

Alemtuzumab for relapsing remitting multiple sclerosis: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted and actual utilisation of alemtuzumab for relapsing remitting multiple sclerosis (RRMS) since it was PBS listed for this indication.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Alemtuzumab was PBS listed for the treatment of RRMS on 1 April 2015.

Data Source / methodology

The analysis used data from the Department of Human Services (DHS) Supplied Prescriptions database.

Key Findings

- In 2018, 18,715 patients were supplied a PBS-listed medicine for RRMS and, of these, 459 (2.5%) patients were supplied alemtuzumab.
- The addition of alemtuzumab in April 2015 had minimal effect on the RRMS market.
- 84% of patients supplied alemtuzumab had a prior supply of another PBS listed RRMS medicine.
- 90% of patients treated with alemtuzumab received two treatment courses (initial and continuing) of PBS subsidised alemtuzumab.
- The most common time to prescription refill between the initial and continuing treatment course was 364 days.
- 6.7% of alemtuzumab treated patients were supplied another PBS-listed medicine for RRMS within 2 years of the initial supply of alemtuzumab.
- Number of patients, prescriptions and the government expenditure for alemtuzumab was higher than predicted in Year 1 but was lower than predicted in Year 3 and Year 4.

Purpose of analysis

To compare the predicted and actual utilisation of alemtuzumab for relapsing remitting multiple sclerosis (RRMS) since it was PBS listed for this indication.

Background

Clinical situation

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system.¹ MS affects over 25,600 people in Australia with more than two million diagnosed worldwide. Most people are diagnosed between the ages of 20-40, but it can also affect younger and older people. Three quarters of all people with MS are women. RRMS is the most common MS disease course, characterised by clearly defined attacks followed by periods of complete or partial recovery. RRMS can be characterised as either active or non-active disease activity, as well as worsening (a confirmed increase in disability over a specified period of time following a relapse) or non-worsening. Approximately 85% of people with MS are initially diagnosed with RRMS.^{2,3}

Pharmacology

In MS, certain types of white blood cells called lymphocytes play a role in destroying myelin, the protective sheath that surrounds nerve fibres and helps with the efficient flow of nerve signals or messages to and from the brain and various parts of the body.² Alemtuzumab is a monoclonal antibody that binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. The mechanism by which alemtuzumab exerts its therapeutic effect in MS is unknown, but may involve immunomodulation through the depletion and repopulation of lymphocytes so that it may reduce the impact of the disease on the nervous system.^{2,4,5}

Dosage and administration

Alemtuzumab treatment should be initiated and supervised by a neurologist. Specialists and equipment required for the timely diagnosis and management of serious adverse

¹ Broadley SA, Barnett MH, Boggild M et al. A new era in the treatment of multiple sclerosis. MJA. 2015 Aug 3; 203(3):139-41.

² MS Australia (Internet). Understanding multiple sclerosis an introductory guide. Accessed on 28 November 2019, Available from: <https://www.msaustralia.org.au/what-ms>

³ MS Australia (Internet). Key facts and figures about multiple sclerosis (updated June 2019). Accessed on 5 December 2019, Available from: <https://www.msaustralia.org.au/about-ms/information-sheets>

⁴ LEMTRADA® (Alemtuzumab). Australian Approved Product Information. NSW: sanofi-aventis pty ltd. Approved 18 December 2013. Most recent revision 28 June 2019. Available from <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02549-1&d=201911281016933>

⁵ MS Australia (Internet). Treatments for MS: Lemtrada® (alemtuzumab). Accessed on 28 November 2019, Available from: https://www.msaustralia.org.au/sites/default/files/Lemtrada%20%28alemtuzumab%29_0.pdf

reactions, especially autoimmune conditions and infections, should be available. Facilities for the management of hypersensitivity and/or anaphylactic reactions should be available.

Patients treated with alemtuzumab must be given the Patient Wallet Card and Patient Guide and be informed about the risks of alemtuzumab.

The recommended dose of alemtuzumab is 12 mg/day administered by IV infusion for two or more treatment courses.⁴

Initial treatment of two courses

- First treatment course: 12 mg/day on five consecutive days (60 mg total dose)
- Second treatment course: 12 mg/day on three consecutive days (36 mg total dose) administered 12 months after the first treatment course.

Additional as-needed treatment course(s)

- Additional treatment with a third or fourth course: 12 mg/day on three consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course (not PBS subsidised).

Follow-up of patients

The therapy is recommended as an initial treatment of two courses with safety follow-up of patients from initiation of the first treatment course and until 48 months after the last infusion of the second treatment course. If an additional course is administered, continued safety follow-up is recommended until 48 months after the last infusion.⁴

Consideration by international regulatory bodies

In November 2018, the U.S. Food and Drug Administration (FDA) released a drug safety announcement warning that rare but serious cases of stroke and tears in the lining of arteries in the head and neck have occurred in patients with multiple sclerosis shortly after they received alemtuzumab. The FDA noted that these problems could lead to permanent disability and even death. As a result, the FDA included a new warning about these risks to the prescribing information in the drug label and to the patient Medication Guide. The FDA also added the risk of stroke to the existing Boxed Warning, FDA's most prominent warning.⁶ The European Medicines Agency (EMA) recommended that alemtuzumab should only be used to treat RRMS if the disease is highly active despite treatment with at least one disease-modifying therapy or if the disease is worsening rapidly. Alemtuzumab must also no longer be used in patients with certain heart, circulation or bleeding disorders or in patients who have autoimmune disorders other than multiple sclerosis.⁷ In Australia, the

⁶ Food and Drug Administration (FDA) (Internet). Accessed on 03 December 2019, Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-serious-risks-stroke-and-blood-vessel-wall-tears-multiple-sclerosis-drug>

⁷ The European Medicines Agency (EMA). Accessed on 03 December 2019, Available from: <https://www.ema.europa.eu/en/medicines/human/referrals/lemtrada>

Sponsor circulated a letter to health professionals in July 2019 regarding the adverse events that lead to the restrictions in Europe.⁸

PBS listing details (Current as at November 2019)

Table 1: PBS listing of alemtuzumab

Item	Name, form & strength, pack size	Max. qty packs.	Max. qty units.	Rpts	DPMQ	Brand name and manufacturer
10228H	alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	5	5	0	\$56970.00	Lemtrada® sanofi-aventis Australia Pty Ltd
10232M	alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	3	3	0	\$34182.00	Lemtrada® sanofi-aventis Australia Pty Ltd
10243D	alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	5	5	0	\$57017.39	Lemtrada® sanofi-aventis Australia Pty Ltd
10246G	alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	3	3	0	\$34229.38	Lemtrada® sanofi-aventis Australia Pty Ltd

Source: the [PBS website](#). Special Pricing Arrangements apply.

Neurologists prescribing PBS-subsidised alemtuzumab must be registered with the Lemtrada monitoring program.

No increase in the maximum quantity or number of units may be authorised.

No increase in the maximum number of repeats may be authorised.

Restriction

Multiple sclerosis

Treatment Phase: Initial treatment

Clinical criteria:

The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; or

The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance

⁸ Therapeutic Goods Administration (TGA) email correspondence: Alemtuzumab for RRMS. E-mail to DUSC secretariat 2019 December 12 (cited 2019 December 12)

imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient, and

The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, and

Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition, and

Patient must be ambulatory (without assistance or support)

Treatment criteria:

Must be treated by a neurologist.

Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

Treatment Phase: Continuing treatment

Clinical criteria:

Patient must have previously received PBS-subsidised treatment with this drug for this condition, 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 disease modifying therapy for this condition, and

Patient must have demonstrated compliance with, and an ability to tolerate this therapy.

Treatment criteria:

Must be treated by a neurologist.

For details of the current PBS listing refer to the [PBS website](#).

Date of listing on PBS

Alemtuzumab was listed as a Section 100 Highly Specialised Drug (HSD) as Authority Required for private hospital prescriptions and as Authority Required (STREAMLINED) for public hospitals on 1 April 2015.

Changes to listing

From 1 October 2019, alemtuzumab S100 HSD Private item codes 10243D and 10246G changed from Authority Required to Authority Required (STREAMLINED).

Current PBS listing details are available from the [PBS website](#).

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

July 2014

The PBAC recommended the Authority Required Section 100 HSD listing of alemtuzumab for the treatment of RRMS, on the basis of non-inferior effectiveness and a different safety profile to fingolimod and natalizumab.

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.

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 considered that cost-minimisation based on two years of treatment with fingolimod or natalizumab was supported by the available data.

This submission was not considered by DUSC. The commentary considered the submission appeared to substantially underestimate the costs associated with alemtuzumab and to substantially overestimate the cost-offsets associated with comparator therapies.

The commentary considered alemtuzumab may grow the market for multiple sclerosis therapies by providing another line of therapy. The submission argued 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 suggested that patients are unlikely to be prescribed another disease modifying therapy after alemtuzumab.

November 2014

Re-submission to 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, at a higher price than recommended by the PBAC in July 2014.

The PBAC reiterated its previous recommendation for the Authority Required Section 100 HSD 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.

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 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.

The PBAC 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.

November 2018

The PBAC did not recommend the request to increase the price per vial for alemtuzumab for 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 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 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 which formed the basis of the two requests.

For further details refer to the [Public Release Documents](#)

Previous reviews by the DUSC

June 2013

Disease modifying treatments (DMT) for multiple sclerosis

The utilisation analysis included the disease modifying treatments: the interferons, fingolimod and natalizumab. DUSC noted that the number of people supplied with a DMT for RRMS appeared to have increased with the introduction of the oral agent fingolimod. DUSC considered that revisions to the diagnostic criteria and the availability of oral treatment will potentially increase the number of people with multiple sclerosis treated with a DMT.

DUSC commented that the natural history of multiple sclerosis can result in patients having long periods of stability between attacks. It was noted that lifestyle is important in managing multiple sclerosis and that patients may choose to have a treatment break for various reasons, including pregnancy or adverse events. DUSC considered that a better understanding of the patient experience would assist in understanding how DMTs are used in practice.

DUSC recommended a mechanism be developed through which additional consumer input to DUSC analyses can be received and considered in the future. Patient experience is likely to inform use in practice including uptake rates and duration of treatment.

For details of the DUSC considerations refer to the [Outcome Statement](#) from the June 2013 DUSC meeting.

October 2015

Multiple sclerosis: predicted versus actual analysis

The review considered the utilisation of PBS listed medicines for RRMS, including an assessment of the predicted versus actual use of the oral therapies, dimethyl fumarate, teriflunomide and fingolimod.

DUSC noted that the usage of medicines for RRMS had increased with the availability of oral therapy. DUSC considered that this indicated a greater willingness of patients to receive treatment with oral medicines. Patients appeared to persist longer on oral compared to injectable therapy based on a length of treatment analysis of fingolimod.

In its first year of listing the utilisation of dimethyl fumarate had been higher than predicted. DUSC considered that this could relate to the broadening of the McDonald criteria for the diagnosis of multiple sclerosis, concerns over the cardiac side effects for fingolimod and an underestimation of the growth in the RRMS market. The usage of teriflunomide in its first listing year was substantially lower than expected.

For details of the DUSC consideration of multiple sclerosis refer to the [Public Release Document](#) from the October 2015 DUSC meeting.

Approach taken to estimate utilisation

An epidemiological approach was taken to estimate the number of RRMS patients who would receive treatment with alemtuzumab. The number of prevalent RRMS patients was used as a starting point to estimate the treatment experienced RRMS patients and the incidence of newly diagnosed MS patients was used as a starting point for estimating the number of treatment-naïve RRMS patients with aggressive disease.

Treated RRMS patients with aggressive disease (prevalent patients)

A report published by Multiple Sclerosis Research Australia (MSRA) in 2011, was used to estimate the number of Australians with multiple sclerosis. Of these patients, 85% were

assumed to have RRMS. A treatment rate was then applied to the prevalent patient pool to estimate the 'treatment experienced' RRMS patient population.

As part of the submission, a survey of neurologists experienced in the treatment of MS was conducted to identify current treatment practice and expected practice following listing of alemtuzumab on the PBS (AMSTS, 2014). Results indicated that, amongst patients receiving DMT therapy for RRMS, approximately 18% per year will require a change or escalation of therapy and of these patients approximately 25% would be considered appropriate for alemtuzumab.

Treatment-naïve RRMS patients with aggressive disease (incident patients)

According to the MSRA 2011 report, there were approximately 1,000 new cases of MS diagnosed per year, and approximately 85% of these were RRMS patients. Results of the Australian treatment survey indicated that of these newly diagnosed patients, approximately 26% had highly active disease requiring DMT therapy, and, of these, approximately 31% were eligible to receive alemtuzumab (AMSTS, 2014).

It was assumed that not all patients identified as eligible for alemtuzumab would receive treatment immediately. It was assumed that in year 1 of listing of alemtuzumab on the PBS approximately 50% of patients eligible for treatment with alemtuzumab would actually receive treatment, increasing to approximately 70% in year 5 (AMSTS, 2014).

Patients treated with alemtuzumab receive five vials during the first course of treatment and three vials during the second course. Based on the alemtuzumab clinical studies, it was assumed that approximately 96% of patients who receive an initial course of treatment will receive the second course.

Methods

The analyses used data from the Department of Human Services (DHS) supplied prescriptions database for dates of supply up to and including 30 September 2019; extracted 22 November 2019. The DHS supplied prescriptions database includes data submitted to DHS for payment of a PBS or Repatriation PBS (RPBS) subsidy by the Government by all approved pharmacies in Australia. The prescription data were used to determine the number of prescriptions supplied.

The DHS supplied prescriptions database includes a unique patient identification number (PIN) that allows supplied prescriptions to be attributed to a particular patient. The number of patients supplied alemtuzumab and other medicines for RRMS under the PBS was determined by counting the number of de-identified PINs in the prescription data over the specified time. This was used for the patient level analyses, including age and gender, prescriber type, prior prescription, treatment courses, time to refill and co-administration.

New (initiating) patients were defined as those with no prior prescription for alemtuzumab based on the date of first supply of PBS-subsidised alemtuzumab from the date of listing.

Patients were identified as being on treatment (prevalent) if they had received at least one dispensing of alemtuzumab in the specified period.

Co-administration was imputed if another PBS-listed medicine for RRMS was supplied within a defined time period following the supply of the initial alemtuzumab prescription. The complete list of all PBS-listed medicines for RRMS considered in the analysis is provided in Appendix 1. Three follow up periods were analysed:

- 1 year - cohort of patients who initiated alemtuzumab on or before 1 October 2018. Each patient followed-up for 365 days after their initial supply.
- 2 years - cohort of patients who initiated alemtuzumab on or before 1 October 2017. Each patient was followed-up for 730 days (i.e. 365×2) from their initial supply.
- 4 years - cohort of patients who initiated on or before 1 October 2015. Each patient was followed-up for 1,461 days (i.e. $4 \times 365 + 1$ to account for a leap year).

Prescriber type was attributed to the de-identified approval number of the prescriber by the DHS and was based on the major field of specialty, derived from the combination of the current registered specialty and the most Medicare services provided per quarter. Prescribers can work in several different specialties but are allocated by DHS to one major field of specialty per quarter. The prescriber type attributed to the initial alemtuzumab prescription for patients who initiated treatment in 2018 was used for this analysis.

As this analysis used date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.⁹

Data manipulation was undertaken using SAS.

Results

Analysis of drug utilisation

⁹ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

Overall utilisation

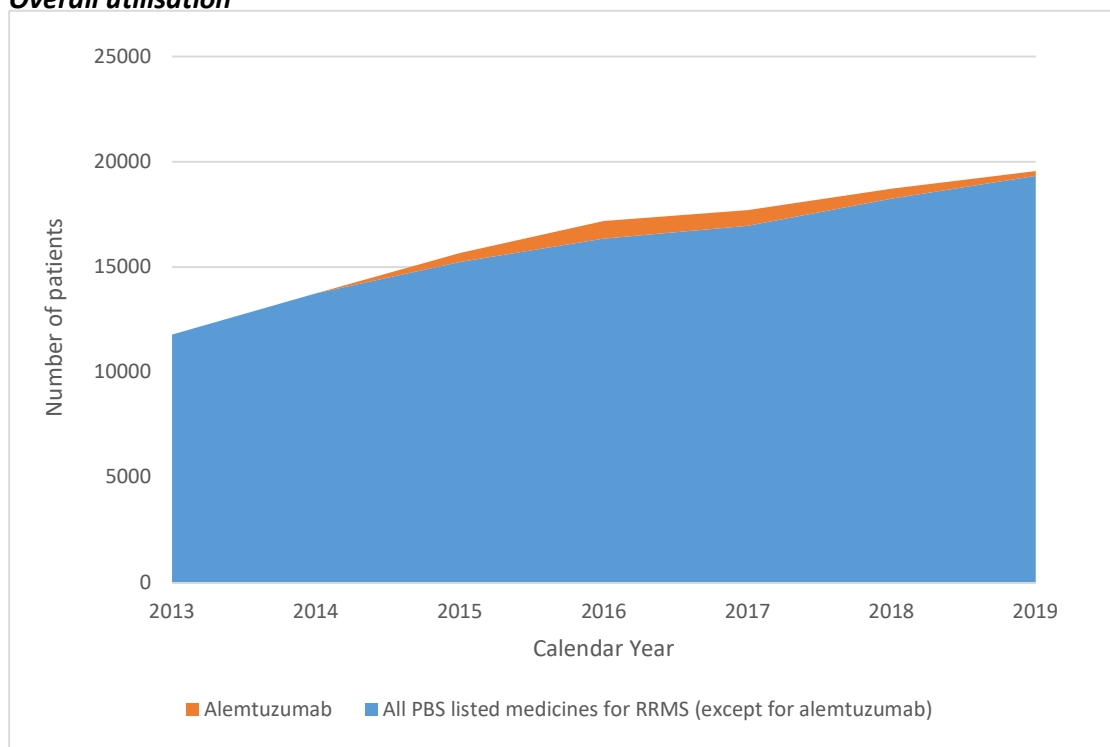


Figure 1: Alemtuzumab prevalent patients in RRMS market context by calendar year of supply

Note: 2019 is a part year (1 January to 30 September 2019)

Source: DHS PBS prescription database, extracted November 2019

Figure 1 shows the number of prevalent patients per calendar year treated with a PBS-listed medicine for RRMS (excluding alemtuzumab) and the number of prevalent patients treated with alemtuzumab for the same period. The total number of patients treated with a PBS listed medicine for RRMS increased over the six-year period.

In 2018, 18,715 patients were supplied a PBS-listed medicine for RRMS and, of these, 459 (2.5%) patients were supplied alemtuzumab. The addition of alemtuzumab in April 2015 had minimal effect on the overall market.

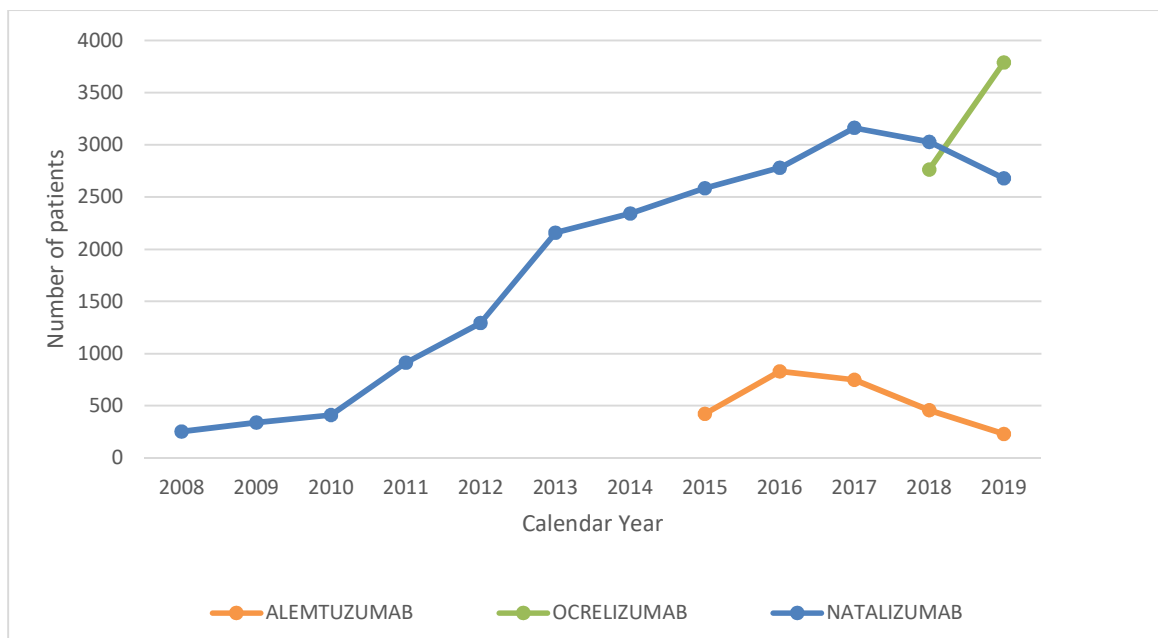


Figure 2: Prevalent patients supplied RRMS biologics by calendar year of supply

Note: 2019 is a part year (1 January to 30 September 2019)

Source: DHS PBS prescription database, extracted November 2019

Figure 2 compares alemtuzumab use with other biologics listed for RRMS on the PBS. Natalizumab was PBS-listed on 1 July 2008 and ocrelizumab on 1 February 2018 for the treatment of RRMS. Ocrelizumab is also TGA registered for the treatment of patients with primary progressive multiple sclerosis (but not PBS-listed for this indication). The number of patients supplied PBS-listed alemtuzumab was considerably fewer than the number of patients who received a supply of natalizumab or ocrelizumab for the treatment of RRMS.

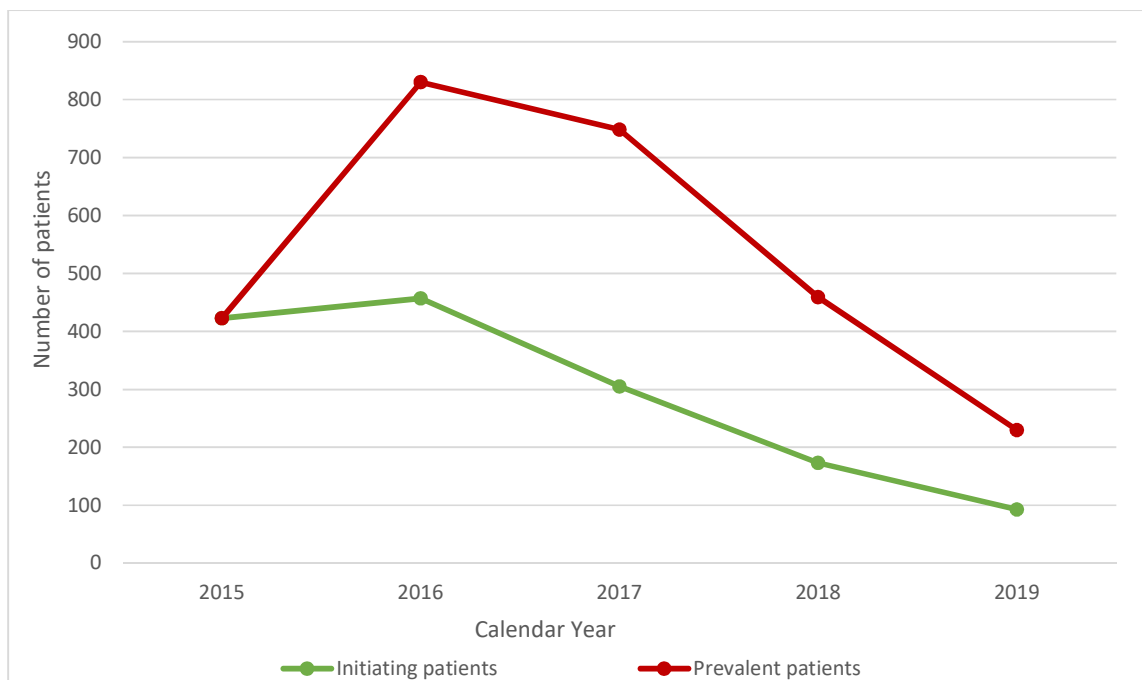


Figure 3: Number of initiating and prevalent patients treated with alemtuzumab by calendar year of supply

Note: 2019 is a part year (1 January to 30 September 2019)

Source: DHS PBS prescription database, extracted November 2019

Figure 3 depicts the number of prevalent and initiating patients to alemtuzumab for RRMS.

Table 1: Number and percentage growth of initiating and prevalent patient supplied alemtuzumab

Calendar Year	Prevalent patients (% growth from previous year)	Initiating patients (% growth from previous year)
2015	423	423
2016	830 (96%)	457 (8%)
2017	748 (-10%)	305 (-33%)
2018	459 (-39%)	173 (-43%)

Source: DHS PBS prescription database, extracted November 2019

Figure 3 and Table 1 illustrate that after the initial uptake in 2015 and 2016, the number of patients initiating alemtuzumab for RRMS and the prevalent number of patients treated with alemtuzumab have declined.

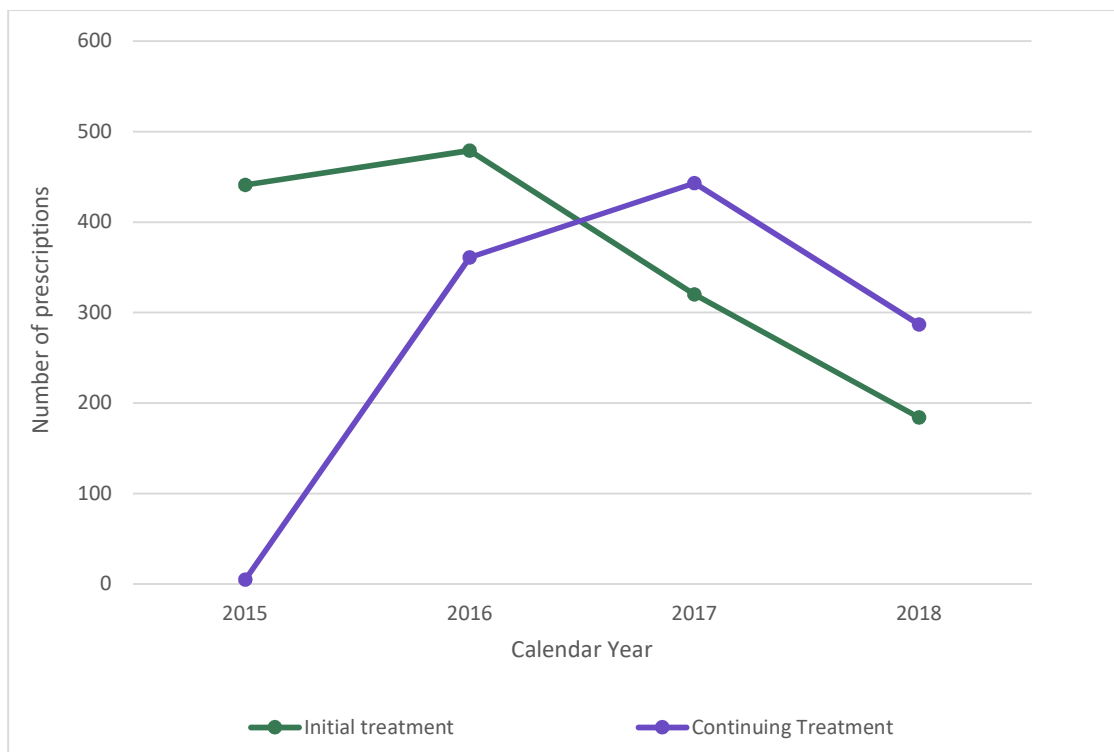


Figure 4: Number of prescriptions of alemtuzumab supplied by treatment course by calendar year of supply

Source: DHS PBS prescription database, extracted November 2019

According to the current PBS restriction, patients can be supplied the first treatment course (PBS Item codes 10228H and 10243D) for initial treatment, followed by a second treatment course (PBS Item codes 10232M and 10246G) as continuing treatment. Consistent with the decrease in the number of prevalent and initiating patients (Figure 3), Figure 4 shows the number of prescriptions for alemtuzumab supplied under the initial treatment item codes declined after 2016 and the number of prescriptions supplied under the continuing treatment codes declined after 2017. Sixty-one percent of the prescriptions for alemtuzumab were supplied under the S100 HSD public item codes (10228H and 10232M).

Alemtuzumab is positioned as first line treatment in patients with aggressive disease, as well as a second-line treatment in patients failing other disease modifying therapy. Eighty-four percent of patients supplied alemtuzumab had a prior supply of another PBS listed RRMS medicine.

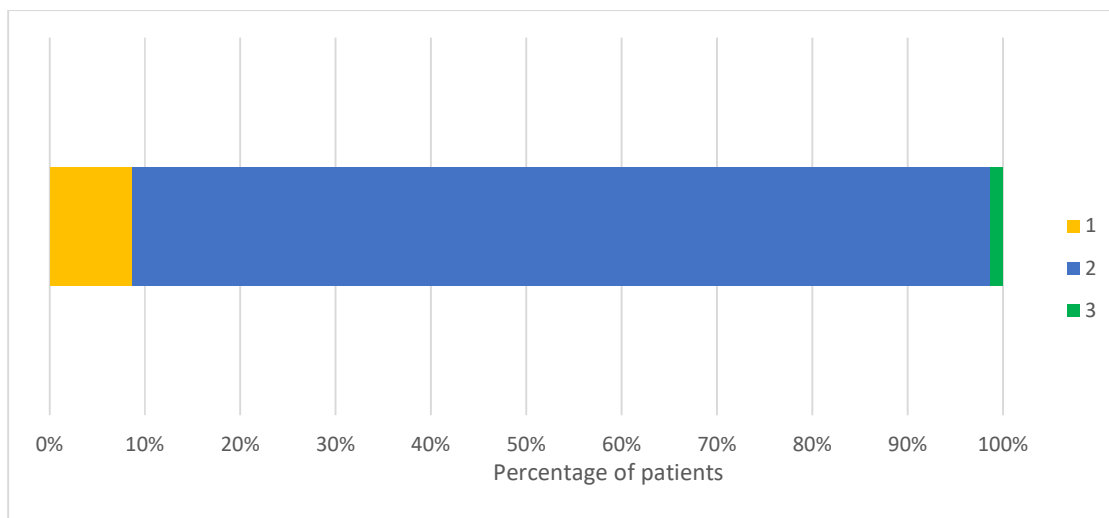


Figure 5: Proportion of patients supplied alemtuzumab by number of treatment courses

Source: DHS PBS prescription database, extracted November 2019

Note: Patients initiating alemtuzumab from 1 April 2015 to 1 October 2018 to allow patients time to have more than the initial treatment course

Alemtuzumab is registered with the TGA for initial treatment with two treatment courses and for an additional third or fourth treatment course if needed at least 12 months after the prior treatment course. The first two treatment courses are currently listed on the PBS but the additional third and fourth courses are not listed on the PBS. Figure 5 demonstrates that majority of patients (90%) received two treatment courses of PBS subsidised alemtuzumab as per the PBS restriction. A small proportion of patients (1.3%) were supplied an additional third course of PBS subsidised alemtuzumab.

The recommended dose of alemtuzumab is 12 mg (one vial) daily for five consecutive days for the first treatment course, followed 12 months later by 12 mg (one vial) daily for three consecutive days for the second treatment course. Ninety-eight percent of patients were supplied a quantity of five vials for the first treatment course and 99% of patients were supplied a quantity of three vials for the second treatment course. A very small proportion of patients were supplied extra vials within 28 days of their first supply of alemtuzumab.

Time to prescription refill analysis

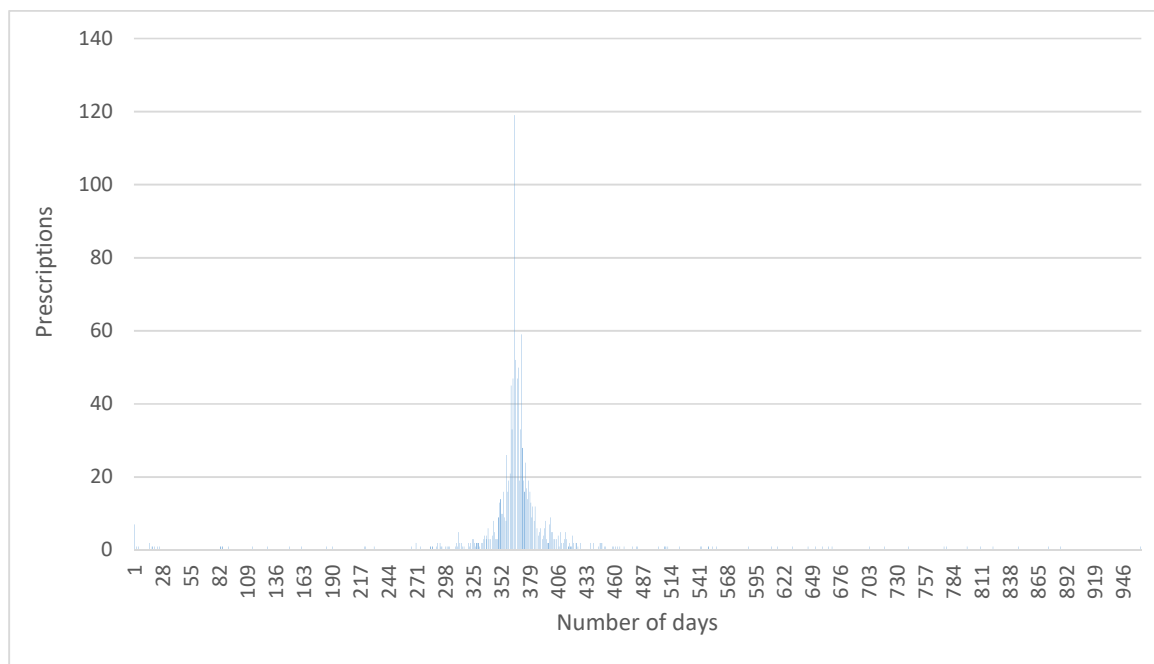


Figure 6: Time to refill between initial and continuing prescriptions

Source: DHS PBS prescription database, extracted November 2019

Figure 6 presents the number of days between the supply of the initial prescription for alemtuzumab and the continuing prescription for patients. The most common time to refill between the initial prescription for the first treatment course and continuing prescription for the second treatment course was 364 days. This is consistent with the product information which recommends the second treatment course be administered 12 months after the first treatment course. Forty-four percent of the continuing prescriptions were supplied < 365 days from the supply of the initial prescription. Eighty-one percent of continuing prescriptions were supplied within 30 days before or after the expected 365 days from the initial prescription. Less than 1% of continuing prescriptions were supplied after two years had elapsed since the supply of the initial prescription.

Utilisation by patient Demographics

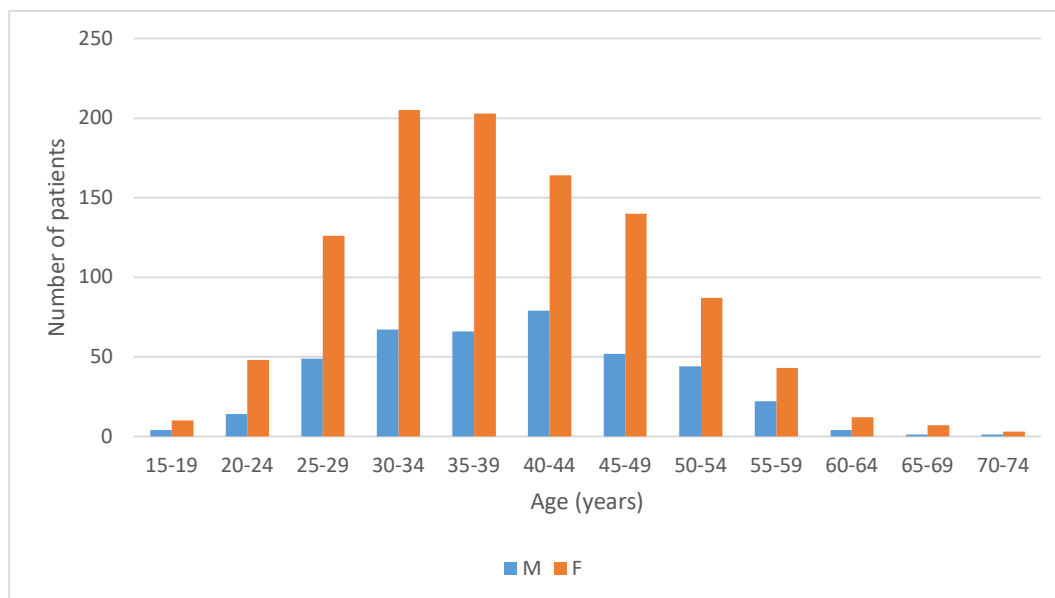


Figure 7: Patient age and sex for initiators on alemtuzumab

Source: DHS PBS prescription database, extracted November 2019

In Australia, three quarters of all people with MS are woman and most patients are diagnosed with MS between the ages of 20 and 40 years.² This is consistent with the demographic profile of patients initiating PBS-listed alemtuzumab (Figure 7).

Utilisation by prescriber type

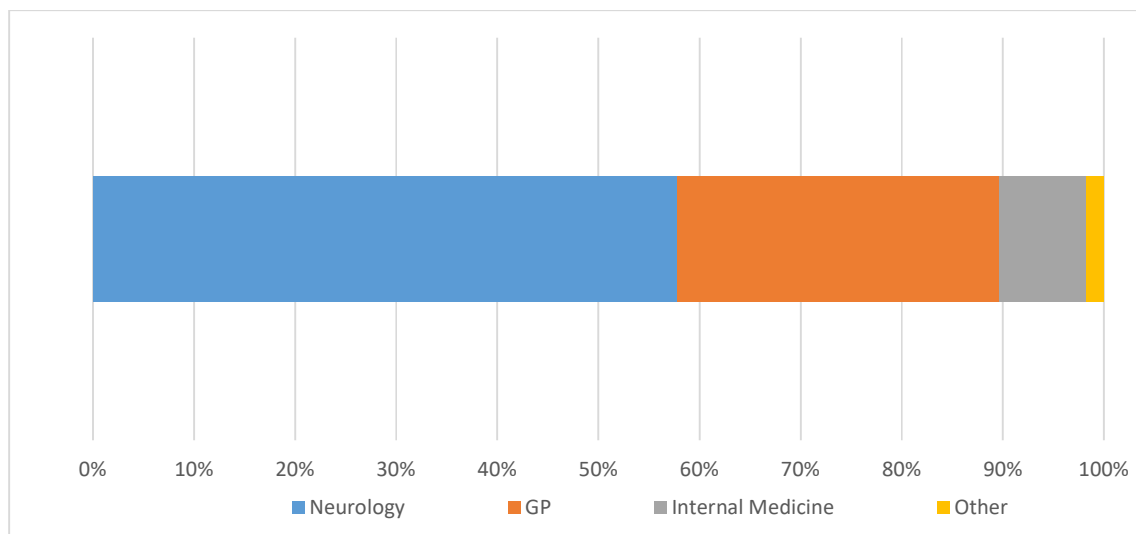


Figure 8: Proportion of patients initiating alemtuzumab for RMMS by prescriber type in 2018

Source: DHS PBS prescription database, extracted November 2019

The PBS restriction for alemtuzumab requires that the patient must be treated by a neurologist. Figure 8 illustrates the type of prescribers who initiated PBS-subsidised alemtuzumab in 2018. The largest proportion of patients initiating alemtuzumab had their first prescription written by a neurologist (58%); followed by General Practitioners (GPs) and internal medicine specialists.

Co-administration analysis

Table 2: Proportion of patients supplied another PBS listed medicine with alemtuzumab

Follow up period	1 Year (1323 patients)	2 Years (1141 patients)	4 Years (287 patients)
% of patients who were supplied another PBS listed medicine for RRMS	4.2%	6.7%	19.5%

The PBS restriction for alemtuzumab stipulates that the treatment must be the sole PBS-subsidised disease modifying therapy for this condition. Patients were considered to have co-administered medicines if the supply date of another PBS-listed medicine for RRMS was within two years of the supply date of alemtuzumab. Sensitivity analyses were conducted for one year and four years after the alemtuzumab supply. Table 2 illustrates that a small proportion of patients were supplied another PBS-listed medicine for RRMS during the one and two year follow up period after the initial prescription of alemtuzumab, contravening the PBS restriction. Approximately 20% of patients were supplied another RRMS medicine within four years of the initial treatment course of alemtuzumab.

Analysis of actual versus predicted utilisation

A comparison of the predicted utilisation of alemtuzumab for RRMS versus actual use is shown in Table 3.

Table 3: Alemtuzumab: actual versus predicted utilisation for RRMS

		Year 1	Year 2	Year 3	Year 4
Patients	Predicted	445	942	1,080	1,214
	Actual	545	947	660	399
	%Difference	22%	1%	-39%	-67%
Prescriptions	Predicted	445	942	1,080	1,214
	Actual	571	966	672	409
	%Difference	28%	3%	-38%	-66%

Source: Alemtuzumab Final Estimates 2015 (predicted), DHS prescription database (actual), extracted November 2019.

The number of patients, prescriptions and the corresponding expenditure to the government was higher than predicted in year 1 and close to the predicted estimates in Year 2. In Year 3 and 4, all three values were considerably lower than the predicted.

In the June 2014 submission, based on alemtuzumab clinical studies, it was assumed that approximately 96% of patients who received the initial course of treatment would receive a second course. The current analysis shows that 90% of patients received two treatment courses of PBS-listed alemtuzumab.

Discussion

The PBS-listing of alemtuzumab in April 2015 had minimal effect on the overall RRMS market. Alemtuzumab was used considerably less than the other RRMS biologics, natalizumab and ocrelizumab. The actual number of patients, prescriptions and the corresponding expenditure for alemtuzumab was higher than predicted in Year 1 of listing but declined in the three subsequent years. The listing of ocrelizumab in February 2018 could have contributed to the lower than predicted number of patients treated with alemtuzumab in the most recent two listing years of alemtuzumab. Recent safety concerns due to rare but potentially serious side effects reported by international regulatory bodies may have also influenced the declining use of alemtuzumab.

In October 2015, when considering the MS report, DUSC suggested that when more mature data were available for alemtuzumab that its potential use in combination with other RRMS medicines should be assessed. In November 2018, PBAC considered a resubmission seeking an increase in the price per vial based on a claim of extended clinical benefit from two years to six years for alemtuzumab; and reimbursement of up to two additional courses of treatment for patients who meet the proposed re-treatment criteria. The PBAC did not recommend the request and concluded that the clinical evidence presented in the resubmission was insufficient to support the claimed extended clinical benefit of alemtuzumab to six years. The current analysis shows that a small proportion of patients were supplied another PBS-listed medicine for RRMS during the one and two year follow up period after the initial prescription of alemtuzumab. Approximately 20% of patients were supplied another RRMS medicine within four years of initial treatment course of alemtuzumab.

DUSC Consideration

DUSC recalled the submission for alemtuzumab from July 2014 was not considered by DUSC. DUSC noted the submission used an epidemiological approach to estimate the number of RRMS patients who should receive treatment with alemtuzumab. DUSC considered this was a reasonable approach to estimate utilisation, given that the RRMS treatment landscape was evolving at the time. However, DUSC highlighted that a number of the sources used in the epidemiological approach, while they may have been the best available evidence, introduced uncertainties, such as the use of survey data to identify treatment practice.

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corresponding expenditure for alemtuzumab was higher than predicted in Year 1 of listing but declined in the three subsequent years. The listing of ocrelizumab in February 2018 could have contributed to the lower than predicted number of patients treated with alemtuzumab in the most recent two listing years of alemtuzumab. Recent safety concerns due to rare but potentially serious side effects reported by international regulatory bodies may have also influenced the declining use of alemtuzumab. DUSC considered the safety concerns with alemtuzumab and PBS listing of new medicines for RRMS may have contributed to the declining use of alemtuzumab. In particular, DUSC noted the large number of patients treated with ocrelizumab from its time of listing in 2018. DUSC noted the number of prevalent patients supplied alemtuzumab is most likely underestimated in the analysis, as the Pre-Sub Committee Response (PSCR, p1) indicated Sanofi currently provides all additional courses of alemtuzumab free of charge to patients who require more than two courses of treatment via a compassionate access program.

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The product information for alemtuzumab outlines the need for safety follow-up of patients from initiation of the first treatment course of alemtuzumab to until 48 months after the last infusion. DUSC discussed the importance of this follow up and noted the absence of follow up data to ensure compliance with the above recommendation.

DUSC noted a small proportion of patients were supplied an additional third course of PBS subsidised alemtuzumab. In the PSCR (p1), the Sponsor explained that the clinical criteria for continuing treatment for PBS subsidised alemtuzumab does not explicitly state that a patient must not have more than two treatment courses in total. The Sponsor proposed that the PBS restriction for continuing alemtuzumab treatment be amended to make it clear to prescribers that a maximum of two courses of treatment per patient is subsidised via the PBS. Sanofi are prepared to work with the Restrictions Working Group on this restriction change.

DUSC considered patients with multiple sclerosis (MS) are well informed and have good awareness of the disease and management options for MS. DUSC noted that better understanding of the patient experience would assist in understanding the management of MS and suggested seeking consumer input for future DUSC reviews on MS.

DUSC noted the PBS restriction for alemtuzumab requires that the patient must be treated by a neurologist and the restriction also includes a note specifying that neurologists prescribing PBS-subsidised alemtuzumab must be registered with the Lemtrada monitoring program. DUSC highlighted that 42% of patients initiating alemtuzumab did not have their first prescription written by a neurologist. DUSC queried whether all prescribers prescribing alemtuzumab were registered with the Lemtrada program. If not, it is unclear whether they would be aware of the need for 48 month follow up and whether they would have received notification of the safety concerns. DUSC discussed whether the wording of the restriction should be changed to stipulate that alemtuzumab must be prescribed by a neurologist, but questioned if this would reduce access to alemtuzumab for patients living in rural and remotes areas with limited access to a neurologist. In future MS reports, DUSC considered there would be value in including a utilisation analysis by geographical location.

DUSC Actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for Analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' Comments

Sanofi has a well-established and robust risk management plan for Lemtrada in Australia. Sanofi can confirm that all health care practitioners (HCPs) who have indicated their intention to prescribe Lemtrada are required to complete a prescriber training program prior to administration of the first infusion and are also provided with educational

materials. This ensures that HCPs are well informed of the risks associated with Lemtrada and the importance of ongoing monthly monitoring for patients until 48 months after their last infusion.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix 1: Medicines listed on PBS for RRMS as at November 2019

Drug name, form and strength	PBS Item code	ATC Code
alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	10228H	L04AA34
alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	10232M	L04AA34
alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	10243D	L04AA34
alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial	10246G	L04AA34
cladribine 10 mg tablet, 1	11603Q	L04AA40
cladribine 10 mg tablet, 4	11604R	L04AA40
cladribine 10 mg tablet, 6	11611D	L04AA40
dimethyl fumarate 120 mg enteric capsule, 14	2896K	L04AX07
dimethyl fumarate 120 mg enteric capsule, 14	2943X	L04AX07
dimethyl fumarate 240 mg enteric capsule, 56	2966D	L04AX07
fingolimod 250 microgram capsule, 28	11818B	L04AA27
fingolimod 500 microgram capsule, 28	5262Y	L04AA27
glatiramer acetate 40 mg/mL injection, 12 x 1 mL syringes	10416F	L03AX13
interferon beta-1a 12 million units (44 microgram)/0.5 mL injection, 12 x 0.5 mL pen devices	8968B	L03AB07
interferon beta-1a 12 million units (44 microgram)/0.5 mL injection, 12 x 0.5 mL syringes	8403G	L03AB07
interferon beta-1a 36 million units (132 microgram)/1.5 mL injection, 4 x 1.5 mL cartridges	9332E	L03AB07
interferon beta-1a 6 million units (30 microgram)/0.5 mL injection, 4 x 0.5 mL syringes	8805K	L03AB07
interferon beta-1b 8 million international units (250 microgram) injection [15 x 250 microgram vials] (&) inert substance diluent [15 x 1.2 mL syringes], 1 pack	8101J	L03AB08
natalizumab 300 mg/15 mL injection, 15 mL vial	9505G	L04AA23
natalizumab 300 mg/15 mL injection, 15 mL vial	9624M	L04AA23
ocrelizumab 300 mg/10 mL injection, 10 mL vial	11237K	L04AA36
ocrelizumab 300 mg/10 mL injection, 10 mL vial	11242Q	L04AA36
peginterferon beta-1a 125 microgram/0.5 mL injection, 2 x 0.5 mL pen devices	10212L	L03AB13
peginterferon beta-1a 125 microgram/0.5 mL injection, 2 x 0.5 mL pen devices	10220X	L03AB13
peginterferon beta-1a 63 microgram/0.5 mL injection [0.5 mL pen device] (&) peginterferon beta-1a 94 microgram/0.5 mL injection [0.5 mL pen device], 1 pack	10218T	L03AB13
teriflunomide 14 mg tablet, 28	2898M	L04AA31