits in terms of a reduced annualised relapse rate and accumulation of disability observed after two years of follow-up was maintained for a minimum of six years with two courses of treatment for some patients (■■■■%), with others (■■■■%) requiring one or two additional courses of treatment to maintain clinical benefit (an additional ■■■% of patients switched to alternative DMTs during the extension). This may not be supported as:

- The CARE-MS extension showed that patients continued to maintain similar annualised rates of sustained accumulated disability for up to 6 years with additional treatment as-needed. Patients however continued to progress, with a smaller proportion remaining relapse-free over time (77.6%/65.4% at 2 years to ■■■%/■■■% at 6 years in CARE-MS I and II, respectively). Additionally, the claim of sustained benefit on the basis of similar annualised rates over two years versus six years may not be appropriate. In a traditional economic evaluation, disability progression over time would be accounted for, so even if the rate remained similar, the same overall level of benefit would be lower over six years;
- The CARE-MS extension study was susceptible to high risk of bias (open label, single intervention) that could overestimate the sustained benefit of alemtuzumab with or without additional as-needed treatment; and
- The resubmission's presentation of re-treatment rates was poorly described and appeared biased due to the selective reporting of outcomes using alternative analysis sets.

The PBAC agreed with the ESC that the proportion of patients requiring more than two doses of alemtuzumab or an alternative DMT at ■■■% was considerable and therefore contradictory to the resubmission's assumption that the benefit of treatment is equivalent over six years for all patients.

- 6.32 The resubmission (p65) claimed that treatment with alemtuzumab represents a “favourable risk-benefit” profile with no new safety signals observed. As expected patients who were treated with more courses of alemtuzumab reported higher rates of AEs. The PBAC agreed with the resubmission’s claim that no new safety signals were evident for treatment with alemtuzumab. The PBAC also noted the ongoing sponsor-funded Lemtrada safety monitoring program.
- 6.33 No comparative claims on efficacy or safety compared to fingolimod or natalizumab (or ocrelizumab or cladribine) were made. The clinical evidence presented in the resubmission does not adequately provide a justification for an increase in the requested price, as a comparison to other DMTs was not presented. The ESC noted results from Kalincik et al 2017 indicated that alemtuzumab may be inferior to natalizumab. The ESC noted that natalizumab is only used in RRMS patients who are JC virus antibody negative.
- 6.34 The PBAC considered that the claim of extended clinical benefit from two years to six years was not adequately supported by the data.
- 6.35 The PBAC considered that the claim of comparable annual rates of adverse events between those who received alemtuzumab for two years and those who received a third or fourth course of alemtuzumab was reasonable.

### ***Economic analysis***

- 6.36 The resubmission presented a cost analysis which compared the cost per year of benefit with two courses of alemtuzumab (cost of two courses divided by two years of benefit) with that for up to four courses of alemtuzumab (cost of up to 4 courses divided by up to 6 years of benefit).
- 6.37 The most critical issue affecting the validity of the cost analysis presented in the resubmission is that the resubmission’s nominated comparator is likely to be inappropriate, and a cost effectiveness analysis against an alternative comparator (fingolimod, natalizumab, ocrelizumab or cladribine) should have been the basis for the analysis. The pre-PBAC response (p3) argued that while the current price per vial of alemtuzumab is based on the recognition of two years of clinical benefit, the requested price per vial is based on more recent data demonstrating a minimum of six years of benefit. Hence, the pre-PBAC response (p3) stated that the cost comparison presented appropriately reflects the clinical data presented. The PBAC disagreed with the sponsor and considered that a cost effectiveness analysis against an alternative comparator was the appropriate basis for the analysis.
- 6.38 Table 13 presents a summary of the cost-analysis.

**Table 13: Key assumptions and components of the cost-analysis approach**

Component	Claim or assumption
Evidence base	CARE-MS extension single arm study and original CARE-MS core trials
Therapeutic claim: effectiveness	Effectiveness of alemtuzumab is assumed to be sustained beyond the two-year period for which alemtuzumab is currently reimbursed. The resubmission considers that the magnitude of the benefit observed for alemtuzumab at two years is maintained for a minimum of six years, with up to two additional courses of treatment beyond what is currently subsidised.
Therapeutic claim: safety	The resubmission considered that the annual rates of adverse events were comparable between those who receive alemtuzumab for two years and those who received a third or fourth course of alemtuzumab. Additional courses of treatment showed higher rates of adverse event.
Cost analysis	A cohort approach to calculate the average number of alemtuzumab courses required over the six-year period. The majority of patients (52.8%) receive two courses (8 vials of alemtuzumab). A third or fourth course of alemtuzumab is given to patients if they met the proposed re-treatment criteria (described paragraph 2.4)
Direct medicine costs	The current cost of alemtuzumab is \$ [REDACTED] per vial. The requested price increase is to \$ [REDACTED] per vial.

Source: Table 3.1.1, p66 of the resubmission.

- 6.39 The cost-analysis included the pharmaceutical costs associated with alemtuzumab over 6 years. The resubmission stated that the clinical benefit derived from treatment with alemtuzumab goes beyond the two years previously accepted by the PBAC, and upon which the drug cost was previously based. The resubmission also stated that the effectiveness of the initial two treatment courses of alemtuzumab lasts for at least 6 years in the majority of patients, while for a minority of patients, additional courses of alemtuzumab are required to achieve this benefit. While the resubmission claimed that only a minority of patients will receive additional courses, the PBAC noted that the cost analysis results (below) show that [REDACTED]% of patients will require more than two courses
- 6.40 Results of the cost analysis are presented in Table 14. The vial price was adjusted (increased) so that the cost per year of benefit was maintained at \$ [REDACTED] with the benefit being maintained over 5.7 years, thereby increasing the total cost from \$ [REDACTED] per patient to \$ [REDACTED] per patient.

Table 14: Results of cost analysis

Courses of alemtuzumab	Proportion of patients	Vial cost	Number of vials	Total cost	Assumed benefit, years	Cost per year of benefit
<b>Current scenario</b>						
2 courses	█%	\$█	8	\$█	█	\$█
<b>Proposed scenario</b>						
2 courses	█%	\$█	8	\$█	█	
2 courses (reduced benefit as switched to alternative DMT)	█%	\$█	8	\$█	█	
3 courses	█%	\$█	11	\$█	█	
4 courses	█%	\$█	14	\$█	█	
4 courses (reduced benefit as 5/6 courses received)	█%	\$█	14	\$█	█	
Weighted				\$█	█	\$█

Source: Table 3.2.1,p68;Table 3.2.2,p69 and Table 3.4.1, p70 of the resubmission

- 6.41 The PBAC noted that the magnitude of the requested increased price per vial derived from the cost analysis was largely driven by the assumption of sustained benefit over 6 years.
- 6.42 The approach of comparing annualised benefit over two years compared with six years may not be internally valid. A traditional cost-effectiveness approach would aggregate benefit over a single time horizon (e.g. patients remaining relapse-free, or disability-free) and the clinical evidence suggests that in such an approach, benefit would decrease in the aggregate over time. Consequently, in addition to the risk of bias associated with the CARE-MS extension, the nature of the comparison of two-year data and six-year data may not allow for the cost-analysis’s premise of sustained benefit.
- 6.43 The calculation of estimated benefit in the cost analysis and the calculation of the number of vials required was based on the re-treatment memo sourced re-treatment rates. Neither benefits nor costs in the cost analysis were subject to discounting.
- 6.44 Since the alemtuzumab re-treatment rates in the re-treatment memo appeared to be based on the number of patients who received at least one intervention in the core CARE-MS trials, and the alternative DMT rates from the re-treatment memo appeared to be based on the number of patients enrolled in the extension study, there was a general lack of clarity around the patients who discontinue alemtuzumab, switch to alternative therapy, are lost to follow up prior to two years or did not enrol in the extension in the cost-analysis. It is likely that explicitly including limits on benefits for these patients would decrease the average duration of benefit estimated by the resubmission.
- 6.45 The resubmission assumed that patients that received a third or fourth course, would still have the same level of benefit as patients who did not (six years). This did not factor in the loss of benefit required to be prescribed another dose, and thus overestimated benefit in these patients. Further, the resubmission unreasonably

assumed that patients who switched treatments after two courses would derive more than two years of benefit. The ESC agreed with the evaluation that the assumption that patients who require more than two courses of treatment would derive equal benefit over 6 years to patients who were treated with only two courses was unjustified.

- 6.46 Cost-offsets for DMTs switched to during the time horizon for which the benefit of alemtuzumab is claimed were not included which led to an increased effective price. The PSCR (p4) stated that the cost-analysis only included the costs and benefits associated with alemtuzumab, with an average of [REDACTED] years of benefit assigned to the [REDACTED]% of patients who switched to alternative DMTs during the extension.
- 6.47 Overall, the PBAC agreed with the ESC that in the absence of comparative evidence of efficacy, safety and cost-effectiveness between up to four treatment courses of alemtuzumab and alternative DMTs, the cost analysis presented was inappropriate to value the durability of alemtuzumab treatment. As such, the PBAC considered there was insufficient justification for the requested increase in the price of alemtuzumab.
- 6.48 The ESC considered that a cost utility analysis comparing up to two additional courses of alemtuzumab with alternative DMTs (i.e. fingolimod, natalizumab, ocrelizumab, cladribine) would be more appropriate to value the treatment effect of alemtuzumab over 6 years. In particular, the ESC considered that utilities could be used to reflect the variation of treatment benefit between patients over time.
- 6.49 The PSCR (p6) presented a supplementary cost-minimisation analysis of alemtuzumab versus fingolimod and natalizumab. However, the PBAC considered that this analysis was not informative as the analysis, as per the cost-analysis presented in the resubmission, assumes equivalent efficacy and safety between alemtuzumab and alternative DMTs over 6 years which has not been adequately supported by data in the resubmission. The analysis also did not consider the comparative efficacy and cost of treatment versus ocrelizumab or cladribine.

### ***Drug cost/patient/courses***

- 6.50 The initial cost of alemtuzumab for two courses of treatment will be \$ [REDACTED] based on a requested vial price of \$ [REDACTED] and an estimated 8 vials required for the first two courses (5 vials for first course; 3 for second).
- 6.51 Additional treatment courses, as-needed, will cost \$ [REDACTED], based on the same requested vial price and an estimated 3 vials per additional, as-needed course.

### ***Estimated PBS usage & financial implications***

- 6.52 This resubmission was not considered by DUSC. Estimated use and financial implications were primarily based on PBS data of patients initiating alemtuzumab for RRMS and re-treatment rates derived from the sponsor's re-treatment memo. The estimated use and financial implications are presented in Table 15.

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6.53 The resubmission calculated financial estimates based on re-treatment rates from the re-treatment memo. The PBAC noted that these could not be verified and considered they may be underestimated.

6.54 The resubmission’s approach to calculation of market growth (-2.7% per year) based on past alemtuzumab use may not have been appropriate, as it was unclear whether future market entrants would continue to put similar pressure on alemtuzumab use as past entrants.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use (total first, second, third and fourth courses)</b>						
First course						
Second course						
Third course						
Fourth course						
<b>Estimated financial implications of alemtuzumab (using \$ per vial; proposed effective price)</b>						
First course	\$	\$	\$	\$	\$	\$
Second course	\$	\$	\$	\$	\$	\$
Third course	\$	\$	\$	\$	\$	\$
Fourth course	\$	\$	\$	\$	\$	\$
Net increase associated with the first and second course	\$	\$	\$	\$	\$	\$
Cost associated with third and fourth course	\$	\$	\$	\$	\$	\$
Net total with increased vial price	\$	\$	\$	\$	\$	\$
Total patient co-payments	\$	\$	\$	\$	\$	\$
Total minus co-payments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for pre-treatment medications (methylprednisolone and acyclovir)</b>						
Total	\$	\$	\$	\$	\$	\$
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Total cost to MBS	\$	\$	\$	\$	\$	\$
Net cost to Government	\$	\$	\$	\$	\$	\$

Source: Table 4.4, p74 to Table 4.18, p 81 of the resubmission

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$20-\$30 million.

6.55 The resubmission noted that between April 2017, and 2018, the sponsor had reimbursed █ patients for a third course of alemtuzumab. The resubmission considered that these patients met the proposed restriction criteria and are comparable with the estimated patient numbers. The resubmission’s financial estimates, however, indicate that █ patients would be expected to initiate a third course in the first year of listing (the year with the smallest number of patients initiating a third course). This was more than double of the sponsor-subsidised treatments. On one hand, this could suggest an overestimation of patients receiving alemtuzumab treatment (either underestimating patients who benefit without additional treatment or more likely underestimating patients who choose alternative

DMT); on the other, details of the sponsor-subsidisation process and criteria have not been provided and could be different than what would be expected in a PBS reimbursement setting. Consequently, number of patients initiating third and fourth courses remained uncertain.

- 6.56 The PSCR (p4) stated that compassionate supply to the ■ patients was provided before the TGA approved the Product information sheet on 1 May 2018 so patients could receive up to two additional courses of treatment. The PSCR clarified that the ■ patients estimated is for 2019 as the number of patients eligible for a third or fourth treatment is expected to increase due to increase in the number of patients receiving a first and second treatment course. The ESC considered the utilisation of alemtuzumab would likely be lower than estimated in the resubmission given current utilisation of alemtuzumab has been low compared to other DMTs and the estimates did not account for recently recommended treatments for RRMS ocrelizumab and cladribine. The pre-PBAC response (p3) stated that ■ patients are estimated to receive a third course of treatment in 2018, with this number increasing to ■ in 2019. The PBAC considered that the proposed number of patients requiring a third course of alemtuzumab was a source of uncertainty.
- 6.57 The ESC noted that the resubmission inappropriately excluded costs for AEs associated with additional courses of alemtuzumab.
- 6.58 At Year 6, the estimated number of patients was ■ for the first course, ■ for the second course, ■ for the third course and ■ for the fourth course of alemtuzumab and the net cost to the PBS would be \$20 - \$30 million (using the proposed effective price of \$ ■ per vial).
- 6.59 The PBAC noted that the net cost to the PBS of listing a third and fourth course of alemtuzumab at the current vial price of \$ ■ is estimated to be \$ ■ in Year 1, increasing to \$ ■ in Year 3 and reducing to \$ ■ in Year 6.
- 6.60 The PBAC considered that the financial estimates presented were inconsistent with a cost-minimisation approach as they did not include modelling or subtraction of cost-offsets for substituted medicines.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the request to increase the price per vial for alemtuzumab for relapsing remitting multiple sclerosis (RRMS) based on a claim of extended clinical benefit from two years to six years. The PBAC also did not recommend a change to the current listing to include an additional continuation restriction for the third and fourth courses of alemtuzumab for patients with RRMS who meet proposed re-treatment criteria. The PBAC did not accept the comparator presented and considered that there was insufficient clinical evidence to support the claimed extended clinical benefit of alemtuzumab from two years to six years which formed the basis of the two requests. The PBAC also considered that the cost analysis

presented was inappropriate to value the durability of alemtuzumab.

- 7.2 The PBAC noted and welcomed the consumer comments received from MS Research Australia which highlighted that patients value additional treatment options for multiple sclerosis.
- 7.3 The PBAC did not accept the main comparator presented in the resubmission of two courses of PBS-funded alemtuzumab plus up to two additional courses of treatment as currently supplied by the sponsor. The PBAC agreed with the ESC that it was not appropriate to conflate the two requests proposed in the resubmission. The PBAC considered an assessment of the claim of extended clinical benefit from two to six years would require comparison of the two currently reimbursed courses of alemtuzumab with appropriate alternative therapies over a 6 year period. The PBAC considered appropriate alternative therapies in this context would likely be fingolimod, natalizumab, ocrelizumab or cladribine. The PBAC also considered an assessment of any incremental benefit provided by the administration of up to two additional courses of alemtuzumab would require a separate comparison with an alternative RMMS medicine or no further treatment after the initial two courses of alemtuzumab.
- 7.4 The PBAC noted that no comparative evidence was presented in the resubmission. Instead, the resubmission's clinical comparison of alemtuzumab over two years versus six years was based on the final results CARE-MS extension study (n=1,314) which the PBAC reiterated was susceptible to bias due to its unblinded, single arm design. The PBAC considered that concerns regarding risk of bias were further increased by discrepancies in the resubmission's presentation of re-treatment rates from the CARE-MS extension study.
- 7.5 The PBAC noted that the resubmission claimed a sustained benefit to up to six years based on the assumption that between 0-2 years and 0-6 years there was a similar average annualised relapse rate and similar annual rates of developing sustained accumulated disability. The PBAC noted a decrease in the point estimates for sustained accumulated disability over time (■■■■%/■■■■% at Year 2, ■■■■% at Year 4 and ■■■■% at Year 6) and considered that this indicated that fewer patients benefit from treatment with alemtuzumab over time.
- 7.6 The PBAC reaffirmed that it considered that the proportion of patients remaining relapse-free would provide a more informative basis for assessing durability of effect. The proportion of patients remaining free of accumulated disability (or free of relapse) in CARE-MS extension decreased over time (77.6%/65.4% at Year 2, ■■■■% at Year 4 and ■■■■% at Year 6). The PBAC considered that this was inconsistent with a claim of sustained benefit. Similarly, the PBAC agreed with the ESC that the proportion of patients requiring at least one additional course of alemtuzumab or an alternative DMT at ■■■■% was considerable and inconsistent with the resubmission's claim of sustained benefit.

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- 7.7 The PBAC agreed with the resubmission's claim that no new safety signals were evident for treatment with alemtuzumab. The PBAC also noted the ongoing sponsor-funded Lemtrada safety monitoring program.
- 7.8 The PBAC noted that no comparative claims of efficacy or safety compared to fingolimod or natalizumab (or ocrelizumab or cladribine) were made in the resubmission. The PBAC concluded that the clinical evidence presented in the resubmission was insufficient to support the claimed extended clinical benefit of alemtuzumab to six years.
- 7.9 The PBAC noted that to support the requested price increase, the resubmission presented a cost-analysis comparing ■■■ vials of alemtuzumab over ■■■ years and 8 vials over 2 years. The PBAC considered that the resubmission's nominated comparator was inappropriate, thereby invalidating the presented cost comparison. In addition, the PBAC noted that a key assumption of the analysis presented was that the same level of benefit is maintained in nearly all patients over six years. The PBAC considered that this assumption was not supported by the clinical evidence presented in the resubmission.
- 7.10 The PBAC agreed with the ESC that in the absence of comparative evidence of efficacy and safety of alemtuzumab against alternative DMTs, the cost analysis presented was inappropriate to value the durability of alemtuzumab treatment. In addition, the PBAC considered that the supplementary cost-minimisation analysis of alemtuzumab versus fingolimod and natalizumab provided in the PSCR was not informative as non-inferiority against alternative DMTs over 6 years was not established in the resubmission. The PBAC concluded that there was insufficient justification for the requested increase in the price of alemtuzumab.
- 7.11 The PBAC considered the financial estimates uncertain due to concerns regarding potential underestimation of re-treatment rates, the approach taken to calculation of market growth and the differences evident between the current (sponsor-subsidised) and the proposed number of patients requiring a third course of alemtuzumab.
- 7.12 The PBAC did not recommend any changes to the listing recommended at the July 2014 meeting.
- 7.13 The PBAC noted that this resubmission is not eligible for an Independent Review as the requested listing is for the same condition for which alemtuzumab is currently subsidised.

**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**

The sponsor had no comment.