Cladribine for relapsing remitting multiple sclerosis: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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## Abstract

### Purpose

To review the utilisation of PBS listed medicines for relapsing-remitting multiple sclerosis (RRMS), including an assessment of the predicted versus actual use of cladribine.

### Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Cladribine was PBS listed for the treatment of RRMS on 1 January 2019.

### Data Source / methodology

Data extracted from the PBS database maintained by Department of Health, processed by Services Australia were used for analyses.

### Key Findings

* In 2019, 179,907 RRMS prescriptions were supplied to 22,153 patients.
* In 2020, 177,884 RRMS prescriptions were supplied to 22,714 patients.
* There were 1,130 and 1,407 patients treated with cladribine during the first and second year of listing respectively, which was | than estimated.
* There were 3,295 cladribine prescriptions dispensed during the first year of listing which was | than estimated. There were 4,147 cladribine prescriptions dispensed during the second year of listing, which was | than estimated.
* The most common age group initiating any RRMS treatment from 2014 onwards was 40-44 years. Overall, there was a greater proportion of females initiating RRMS treatment compared to males (73.4%).
* The most common age group of patients initiating cladribine treatment was 45-49 years old (15.8% of patients). Overall, there was a greater proportion of females initiating cladribine treatment compared to males (73.9%).
* There is a shift in the RRMS market away from the older generation RRMS treatments.

# Purpose of analysis

To assess the utilisation of PBS listed medicines for relapsing-remitting multiple sclerosis (RRMS), including an assessment to compare predicted versus actual utilisation of cladribine, as requested by DUSC at its June 2021 meeting.

# Background

## Clinical situation

Multiple sclerosis (MS) is a chronic and progressive autoimmune disease of the central nervous system. The immune system attacks and damages the myelin sheath on the nerve axon. Myelin sheath are responsible for insulating axons allowing impulse propagation, which is important for normal neural function.[[1]](#footnote-1),[[2]](#footnote-2)

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 years, 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 following a relapse) or non-worsening. Approximately 85% of people with MS are initially diagnosed with RRMS and 15% with a progressive form of MS, known as primary progressive MS (PPMS).[[3]](#footnote-3),[[4]](#footnote-4),[[5]](#footnote-5)

## 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.**Error! Bookmark not defined.**

Cladribine is a nucleotide analogue of deoxyadenosine. It acts on B and T lymphocytes to interrupt the cascade of immune events central to MS. This results in fewer relapses, less disease activity in the brain and less progression of disability.[[6]](#footnote-6)

## Therapeutic Goods Administration (TGA) approved indications

Cladribine is indicated for the treatment of RRMS to reduce the frequency of clinical relapses and to delay the progression of physical disability. Following completion of two treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.

Cladribine is also indicated for:

* Treatment of patients with Hairy Cell Leukaemia.
* Treatment of patients with B-cell chronic lymphocytic leukaemia in whom treatment with alkylating agents has failed.

## Dosage and administration

Table 1: Dosage and administration summary of PBS listed RRMS drugs as at November 2021

|  |  |  |
| --- | --- | --- |
| **Product (Brand name)** | **Dosage** | **Frequency** |
| **Infusion** | | |
| alemtuzumab (Lemtrada®) | 12 mg | Two treatment courses. Over 5 days for initial treatment and over 3 days 12 months after initial treatment. |
| natalizumab (Tysabri®) | 300 mg | every 4 weeks |
| ocrelizumab (Ocrevus®) | 600 mg | Initial dose split into 2 infusions over 2 weeks and every 6 months afterwards. |
| **Injection** | | |
| glatiramer acetate (Copaxone®) | 40 mg | 3 times a week |
| interferon beta-1a (Avonex®) | 6 million IU= 30 µg | Weekly |
| interferon beta-1a (Rebif®) | 12 million IU= 44 µg | 3 times a week |
| interferon beta-1b (Betaferon®) | 8 million IU = 0.25 mg= 250 µg | On alternate days |
| ofatumumab (Kesimpta®) | 20 mg | Weekly for week 0, 1, 2, followed by subsequent monthly dosing starting at week 4. |
| peginterferon beta-1a (Plegridy®) | 125 µg | Every 2 weeks |
| **Oral** | | |
| cladribine (Mavenclad®) | 3.5 mg/kg body weight | Two treatment courses over 2 years.  Each course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4-5 days where patient receives 10 mg or 20 mg (1 or 2 tablets) as a single daily dose, depending on body weight |
| dimethyl fumarate (Tecfidera®) | 120 mg starting dose for first 7 days  240 mg maintenance dose | Twice a day |
| fingolimod (Gilenya®) | 0.5 mg | Daily |
| ozanimod (Zeposia®) | 230 µg starting dose for first 4 days, 460 µg dose over next 3 days.  920 µg maintenance dose | Daily |
| siponimod (Mayzent®) | 0.25 mg starting dose and uptitrated for the first 5 days (1 up to 5 tablets daily).  2 mg maintenance dose | Daily |
| teriflunomide (APO- teriflunomide ®, Pharmacor teriflunomide ®, TERIFLAGIO®, teriflunomide Dr. Reddy’s ®, teriflunomide GH®, teriflunomide Sandoz® Terimide®) | 14 mg | Daily |

Source: TGA Product Information

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA (Product Information)](http://tga.gov.au/hp/information-medicines-pi.htm) and [the TGA (Consumer Medicines Information)](http://www.tga.gov.au/consumers/information-medicines-cmi.htm).

## PBS listing details (as at November 2021)

Table 2: PBS listing of cladribine as at November 2021

| Item | Name, form & strength, pack size | Max. qty. packs | Max. qty. units | Rpts | DPMQ | Brand name and manufacturer |
| --- | --- | --- | --- | --- | --- | --- |
| 11603Q | cladribine 10 mg tablet, 1 | 1 | 1 | 1 | $3,994.26 | Mavenclad  Merck Health care Pty Ltd |
| 11604R | cladribine 10 mg tablet, 4 | 2 | 8 | 1 | $30,825.54 |
| 11611D | cladribine 10 mg tablet, 6 | 1 | 6 | 1 | $23,159.46 |

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

Note: Special Pricing Arrangements apply.

Source: the [PBS website](http://www.pbs.gov.au/pbs/home).

A summary of all current PBS listings for RRMS is provided at Appendix A. A chronology of listings for RRMS is summarised in Appendix B.

### Abridged Restrictions for RRMS medicines

Infusion treatments (alemtuzumab, natalizumab and ocrelizumab) are listed on Section 100 Highly Specialised Drugs Program (Private and Public Hospital).

Oral treatments (cladribine, dimethyl fumarate, fingolimod, ozanimod, siponimod, teriflunomide) and injection treatments (glatiramer acetate, interferon beta-1a, interferon beta-1b, ofatumumab and peginterferon beta-1a) are listed on Section 85 General Schedule.

All current PBS listings for RRMS are Authority Required (Streamlined) and require:

* diagnosis confirmed by magnetic resonance imaging (MRI) of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient;
* patients to be ambulatory, without assistance or support; and
* access to continuing treatment requires that the patient does not show continuing progression of disability while on treatment and has demonstrated compliance with, and an ability to tolerate, the therapy.

For details of the current PBS listings refer to the [PBS website](file:///\\central.health\DFSGroupData\Sites\CO1\CO\PBD\PEB\EVAL\DUSC\DUSC%20Documents\Predicted%20vs%20actual%20usage\pbs.gov.au).

### Date of listing on PBS

Cladribine was PBS listed for RRMS 1 January 2019.

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

***March 2011 PBAC meeting***

The PBAC did not recommended the listing of cladribine for the treatment of RRMS, on the basis of an inappropriate comparator, uncertain clinical benefit and uncertain and unacceptable cost effectiveness in comparison with the appropriate comparator.

For further details refer to the [Public Summary Document](https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-03/pbac-psd-cladribine-march11) from the March 2011 PBAC meeting.

***November 2017 PBAC meeting***

The PBAC did not recommend the listing of cladribine for the treatment of RRMS, on the basis of uncertainty in the non-inferior efficacy claim of cladribine versus fingolimod over two and four years. The PBAC noted that there were significant uncertainties in the financial analysis, including the persistence rates assumed by the resubmission. The PBAC further noted that the financial analysis estimated a significant net cost to the PBS, which undermines the first principles of a cost minimisation analysis.

For further details refer to the [Public Summary Document](https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2017-11/cladribine-psd-november-2017) from the November 2017 PBAC meeting.

***March 2018 PBAC meeting***

The PBAC did not recommend the listing of cladribine for the treatment of RRMS, on the basis of uncertainty in the non-inferior efficacy claim of cladribine versus fingolimod over two and four years. The PBAC noted that the minor resubmission did not provide additional clinical evidence to address its concerns. The PBAC noted that there remained significant uncertainties in the financial analysis, including the persistence rates assumed by the resubmission. The PBAC further noted that the financial analysis estimated a significant net cost to the PBS, which undermines the first principles of a cost minimisation analysis.

For further details refer to the [Public Summary Document](https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-03/Cladribine-psd-march-2018) from the March 2018 PBAC meeting.

***July 2018 PBAC meeting***

The PBAC recommended the Authority Required listing of cladribine for the treatment of RRMS. The PBAC’s recommendation for listing was based on, amongst other matters, its assessment than the cost-effectiveness of cladribine would be acceptable if it were cost minimised against fingolimod based on a claim that two years of cladribine treatment is non-inferior in efficacy to two years’ of fingolimod treatment.

The PBAC noted that the estimated total financial impact was reduced substantially from the March 2018 and November 2017 resubmissions from net cost of $41 million over six years to a net save of $154.6 million over six years. The PBAC considered the estimated magnitude of cost savings to be uncertain as:

* The financial estimates assumed the listing of cladribine tablets would only displace fingolimod. The PBAC considered that cladribine may replace or displace all PBS listed RRMS treatments (many of which are lower cost) to some extent;
* The financial estimates did not account for costs in Years 3 and 4 from patients who do not persist on therapy due to relapse and switch to other treatments; and
* The assumed cladribine persistence rates were based on a Prospection analysis of Medicare prescription data to determine the persistence rates of fingolimod.
* Further, the PBAC considered that the large difference in estimated financial impact between the current, March 2018 and November 2017 resubmissions was also indicative of the uncertainty in the estimates.

For further details refer to the [Public Summary Document](https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-03/Cladribine-psd-march-2018) from the July 2018 PBAC meeting.

## 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](http://www.pbs.gov.au/industry/listing/elements/dusc-meetings/dos/dusc-dos-jun-2013.pdf) 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](http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2015-10/multiple-sclerosis-dusc-prd-2015-10-abstract) from the October 2015 DUSC meeting.

### February 2020

**Alemtuzumab for RRMS: predicted versus actual analysis**

DUSC considered the PBS listing of alemtuzumab in April 2015 had minimal effect on the overall RRMS market. In 2018, 18,715 patients were supplied a PBS-listed medicine for RRMS and, of these, 459 (2.5%) patients were supplied alemtuzumab. 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. DUSC considered the safety concerns with alemtuzumab and PBS listing of new medicines for RRMS may have contributed to the declining use of alemtuzumab.

For details of the DUSC consideration of alemtuzumab refer to the [Public Release Document](https://www.pbs.gov.au/pbs/industry/listing/participants/public-release-docs/2020-02/alemtuzumab-for-relapsing-remitting-multiple-sclerosis) from February 2020 DUSC meeting.

### October 2020

**Ocrelizumab for RRMS: predicted versus actual analysis**

DUSC reviewed the predicted and actual utilisation of ocrelizumab for relapsing remitting multiple sclerosis (RRMS) since it was PBS listed for this indication. The number of patients treated with ocrelizumab was slightly less than predicted in the first year of listing and close to predicted in the second year of listing. The number of prescriptions was less than predicted in both years due to the number of scripts per patient being slightly less than predicted. The submission assumption that the listing of ocrelizumab would not increase the growth rate of the RRMS market was approximately correct.

The mix of medicines within the RRMS market was dynamic with the more recently listed medicines, ocrelizumab (listed 1 February 2018) and cladribine (listed 1 January 2019), rapidly substituting for older medicines. The distribution of medicine form (i.e. injection, oral or infusion) varied between Very Remote, Remote and non-remote RRMS patients. It appeared that the frequency of dosing and accessibility to infusion services had an effect on the choice of medicine form depending on the remoteness of the patient.

For details of the DUSC consideration of ocrelizumab refer to the [Public Release Document](https://www.pbs.gov.au/pbs/industry/listing/participants/public-release-docs/2020-10/ocrelizumab-for-relapsing-remitting-multiple-sclerosis-octo) from the October 2020 DUSC meeting.

# Methods

Data extracted from the PBS claims database maintained by the Department of Health and processed by Services Australia were used for the analyses. Prescription data were extracted from 1 January 2014 up to and including 30 September 2021. Data were extracted on 29 November 2021.

An analysis start date of January 2014 was selected as the DHS prescriptions database for the Section 100 Highly Specialised Drugs Program first became available from July 2010 and was not fully complete until July 2013. As such, the total number of prevalent patients was under reported prior to July 2013 due to incomplete data for the Section 100 public hospital listing for natalizumab.

Drugs included in the analysis were:

* Infusion DMTs: alemtuzumab, natalizumab and ocrelizumab
* Injection DMTs: daclizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b and peginterferon beta-1a
* Oral DMTs: cladribine, dimethyl fumarate, fingolimod, ozanimod, siponimod and teriflunomide.

Ofatumumab, an injection DMT was PBS listed on 1 October 2021 after the analysis end date and was not included in analyses. Daclizumab was PBS listed on 1 May 2017 and was delisted 1 June 2018.

These data were used to determine the prescription and patients counts, and the age and gender of initiating patients for the overall RRMS market. Prescription counts and the number of initiating patients was determined by drug. Prescription counts, prescriber type and a switching analysis were conducted by RRMS DMT form.

For cladribine, these data were used to determine the number of incident and prevalent patients, number of prescriptions supplied, and to analyse patient demographics such as age and gender. Initiating and prevalent patients were counted by quarter of supply. An initiating patient was defined based on their first date of supply of cladribine.

A coadministration analysis was conducted. If another RRMS drug was supplied within 12 months of the first supply of cladribine, and there was more than one occurrence of this supply, this was identified as a potential co-administration of cladribine with another drug. To exclude possible switching between drugs, co-administration was only counted if there were at least two occurrences where a patient received cladribine and another RRMS drug. Switching was defined as a patient being supplied another RRMS drug after 12 months of the date of supply of cladribine.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.[[7]](#footnote-7)

Data manipulation was undertaken using SAS.

# Results

## Analysis of drug utilisation

### Overall utilisation

Figure 1: Number of total RRMS prescriptions supplied according to supply quarter

From Figure 1, the overall utilisation of the RRMS market has remained relatively stable from 2014 onwards. An average of approximately 45,000 prescriptions were supplied for RRMS per supply quarter.

Figure 2: Number of RRMS prescriptions supplied according to drug and supply quarter

In Figure 2, the most common RRMS DMT since 2014 was fingolimod with an average of approximately 15,000 prescriptions supplied per quarter.

Although the number of alemtuzumab, cladribine and ocrelizumab prescriptions supplied appear to be low, this is due to patients not continuously being treated over time due to the time between administrations as described in Table 1.

Table 3: Number of RRMS prescriptions supplied according to calendar year

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **2019** | **2020** | **2021** | **Annual growth: 2019 vs 2020** |
| Alemtuzumab | 286 | 175 | 75 | -38.8% |
| Cladribine | 3,295 | 4,147 | 2,672 | 25.9% |
| Dimethyl fumarate | 24,063 | 24,487 | 17,940 | 1.8% |
| Fingolimod | 58,955 | 55,348 | 37,895 | -6.1% |
| Glatiramer acetate | 17,205 | 15,573 | 10,413 | -9.5% |
| Interferon beta-1a | 9,312 | 8,130 | 5,102 | -12.7% |
| Interferon beta-1b | 5,575 | 4,657 | 2,889 | -16.5% |
| Natalizumab | 28,236 | 30,915 | 24,971 | 9.5% |
| Ocrelizumab | 7,421 | 9,024 | 7,895 | 21.6% |
| Ozanimod | n/a | n/a | 190 | n/a |
| Peginterferon beta-1a | 6,853 | 6,573 | 4,295 | -4.1% |
| Siponimod | n/a | 235 | 3,524 | n/a |
| Teriflunomide | 18,706 | 18,620 | 13,856 | -0.5% |
| All RRMS drugs | 179,907 | 177,884 | 131717 | -1.1% |

Note: 2021 figures are year-to-date 30 September.

Figure 3: Market share RRMS prescriptions supplied according to drug

Note: 2021 figures are year-to-date 30 September.

From Figure 3, fingolimod had the greatest market share over time, accounting for 29% of the RRMS market in 2021.

Based on the prescription count, cladribine has accounted for 2% of the market.

Figure 4: Number of RRMS prescriptions supplied according to form and supply quarter

Note: Infusion DMTs include alemtuzumab, natalizumab and ocrelizumab. Oral DMTs include cladribine, dimethyl fumerate, fingolimod, ozanimod, siponmiod and teriflunomide. Injection DMTs include daclizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b, ofatumumab and peginterferon beta-1a.

From Figure 4, oral therapies were the most common DMT. In 2014, injection therapies were the second most common therapy and infusions were the least common DMT with natalizumab being the only infusion therapy PBS listed at the time. Over time, prescriptions supplied for infusion therapies have been gradually increasing whereas injection therapies have been decreasing. Infusion therapies overtook injection therapies as the second most common therapy in the third quarter of 2020.

Figure 5: Number of treated RRMS patients by drug according to calendar year

Note: 2021 figures are year-to-date 30 September.

Based on the quarterly patient counts in Figure 5, the number of treated RRMS patients remained relatively stable from 2017 with an average of approximately 21,000 patients treated per calendar year.

Table 3: Number of RRMS treated patients according to calendar year

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **2019** | **2020** | **2021** | **Annual growth 2019 vs 2020** |
| Alemtuzumab | 277 | 173 | 73 | -37.5% |
| Cladribine | 1,130 | 1,407 | 974 | 24.5% |
| Dimethyl fumarate | 2,466 | 2,509 | 2,307 | 1.7% |
| Fingolimod | 5,447 | 5,037 | 4,586 | -7.5% |
| Glatiramer acetate | 1,866 | 1,675 | 1,414 | -10.2% |
| Interferon beta-1a | 895 | 761 | 647 | -15.0% |
| Interferon beta-1b | 624 | 494 | 420 | -20.8% |
| Natalizumab | 2,807 | 3,054 | 3,243 | 8.8% |
| Ocrelizumab | 4,165 | 5,138 | 5,645 | 23.4% |
| Ozanimod | n/a | n/a | 48 | n/a |
| Peginterferon beta-1a | 662 | 623 | 564 | -5.9% |
| Siponimod | n/a | 124 | 558 | n/a |
| Teriflunomide | 1,814 | 1,719 | 1,641 | -5.2% |
| All RRMS drugs | 22,153 | 22,714 | 22,120 | 2.5% |

Note: 2021 figures are year-to-date 30 September.

Figure 7: Number of initiating and prevalent cladribine patients according to supply quarter

From Figure 7, the number of patients initiating and treated with cladribine are yet to be stabilised.

### Utilisation by relevant sub-populations/regions or patient level analysis

Figure 8: Age and gender distribution of RRMS patients who initiated treatment between 1 January 2014 to 30 September 2021

Note: 0.02% of initiating patients’ age and gender were unknown.

In patients who initiated RRMS treatment from 2014, the most common age group were those between 40-44 years. The median age was 43 years and the mean age was 44 years. Of patients who initiated RRMS treatment, 73.4% were female.

Figure 9: Age and gender distribution of initiating cladribine patients

In Figure 9, patients who initiated cladribine treatment, the most common age group were those between 45-49 years. The mean and median age was 46 years. Of patients initiated cladribine treatment, 73.9% were female.

Figure 10: Prescriber distribution of initiating RRMS patients by form between 1 January 2014 and 30 September 2021

Note: Infusion DMTs include alemtuzumab, natalizumab and ocrelizumab. Oral DMTs include cladribine, dimethyl fumerate, fingolimod, ozanimod, siponimod and teriflunomide. Injection DMTs include daclizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b, ofatumumab and peginterferon beta-1a.

In Figure 10, all therapies were prescribed by either neurologists, GPs and internal medicine specialists, with a small proportion being prescribed by other specialist areas.

In infusion and oral therapies, neurologists were the most common prescriber type accounting for approximately 65% and 68% of prescribers, respectively. GPs were second most common prescriber type accounting for approximately 29% and 27% of prescribers, respectively.

In injection therapies, GPs were the most common prescriber type accounting for approximately 56% prescribers. Neurologists were the second most common prescriber type accounting for 38% of prescribers.

Seventy eight percent of patients initiating treatment with cladribine were prescribed by neurologists.

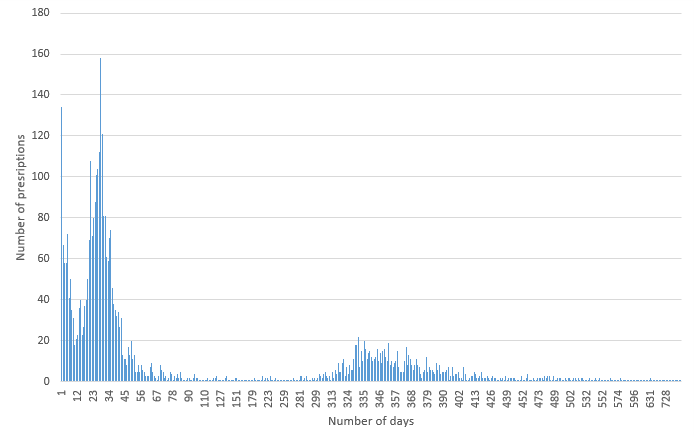


Figure 11: Time to refill cladribine prescriptions

Figure 11 presents the number of days between supply of cladribine prescriptions. The most common time to refill was 28 days. This is consistent with the Product Information which recommends the second treatment week be administered 28 days after the first treatment week. Furthermore, the Product Information describes the second treatment course begins in the following year, corresponding to approximately 337 days (365 days-28 days) from previous dose, as demonstrated in the graph.

Table 4: Proportion of patients receiving cladribine treatment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **First treatment course** | | **Second treatment course**  **(1 year following)** | |
| **First treatment week**  **% (n)** | **Second treatment week (28 days following first treatment week)**  **% (n)** | **First treatment week**  **% (n)** | **Second treatment week (1 month following first treatment week)**  **% (n)** |
| Cladribine | 100% (1,130) | 98.1% (1,108) | 96.4% (1,089) | 95.4% (1,078) |
| Other RRMS drug | 0% | 1.9% (22) | 3.6% (41) | 4.6% (52) |

Table 4 describes the cohort of cladribine patients who initiated treatment in 2019 and the proportion receiving subsequent treatment. Of this cohort, 95.4% of cladribine patients completed the second treatment course.

Table 5: Use of cladribine as a monotherapy and cases of potential co-supply of another RRMS therapy within 12 months of first supply of cladribine

|  |  |
| --- | --- |
| **Drug regimen** | **Proportion of all regimens** |
| Cladribine monotherapy | 99.2% |
| Cladribine co-supply | 0.8% |

From Table 5, less than 1% of regimens were probable cases of co-supply of another RRMS therapy within 12 months of first cladribine supply. Potential co-supplied DMTs included dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab, ocrelizumab and siponimod. Potential co-administration was most common with dimethyl fumarate and fingolimod.

Table 6: Switching sequences for cladribine following 12 months of first supply of cladribine

|  |  |
| --- | --- |
|  | **Percent** |
| CLADRIBINE | 96.0% |
| CLADRIBINE>OCRELIZUMAB | 2.0% |
| CLADRIBINE>NATALIZUMAB | 1.3% |
| OTHER SEQUENCES | 0.8% |

From Table 6, 95.3% of patients who initiated with cladribine treatment remain on cladribine treatment.

Figure 12: Profile of last RRMS DMT before patient switching to cladribine

From Figure 12, 49% of patients who switched to cladribine were previously on oral therapy (dimethyl fumarate, fingolimod, teriflunomide).

Table 7: Switching sequences by RRMS DMT form from 1 October 2020 and 30 September 2021

|  |  |  |
| --- | --- | --- |
| **Sequence** | **Count** | **Percent** |
| oral | 6,855 | 31.3% |
| infusion | 4,806 | 22.0% |
| injection | 2,480 | 11.3% |
| oral>infusion | 2,287 | 10.5% |
| injection>oral | 2,014 | 9.2% |
| injection>infusion | 564 | 2.6% |
| injection>oral>infusion | 454 | 2.1% |
| infusion>oral | 393 | 1.8% |
| other sequences | 2,032 | 9.3% |

Table 7 shows the switching sequences that occurred between 1 October 2020 and 30 September. Approximately 64.6% of patients continued treatment with the same DMT form.

Table 8: Number of prior therapies by patients switching to any new RRMS therapy between 1 October 2020 and 30 September 2021

|  |  |  |
| --- | --- | --- |
| **Number of prior RRMS drugs** | **Count** | **Percent** |
| 1 | 993 | 54% |
| 2 | 556 | 30% |
| 3 | 211 | 11% |
| 4 | 66 | 4% |
| ≥5 | 15 | 1.2% |

Table 8 presents, of all patients who switched to a new RRMS therapy between 1 October 2020 and 30 September, the number of prior RRMS treatments they have received previously.

## Analysis of actual versus predicted utilisation of cladribine

## Approach taken to estimate utilisation

A market share approach was taken based on the combined market share of oral RRMS agents. The resubmission used Medicare services data for fingolimod, teriflunomide and dimethyl fumarate and matched the services for timing. The resubmission assumed cladribine would account for || of the market.

The estimates were calculated on a monthly basis and converted services per month using the number of fingolimod prescriptions in 2016 divided by fingolimod scripts per patient per year. A |||||||| growth rate for Years 4 to 6 after PBS listing was applied based on the 2012-2014 population growth described in the October 2015 DUSC report.

These estimates describe the total patients on a cladribine treatment course, but not necessarily actively receiving treatment as cladribine patients would receive treatment in Years 1 and 2, and are monitored in Years 3 and 4.

The resubmission assumed that no patients would reinitiate treatment with cladribine in Years 7 to 9, but described these patients would remain therapeutically covered. It was assumed the listing of cladribine was not anticipated to grow the market in Australia, as the RRMS market is well established and oral treatments have been PBS listed since 2011. Cladribine was expected to displace therapies that are already PBS listed for RRMS.

For Year 1 to 6, the resubmission assumed an uptake rate of |||| to ||, with an incremental increase of |||| annually. The resubmission assumed there would be 120 grandfather patients in Year 1.

Table 8: Cladribine actual versus predicted utilisation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **cladribine listing years** | | **Year 1** | **Year 2** | **Year 3** |
| **January 2019 – December 2019** | **January 2020 – December 2020** | **January 2021- December 2021** |
| Patients | Predicted | | | | | | |
| Actual | 1,130 | 1,407 | 974 |
| Difference | | | | | | |
| Prescriptions | Predicted | | | | | | |
| Actual | 3,295 | 4,147 | 2,672 |
| Difference | | | | | | |

Note: Year 3 predicted numbers are for the full year, actual numbers are nine months of data (January 2021 to September 2021 inclusive).

The resubmission estimated a persistence rate of 100% in Year 1 and 80% in Year 2. As described in Table 4, 95.4% of patients who received the second treatment course was higher than estimated.

# Discussion

Overall the RRMS market appears to be stable as shown in Figures 1 and 5. Oral therapies continue to be the preferred form of therapy, with fingolimod being the highest utilised DMT. Infusion therapies are now the second preferred form over injections, likely due to increased infusion options being PBS listed: alemtuzumab (PBS listed April 2015) and ocrelizumab (PBS listed February 2018) in addition to natalizumab.

The above analyses report prescription and patient counts by calendar year or supply quarter. In interpreting the utilisation of individual medicines based on these counts it should be noted that some involve irregular dosing regimens and shorter treatment courses, particularly alemtuzumab, cladribine and ocrelizumab:

* Alemtuzumab is administered across two treatment courses. The first treatment course is administered over 5 days and the second treatment course is administered over 3 days, 12 months after initial treatment.
* Ocrelizumab is initially administered through a dose split into 2 infusions over 2 weeks and then is administered every 6 months afterwards.
* Cladribine is administered across two treatment courses over 2 years. Each course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month.

From the above analyses, there is a change in the RRMS market away from the older RRMS drugs.[[8]](#footnote-8) This transition may be due the differing efficacy of DMTs and their effect on disease activity. In a recent Norwegian study based on a population-based registry, patients treated with high-efficacy DMTs were more likely to achieve no evidence of disease activity at Years 1 and 2 compared to those on moderate efficacy DMTs. High-efficacy DMTs included natalizumab, fingolimod, alemtuzumab, whilst moderate efficacy DMTs included interferons, glatiramer acetate, teriflunomide and dimethyl fumarate. No evidence of disease activity was described as no history of a clinical relapse, no new activity on magnetic resonance imaging (MRI) and no sign of clinical disease progression measured by expanded disability status scale (EDSS) in the past year.[[9]](#footnote-9) The PBAC noted at its March 2021 meeting the different efficacy tiers in its consideration of ofatumumab. Higher tier treatments include alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab and ozanimod. Whilst lower tier treatments include dimethyl fumarate, glatiramer acetate and interferon beta-1a/1b, peginterferon beta-1a and teriflunomide (ofatumumab, Public Summary Document, March 2021 PBAC Meeting).

The PBS restrictions vary according to the drug form of either: infusion (alemtuzumab, natalizumab and ocrelizumab), injection (glatiramer acetate, interferon beta-1a, interferon beta-1b and peginterferon beta-1a) or oral therapy (cladribine, dimethyl fumarate, fingolimod, ozanimod, siponimod and teriflunomide) (Appendix C). Although infusion therapies specify treatment by a neurologist, neurologists accounted for 65% of prescribers. The restrictions for infusion and oral therapies specify they must be the only PBS drug for this condition. Based on the coadministration analysis in Table 8, there was only 3.9% to be probable cases of cladribine coadministration.

Although the RRMS market is well established, there is a potential for off-label use in other types of MS. Two submissions have been made for siponimod for secondary progressive MS. It was not recommended by the PBAC at its November 2019 Meeting (siponimod, [Public Summary Document](https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2019-11/siponimod-tablet-250-micrograms-tablet-2-mg-mayzent) November 2019 PBAC Meeting). Its resubmission at the July 2020 PBAC Meeting was recommended for secondary progressive MS (siponimod, [Public Summary Document](https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2020-07/siponimod-tablet-250-micrograms-tablet-2-mg-mayzent) July 2020 PBAC Meeting). At the time of this review, it has yet to be PBS listed for this indication. Two submissions have been made for ocrelizumab which were not recommended: primary progressive multiple sclerosis (ocrelizumab, [Public Summary Document](https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2017-11/ocrelizumab-psd-november-2017), November 2017 PBAC Meeting) and for early (diagnosed within the past five years), MRI-active primary progressive MS (ocrelizumab, [Public Summary Document](https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2020-07/ocrelizumab-solution-concentrate-for-iv-infusion-300-mg) July 2020 PBAC Meeting).

# DUSC consideration

DUSC noted the changes in RRMS market share over time, such as oral therapies becoming the most preferred therapy and the shift away from the older generation RRMS treatments. DUSC considered that there would likely to be continued market share changes in the future and noted the recent PBS listings of siponimod (November 2020) and ozanimod (October 2021). DUSC noted the Pre-Sub-Committee Responses (PSCR) from the sponsors of dimethyl fumarate, interferon beta-1a, natalizumab and peginterferon as well as the sponsor of interferon beta-1b, who both acknowledged the preference for oral therapies and the shift away from older medicines could be due to the potential convenience associated with less frequent dosing.

DUSC noted a high proportion of injection prescriptions were initiated by GPs, despite the restriction specifying treatment by neurologist. DUSC considered that it may have been due to coding errors for Authority Required (Streamlined) prescriptions. Additionally, DUSC commented it could have been due to cases of neurologists advising GPs of the appropriate treatment plan to which GPs would initiate treatment for the patient or the patient’s lack of accessibility to neurologists.

DUSC noted the number of patients treated with cladribine during the first and second year of listing was |||||| than estimated. DUSC noted the number of prescriptions supplied was |||||| than estimated during the first year of listing and was |||||| than estimated during the second year of listing. DUSC considered there may have been an impact of the COVID-19 pandemic, and commented that the number of patients initiating cladribine treatment is yet to be stabilised.

DUSC noted cladribine is administered to patients via two courses over two years. DUSC noted the high proportion of persistence in Year 2 of cladribine treatment. DUSC considered the assumption of || persistence rate was |||||||||||||||||||||| and commented that the yearly dosing regimen may have |||||||||||| persistence. DUSC noted the time to resupply varied between the first and second year. DUSC commented that there was larger variation when patients received their treatment course in the second year, compared to the first year.

DUSC noted the submission assumed cladribine would displace fingolimod. DUSC commented that a proportion of patients switching to cladribine were previously treated with fingolimod, however, not all patients switching to cladribine treatment were previously treated with fingolimod.

DUSC sought consumer input from MS Australia and noted the following comments from this organisation:

* Cladribine’s dosing regimen and oral administration is a great option for patients, particularly for young newly diagnosed patients. The dosing regimen gives them a sense that they are still in control.
* Whether cladribine patients would require treatment after their two treatment courses and if so, whether patients are treated with cladribine again or a different disease modifying therapy (DMT).
* Neurologists in remote or regional areas may have only provided MS patients with a small number of treatment options.
* There has been a trend amongst MS neurologists towards no evidence of disease of activity (NEDA: no relapses or new MRI lesions and no sign of disease progression) and to achieve that, there is a tendency towards the treatments considered to be high efficacy.
* MS is a complex disease course and every patient experiences MS differently. Therefore, a complex decision making process is required for MS patients and their healthcare team. Following a discussion with their neurologist and determining the appropriate treatment, most patients’ expectations regarding benefits and health outcomes are initially met. Although some patients would experience new side effects.
* Utilisation numbers for 2021 and 2022 will help understand the impact of the COVID-19 pandemic, and whether different decisions have been made with respect to DMTs.

# DUSC actions

The report was 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

Alphapharm Pty Ltd: This sponsor has no comment.

Apotex Pty Ltd: This sponsor has no comment.

Arrow Pharma Pty Ltd: This sponsor has no comment.

Bayer Australia Ltd: Although there is a shift away from injectables for patients with relapsing remitting multiple sclerosis, Bayer believe that for some patients, medicines such as interferon beta-1b are highly effective.

Biogen Australia Pty Ltd: This sponsor has no comment.

Celgene Pty Limited: This sponsor has no comment.

Dr Reddy’s Laboratories (Australia) Pty Ltd: This sponsor has no comment.

Generic Health Pty Ltd: This sponsor has no comment.

Merck Healthcare Pty Ltd: Merck would like to thank DUSC for reviewing the utilisation of Cladribine for relapsing-remitting multiple sclerosis (RRMS).

Novartis Pharmaceuticals Pty Limited: This sponsor has no comment.

Pharmacor Pty Limited: This sponsor has no comment.

Roche Products Pty Ltd: This sponsor has no comment.

Sandoz Pty Ltd: This sponsor has no comment.

sanofi-aventis Australia Pty Ltd: This sponsor has no comment.

Teva Pharma Australia Pty Ltd: This sponsor has no comment.

# 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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# References

Gruchot J, Weyers V, Göttle P, Förster M, Hartung H-P, Küry P, Kremer D. The Molecular Basis for Remyelination Failure in Multiple Sclerosis. Cells (2019),8, 825, doi:10.3390/cells8080825

Simonsen C.S, Flemmen H.O, Broch L, Brunborg C, Berg-Hansen P, Moen S.M et al. Early High Efficacy Treatment in Multiple Sclerosis is the best predictor of future disease activity over 1 and 2 years in a Norwegian population-based registry. Frontiers in Neurology (2021). doi: 10.3389/fneur.2021.693017

Lemus H.N, Warrington A.E, Rodriguez M. Multiple Sclerosis: Mechanisms of Disease and Strategies for Myelin and Axonal Repair. Neurol Clin (2018), 36; 1-11. https://doi.org/10.1016/j.ncl.2017.08.002

Mavenclad (cladribine). Australian Approved Product Information. Macquarie Park: Merck Healthcare Pty Ltd. Approved 9 September 2010, updated 3 May 2021. Available from < <https://www.tga.gov.au/product-information-pi>.>

1. MS Australia (Internet). What is Multiple Sclerosis (MS) Accessed on 12 November 2021, Available from: https://www.msaustralia.org.au/what-ms
2. MS Australia (Internet). Key facts and figures about multiple sclerosis (updated September 2020). Accessed on 12 November 2021, Available from: https://www.msaustralia.org.au/about-ms/information-sheets

MS Australia (Internet). Understanding Multiple Sclerosis: A Brief Overview. Accessed on 12 November 2021, Available from: <https://www.msaustralia.org.au/about-ms/information-sheets>

PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Simonsen C.S, Flemmen H.O, Broch L, Brunborg C, Berg-Hansen P, Moen S.M et al. Early High Efficacy Treatment in Multiple Sclerosis is the best predictor of future disease activity over 1 and 2 years in a Norwegian population-based registry. Frontiers in Neurology (2021). doi: 10.3389/fneur.2021.693017

# Appendix

## Appendix A: PBS items indicated for the treatment of MS as at November 2021

| 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 | $54,121.50 | Lemtrada  sanofi-aventis Australia Pty Ltd |
| 10232M | alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial | 3 | 3 | 0 | $32,472.90 |
| 10243D | alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial | 5 | 5 | 0 | $54,169.28 |
| 10246G | alemtuzumab 12 mg/1.2 mL injection, 1.2 mL vial | 3 | 3 | 0 | $32,520.67 |
| 11603Q | cladribine 10 mg tablet, 1 | 1 | 1 | 1 | $3994.26 | Mavenclad  Merck Healthcare Pty Ltd |
| 11604R | cladribine 10 mg tablet, 4 | 2 | 8 | 1 | $30,825.54 |
| 11611D | cladribine 10 mg tablet, 6 | 1 | 6 | 1 | $23,159.46 |
| 2896K | dimethyl fumarate 120 mg enteric capsule, 14 | 2 | 28 | 0 | $649.96 | Tecfidera  Biogen Australia Pty Ltd |
| 2943X | dimethyl fumarate 120 mg enteric capsule, 14 | 2 | 28 | 0 | $649.96 |
| 2966D | dimethyl fumarate 240 mg enteric capsule, 56 | 1 | 56 | 5 | $1291.80 |
| 11818B | fingolimod 250 microgram capsule, 28 | 1 | 28 | 5 | $2,219.51 | Gilenya  Novartis Pharmaceuticals Australia Pty Limited |
| 5262Y | fingolimod 500 microgram capsule, 28 | 1 | 28 | 5 | $2,219.51 |
| 10416F | glatiramer acetate 40 mg/mL injection, 12 × 1 mL syringes | 1 | 12 | 5 | $895.04 | Copaxone  Teva Pharma Australia Pty Ltd |

| **Item** | **Name, form & strength, pack size** | **Max. qty. packs** | **Max. qty. units** | **Rpts** | **DPMQ** | **Brand name and manufacturer** |
| --- | --- | --- | --- | --- | --- | --- |
| 8805K | interferon beta-1a 6 million units (30 microgram)/0.5 ml injection, 4 × 0.5 ml syringes | 1 | 4 | 5 | $865.62 | Avonex  Biogen Australia Pty Ltd |
| 8403G | interferon beta-1a 12 million units (44 microgram)/0.5 ml injection, 12 × 0.5 ml syringes | 1 | 12 | 5 | $865.62 | Rebif 44  Merck Healthcare Pty Ltd |
| 8968B | interferon beta-1a 12 million units (44 microgram)/0.5 ml injection, 12 × 0.5 ml syringes | 1 | 12 | 5 | $865.62 |
| 9332E | interferon beta-1a 36 million units (132 microgram)/1.5 ml injection, 4 × 1.5 ml cartridges | 1 | 4 | 5 | $865.62 |
| 8101J | interferon beta-1b 8 million units (250 microgram) injection [15 vials] (&) inert substance diluent [15 × 1.2 ml syringes], 1 pack | 1 | 15 | 5 | $997.66 | Betaferon  Bayer Australia Ltd |
| 9505G | natalizumab 300 mg/15 ml injection, 15 ml vial | 1 | 1 | 5 | $1340.68 | Tysabri  Biogen Australia Pty Ltd |
| 9624M | natalizumab 300 mg/15 ml injection, 15 ml vial | 1 | 1 | 5 | $1388.46 |
| 11237K | ocrelizumab 300 mg/10 ml injection, 10 ml vial | 2 | 2 | 0 | $17580.78 | Ocrevus  Roche Products Pty Ltd |
| 11242Q | ocrelizumab 300 mg/10 ml injection, 10 ml vial | 2 | 2 | 0 | $17533.00 |
| 12641H | ofatumumab 20 mg/0.4 ml injection, 0.4 ml pen device | 1 | 1 | 5 | $2183.42 | Kesimpta  Novartis Pharmaceuticals Australia Pty Limited |
| 12642J | ofatumumab 20 mg/0.4 ml injection, 0.4 ml pen device | 3 | 3 | 0 | $6336.10 |
| 12271W | ozanimod 920 microgram capsule, 28 | 1 | 28 | 5 | $2219.51 | Zeposia  Celgene Pty Limited |
| 12278F | ozanimod 230 microgram capsule [4] (&) ozanimod 460 microgram capsule [3], 7 | 1 | 1 | 0 | $588.01 |

| **Item** | **Name, form & strength, pack size** | **Max. qty. packs** | **Max. qty. units** | **Rpts** | **DPMQ** | **Brand name and manufacturer** |
| --- | --- | --- | --- | --- | --- | --- |
| 10212L | peginterferon beta-1a 125 microgram/0.5 ml injection, 2 × 0.5 ml pen devices | 1 | 2 | 4 | $1001.59 | Plegridy  Biogen Australia Pty Ltd |
| 10218T | 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 | 1 | 1 | 0 | $1001.59 |
| 10220X | peginterferon beta-1a 125 microgram/0.5 ml injection, 2 × 0.5 ml pen devices | 1 | 2 | 5 | $1001.59 |
| 12158X | siponimod 2 mg tablet, 28 | 1 | 28 | 5 | $2219.51 | Mayzent  Novartis Pharmaceuticals Australia Pty Limited |
| 12172P | siponimod 250 microgram tablet, 12 | 1 | 12 | 0 | $239.46 |
| 12160B | siponimod 250 microgram tablet, 120 | 1 | 120 | 5 | $2219.52 |
| 2898M | teriflunomide 14 mg tablet, 28 | 1 | 28 | 5 | $497.86 | APO-TERIFLUNOMIDE  Apotex Pty Ltd  Pharmacor Teriflunomide  Pharmacor Pty Limited  TERIFLAGIO  Arrow Pharma Pty Ltd  Teriflunomide Dr. Reddy’s  Dr Reddy’s Laboratories (Australia) Pty Ltd  Teriflunomide GH  Generic Health Pty Ltd  Teriflunomide Sandoz  Sandoz Pty Ltd  Terimide  Alphapharm Pty Ltd |

## Appendix B: Chronology of PBS listed MS treatments

| **Drug** | **Brand name** | **Item**  **code** | **First listing**  **date** | **Form and strength** |
| --- | --- | --- | --- | --- |
| interferon beta-1b | Betaferon | 08101J | 1 Nov 1996 | injection set comprising 1 vial powder for injection providing a final dose of 250 micrograms (8,000,000 i.u.) and 2.25 ml pre-filled syringe with 1.2ml solvent |
| interferon beta-1aa | Avonex | 08289G | 1 Feb 1999 | injection set comprising 1 vial powder for injection 30 micrograms (6,000,000 i.u.) and 1 ampoule solvent 2 ml |
| glatiramer acetateb | Copaxone | 08352N | 1 Nov 1999 | powder for subcutaneous injection 20 mg in single use vial and 1 ampoule diluent 1.1 ml |
| interferon beta-1a | Rebif 22 | 08402F | 1 May 2000 | injection 22 micrograms (6,000,000 i.u.) in 0.5 ml single dose pre-filled syringe |
| interferon beta-1a | Rebif 44 | 8403G | 1 May 2000 | injection 44 micrograms (12,000,000 i.u.) in 0.5 ml single dose pre-filled syringe |
| glatiramer acetatec | Copaxone | 08726G | 1 May 2004 | injection 20 mg in 1 ml single dose pre-filled syringe |
| interferon beta-1a | Avonex | 08805K | 1 Apr 2005 | injection 30 micrograms (6,000,000 i.u.) in 0.5 ml single dose pre-filled syringe |
| natalizumab | Tysabri | 09624M | 1 Jul 2008 | solution concentrate for i.v. infusion 300 mg in 15 ml |
| interferon beta-1a | Rebif 44 | 09332E | 1 May 2010 | solution for injection 132 micrograms in 1.5 ml multidose cartridge |
| natalizumab | Tysabri | 09505G | 1 Jul 2010 | solution concentrate for i.v. infusion 300 mg in 15 ml |
| interferon beta-1a | Rebif 44 | 08968B | 1 May 2011 | injection 44 micrograms (12,000,000 i.u.) in 0.5 ml single dose autoinjector |
| fingolimod | Gilenya | 05262Y | 1 Sep 2011 | capsule 500 micrograms (as hydrochloride) |
| dimethyl fumarate | Tecfidera | 02896K | 1 Dec 2013 | capsule (modified release) 120 mg |
| dimethyl fumarate | Tecfidera | 02943X | 1 Dec 2013 | capsule (modified release) 120 mg |
| dimethyl fumarate | Tecfidera | 02966D | 1 Dec 2013 | capsule (modified release) 240 mg |
| teriflunomide | Aubagio | 02898M | 1 Dec 2013 | tablet 14 mg |
| peginterferon beta-1a | Plegridy | 10212L | 1 Mar 2015 | single use injection pen containing 125 micrograms in 0.5 ml |
| peginterferon beta-1a | Plegridy | 10218T | 1 Mar 2015 | pack containing single use injection pens containing 63 micrograms in 0.5 ml and 94 micrograms in 0.5 ml |
| peginterferon beta-1a | Plegridy | 10220X | 1 Mar 2015 | single use injection pen containing 125 micrograms in 0.5 ml |
| alemtuzumab | Lemtrada | 10228H | 1 Apr 2015 | solution concentrate for i.v. infusion 12 mg in 1.2 ml |
| alemtuzumab | Lemtrada | 10232M | 1 Apr 2015 | solution concentrate for i.v. infusion 12 mg in 1.2 ml |
| alemtuzumab | Lemtrada | 10243D | 1 Apr 2015 | solution concentrate for i.v. infusion 12 mg in 1.2 ml |
| alemtuzumab | Lemtrada | 10246G | 1 Apr 2015 | solution concentrate for i.v. infusion 12 mg in 1.2 ml |
| glatiramer acetate | Copaxone | 10416F | 1 Aug 2015 | 40 mg/mL, 12 × 1 mL syringes |
| daclizumabd | Zinbryta | 11101G | 1 May 2017 | 150 mg/mL injection, 1 mL injection device |
| Teriflunomidee | Aubagio | 02898M | 1 Jun 2017 | tablet 14 mg |
| ocrelizumab | Ocrevus | 11237K | 1 Feb 2018 | 300 mg/ 10 mL injection, 10 mL vial |
| ocrelizumab | Ocrevus | 11242Q | 1 Feb 2018 | 300 mg/ 10 mL injection, 10 mL vial |
| cladribine | Mavenclad | 11611D | 1 Jan 2019 | 10 mg tablet |
| cladribine | Mavenclad | 11603Q | 1 Jan 2019 | 10 mg tablet |
| cladribine | Mavenclad | 11604R | 1 Jan 2019 | 10 mg tablet |
| Teriflunomide | Teriflunomide Sandoz | 2898M | 1 Jun 2019 | Tablet 14 mg |
| Teriflunomide | Teriflago | 2898M | 1 Sept 2019 | Tablet 14 mg |
| Teriflunomide | APO-teriflunomide | 2898m | 1 Nov 2019 | Tablet 14 mg |
| Teriflunomide | Pharmacor Teriflunomide | 2898M | 1 Jan 2020 | Tablet 14 mg |
| Teriflunomide | Teriflunomide GH | 2898M | 1 Jan 2020 | Tablet 14 mg |
| Teriflunomide | Teriflunomide Dr Reddy’s | 2898M | 1 Mar 2020 | Tablet 14 mg |
| siponimod | Mayzent | 12172P | 1 Nov 2020 | Tablet 2 mg |
| siponimod | Mayzent | 12158X | 1 Nov 2020 | Tablet 250 microgram |
| siponimod | Mayzent | 12160B | 1 Nov 2020 | Tablet 250 microgram |
| ozanimod | Zeposia | 12278F | 1 Mar 2021 | 230 microgram capsule [4] (&) 460 microgram capsule [3] |
| Teriflunomide | Terimide | 2898M | 1 Apr 2021 | Tablet 14 mg |
| ofatumumab | Kesimpta | 12641H | 1 Oct 2021 | 20 mg/0.4 mL injection, 0.4 mL pen device |
| ofatumumab | Kesimpta | 12642J | 1 Oct 2021 | 20 mg/0.4 mL injection, 0.4 mL pen device |

Note:

a Delisted 31 January 2017

b Delisted 30 November 2004

c Delisted 30 June 2019

d daclizumab (2898M) was delisted 31 May 2018.

e Aubagio brand delisted 1 October 2021.

## Appendix C: Summary of restrictions as at November 2021

Infusion treatments (alemtuzumab, natalizumab and ocrelizumab) are listed on Section 100 Highly Specialised Drugs Program (Private and Public Hospital).

Oral treatments (cladribine, dimethyl fumarate, fingolimod, ozanimod, siponimod, teriflunomide) and injection treatments (glatiramer acetate, interferon beta-1a, interferon beta-1b, ofatumumab and peginterferon beta-1a) are listed on Section 85 General Schedule.

All current PBS listings for RRMS are Authority Required (Streamlined).

All listings for initial treatment require:

* diagnosis confirmed by magnetic resonance imaging (MRI) of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient; and
* patients to be ambulatory, without assistance or support;

Initial treatment with infusion and oral treatments specify the requirement to be that it must be sole PBS-subsidised disease modifying therapy for this condition.

Initial treatment with infusion treatments specify the requirement for treatment with a neurologist. Initial treatment with cladribine specifies the requirement for the condition to be diagnosed by a neurologist.

Initial treatment with siponimod specifies the requirement for mild disability in at least 3 functional systems or moderate disability in at least 1 functional system. Functional systems include: visual, brain stem, pyramidal, cerebellar, sensory, bowel/bladder and the cerebral/cognitive systems. Appropriate dose and pack size is selected based on the patient’s CYP2C9 metabolising enzyme status.

All listings for continuing treatment require that the patient does not show continuing progression of disability while on treatment and has demonstrated compliance with, and an ability to tolerate, the therapy.

Continuing treatment with alemtuzumab, cladribine, natalizumab and teriflunomide require the condition to be diagnosed as clinically definite RRMS by MRI of the brain and/or spinal cord, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient. Continuing treatment with alemtuzumab only specifies the requirement for the condition to be diagnosed as clinically definite RRMS by MRI.

Continuing treatment with infusion and oral treatments specify the requirement that it must be sole PBS-subsidised disease modifying therapy for this condition.

Continuing treatment with injection therapies as well as fingolimod, ofatumumab, and ozanimod specify the requirement for the condition to be diagnosed as clinically definite RRMS.

Continuing treatment with natalizumab and siponimod specifies the requirement for the patient to be ambulatory, with/without assistance/support

Continuing treatment with alemtuzumab specifies the requirement for patients to not receive more than one PBS-subsidised treatment per year.

Continuing treatment with infusion therapies as well as cladribine specify the requirement for patients to be treated by a neurologist.

Continuing treatment with natalizumab specifies the requirement for patients to 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.

## Appendix D: Summary of PBAC considerations published in Public Summary Documents

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| **Alemtuzumab** | |
| Jul 2014 | The PBAC recommended the Authority Required Section 100 (Highly Specialised Drugs Program) listing of alemtuzumab for the treatment of RRMS, on the basis of non-inferior effectiveness and a different safety profile to fingolimod and natalizumab. |
| Nov 2014 | The PBAC reiterated its previous recommendation for the Authority Required Section 100 (Highly Specialised Drugs Program) listing of alemtuzumab for the treatment of RRMS. The PBAC rejected the re submission to amend the basis of the July 2014 PBAC recommendation to list alemtuzumab. |
| Nov 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 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. |
| **Cladribine** | |
| Mar 2011 | The PBAC did not recommended the listing of cladribine for the treatment of RRMS, on the basis of an inappropriate comparator, uncertain clinical benefit and uncertain and unacceptable cost effectiveness in comparison with the appropriate comparator. |
| Nov 2017 | The PBAC did not recommend the listing of cladribine for the treatment of RRMS, on the basis of uncertainty in the non-inferior efficacy claim of cladribine versus fingolimod over two and four years. The PBAC considered there was insufficient clinical evidence to support the time horizon of four years for estimating the equi-effective doses of cladribine and fingolimod. The PBAC also considered that it was unrealistic to assume that patients who receive cladribine and experience disease relapse would not be prescribed another medicine for RRMS before the four-year period or that patients would be persistent to fingolimod. Therefore, the PBAC did not accept two years of cladribine treatment versus four years of fingolimod treatment as the basis for the cost-minimisation analysis proposed by the resubmission. The PBAC noted that there were significant uncertainties in the financial analysis, including the persistence rates assumed by the resubmission. The PBAC further noted that the financial analysis estimated a significant net cost to the PBS, which undermines the first principles of a cost minimisation analysis. |
| Mar 2018 | The PBAC did not recommend the listing of cladribine for the treatment of RRMS, on the basis of uncertainty in the non-inferior efficacy claim of cladribine versus fingolimod over two and four years. The PBAC recalled that in November 2017 it considered there was insufficient clinical evidence to support the time horizon of four years for estimating the equi-effective doses of cladribine and fingolimod. The PBAC noted that the minor resubmission did not provide additional clinical evidence to address its concerns. Therefore, the PBAC again did not accept two years of cladribine treatment versus four years of fingolimod treatment as the basis for the cost-minimisation analysis proposed by the minor resubmission. The PBAC noted that there remained significant uncertainties in the financial analysis, including the persistence rates assumed by the resubmission. The PBAC further noted that the financial analysis estimated a significant net cost to the PBS, which undermines the first principles of a cost minimisation analysis. |
| Jul 2018 | The PBAC recommended the Authority Required listing of cladribine for the treatment of RRMS. The PBAC’s recommendation for listing was based on, amongst other matters, its assessment than the cost-effectiveness of cladribine would be acceptable if it were cost-minimised against fingolimod based on a claim that two years of cladribine treatment is non-inferior in efficacy to two years’ of fingolimod treatment. |
| **Dimethyl fumarate** | |
| Jul 2013 | The PBAC rejected the listing of dimethyl fumarate at the price requested in the submission, on the grounds that the claims of superior efficacy over the ABCR therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b and glatiramer acetate) and non-inferior efficacy compared to fingolimod were not adequately supported by the evidence presented.  The PBAC considered that the appropriate clinical claim based on the data provided was that dimethyl fumarate is non-inferior to the ABCR therapies in terms of efficacy and safety. Therefore the Committee recommended the listing of dimethyl fumarate on a cost-minimisation basis with the ABCR therapies. |
| Jul 2016 | The PBAC recommended increasing the maximum quantities of 120 mg dimethyl fumarate from one to two packs for both the initial and continuing titration periods. |
| Nov 2019 | The PBAC recommended amending the listing of dimethyl fumarate to Authority Required (STREAMLINED) for the treatment of RRMS. The PBAC also recommended amending the listings of fingolimod, teriflunomide and cladribine to Authority Required (STREAMLINED) for the treatment of RRMS. |
| **Fingolimod** | |
| Mar 2011 | The PBAC recommended out-of-session listing on the basis of an acceptable cost-effectiveness ratio compared with interferon beta-1a. |
| Jul 2019 | The PBAC recommended the Authority Required (telephone) listing of fingolimod, in the form 250 microgram capsules, on the general schedule for treatment of RRMS in patients weighing 40kg or less. In making this recommendation, the PBAC considered that fingolimod 250 mcg used in RRMS patients weighing 40kg or less was equivalent to fingolimod 500 mcg used in RRMS patients weighing more than 40kg. |
| **Glatiramer acetate** | |
| Mar 2015 | The PBAC recommended the listing of glatiramer acetate 40 mg/mL injection for the treatment of multiple sclerosis. The PBAC noted that the TGA was satisfied that the three-times-weekly regimen (providing 480 mg per month) would deliver a similar treatment benefit compared with the daily regimen (providing 560 mg per month), and therefore concluded that the sponsor’s claim of non-inferiority in terms of efficacy and safety was reasonable. |
| Jul 2017 | The PBAC did not recommend the listing of glatiramer acetate for the treatment of patients with clinically isolated syndrome suggestive of multiple sclerosis in patients thought to be at high risk of subsequent diagnosis with multiple sclerosis, on the basis of uncertainty regarding the clinical benefit and resulting cost-effectiveness, concerns about the plausibility of assumptions used in the economic model, and uncertainty with the utilisation estimates associated with difficulties in defining the target PBS population. |
| Mar 2021 | The PBAC recommended the listing of a new brand of glatiramer, Glatira 40 mg/mL injection, and the listing of Glatira 20 mg/mL injection, on the PBS for the treatment of multiple sclerosis. The PBAC recommended the listings on a cost minimisation basis to the Copaxone brand of glatiramer. The PBAC noted that the TGA considered Glatira and Copaxone to be therapeutically equivalent. The PBAC advised, under Section 101 (4AACD) of the National Health Act 1953, that Glatira 40 mg/mL injection and Copaxone 40 mg/mL injection should be considered equivalent for the purposes of substitution. |
| **Interferon beta 1b** | |
| Mar 2007 | The PBAC did not recommend the amendment of the Authority Required criteria to allow patients diagnosed using the McDonald Criteria to access treatment rather than the current Poser Criteria, because of uncertain clinical benefit and uncertain cost effectiveness. |
| **Natalizumab** | |
| Nov 2006 | The PBAC did not recommend the Section 100 Authority Required listing for initial and continuing treatment by neurologists of clinical definite relapsing-remitting multiple sclerosis in ambulatory patients 18 years or older who meet certain criteria, because although it agreed clinical benefit had been demonstrated the cost-effectiveness ratio was unfavourable and uncertain. |
| Nov 2007 | The PBAC recommended the listing of natalizumab on the PBS for initial and continuing treatment by neurologist, of clinically definite relapsing-remitting multiple sclerosis (RRMS) in an ambulatory patient eighteen years of age or older on the basis of a high but acceptable cost-effectiveness ratio compared with interferon beta-1b. |
| Jul 2019 | The PBAC recommended removal of the age restriction from the PBS listings of natalizumab for clinically definite RRMS. In making this recommendation, the PBAC noted the TGA Delegate was satisfied there was sufficient clinical evidence to remove the paediatric contraindication from the registration of natalizumab. |
| **Ocrelizumab** | |
| Jul 2017 | The PBAC recommended the listing of ocrelizumab for the treatment of RRMS on a cost-minimisation basis with fingolimod. The PBAC recommended ocrelizumab on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program – public and private hospital). |
| Nov 2017 | The PBAC did not recommend the listing of ocrelizumab for the treatment of patients with primary progressive multiple sclerosis (PPMS), on the basis of modest clinical benefit and the resulting high and uncertain incremental cost-effectiveness ratio (ICER). The PBAC was concerned about the applicability of trial results to the potential PBS population, and that the base case ICER presented by the submission may be underestimated as ocrelizumab is likely to be less effective in the PBS population than observed in the ORATORIO trial. The PBAC was also concerned about the uncertainty with the utilisation estimates due to issues with defining the target PBS population, and the high and likely underestimated financial impact. |
| Jul 2020 | The PBAC did not recommend extending the Section 100 (Highly Specialised Drugs Program – Public and Private Hospitals) listing of ocrelizumab to include the treatment of patients with early (diagnosed within the past five years), MRI-active primary progressive multiple sclerosis (PPMS). The PBAC considered that the key subgroup analysis that was relied on in the submission was inconsistent with the requested PBS population which led to difficulties in assessing the cost-effectiveness of ocrelizumab. The PBAC considered that the economic model had likely underestimated the ICER as the likely treatment effect and nursing home care costs had been overestimated. |
| **Ofatumumab** | |
| Mar 2021 | The PBAC recommended the Authority Required (STREAMLINED) listing of ofatumumab for the treatment or relapsing-remitting multiple sclerosis (RRMS). The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of ofatumumab would be acceptable if it were cost minimised to the least costly of fingolimod, natalizumab, alemtuzumab, ocrelizumab, cladribine and ozanimod. |
| **Ozanimod** | |
| Mar 2020 | The PBAC deferred making a recommendation for the listing of ozanimod on the PBS as the TGA Delegate’s Overview was not available at the time of consideration. However, the PBAC was of a mind to recommend the Authority Required (STREAMLINED) listing of ozanimod for the treatment of RRMS on a cost minimisation basis with fingolimod |
| Sep 2020 | The PBAC recommended, out of session, the General Schedule, Authority Required (STREAMLINED) listing of ozanimod for the treatment of RRMS, on a cost minimisation basis with fingolimod. In making this recommendation, the PBAC noted it had advised in March it had no additional concerns regarding the listing of ozanimod for RRMS and was awaiting the TGA evaluation to progress further prior to making a recommendation. |
| **Peginterferon beta-1a** | |
| Nov 2014 | The PBAC recommended the listing of peginterferon beta-1a as an Authority Required listing on a cost-minimisation basis compared with interferon beta-1a. The PBAC noted that the listing of peginterferon beta-1a would offer an alternative first line treatment for patients with remitting, relapsing multiple sclerosis. |
| **Siponimod** | |
| Nov 2019 | The PBAC did not recommend the listing of siponimod for the treatment of secondary progressive multiple sclerosis (SPMS). The PBAC acknowledged the high clinical need for effective treatments in this therapeutic area. However, the PBAC considered that the appropriate place of siponimod in the treatment algorithm for multiple sclerosis (MS) was uncertain, and the submission did not provide a reliable basis to assess the cost-effectiveness of siponimod. The PBAC also considered the financial estimates to be uncertain. |
| Jul 2020 | The PBAC recommended the listing of siponimod for patients with secondary progressive MS who are ambulant (with or without support). The PBAC recommended listing on a cost-minimisation basis compared with fingolimod. The PBAC considered that the cost-effectiveness of siponimod when used in a broader patient population than fingolimod was adequately addressed with a reduced price for this population. |
| **Teriflunomide** | |
| Nov 2012 | The PBAC did not recommend the Authority Required listing for the initial and continuing treatment of clinically definite relapsing-remitting multiple sclerosis in ambulatory patients who meet certain criteria, on the basis of uncertain clinical benefit, no formal economic analysis provided and uncertain uptake and hence uncertain cost to the PBS. |
| Jul 2013 | The PBAC recommended teriflunomide 14 mg as an Authority required listing for the initial and continuing treatment of RRMS in ambulatory patients who meet certain criteria on a cost-minimisation basis to interferon beta-1a and interferon beta-1b. |
| Nov 2016 | The PBAC decided not to recommend amending the listing of teriflunomide to Authority Required (STREAMLINED), as it considered that the market for oral therapies for RRMS had not yet stabilised. The PBAC noted the input from the DUSC secretariat with regards to the utilisation of all RRMS therapies, and noted that the utilisation of the other oral therapies, fingolimod and DMF, was higher than teriflunomide and the market for oral treatments was still growing. |

1. Gruchot J, Weyers V, Göttle P, Förster M, Hartung H-P, Küry P, Kremer D. The Molecular Basis for Remyelination Failure in Multiple Sclerosis. Cells (2019),8, 825, doi:10.3390/cells8080825 [↑](#footnote-ref-1)
2. Lemus H.N, Warrington A.E, Rodriguez M. Multiple Sclerosis: Mechanisms of Disease and Strategies for Myelin and Axonal Repair. Neurol Clin (2018), 36; 1-11. https://doi.org/10.1016/j.ncl.2017.08.002 [↑](#footnote-ref-2)
3. MS Australia (Internet). What is Multiple Sclerosis (MS) Accessed on 12 November 2021,

   Available from: https://www.msaustralia.org.au/what-ms [↑](#footnote-ref-3)
4. MS Australia (Internet). Key facts and figures about multiple sclerosis (updated September 2020). Accessed on 12 November 2021, Available from: https://www.msaustralia.org.au/about-ms/information-sheets [↑](#footnote-ref-4)
5. MS Australia (Internet). Understanding Multiple Sclerosis: A Brief Overview. Accessed on 12 November 2021, Available from: https://www.msaustralia.org.au/about-ms/information-sheets [↑](#footnote-ref-5)
6. Mavenclad (cladribine). Australian Approved Product Information. Macquarie Park: Merck Healthcare Pty Ltd. Approved 9 September 2010, updated 3 May 2021. Available from < https://www.tga.gov.au/product-information-pi.> [↑](#footnote-ref-6)
7. PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>. [↑](#footnote-ref-7)
8. Hillen J, Ward M, Slee M, Standord T, Roughead E, Kalisch Ellett L, Pratt N. Utilisation of disease modifying treatment and diversity of treatment pathways in relapsing remitting multiple sclerosis. Multiple Sclerosis and Related Disorders (2022) https://doi.org/10.1016/j.msard.2021.103412 [↑](#footnote-ref-8)
9. Simonsen C.S, Flemmen H.O, Broch L, Brunborg C, Berg-Hansen P, Moen S.M et al. Early High Efficacy Treatment in Multiple Sclerosis is the best predictor of future disease activity over 1 and 2 years in a Norwegian population-based registry. Frontiers in Neurology (2021). doi: 10.3389/fneur.2021.693017 [↑](#footnote-ref-9)