Ocrelizumab for relapsing remitting multiple sclerosis: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2020

Abstract

Purpose

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

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Ocrelizumab was PBS listed for the treatment of RRMS on 1 February 2018.

Data Source / methodology

The analysis used PBS prescriptions data maintained by Department of Health, processed by Services Australia.

Key Findings

- 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 is dynamic with the relatively 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) varies between Very Remote, Remote and non-remote RRMA patients. It appears that the frequency of dosing and accessibility to infusion services have an effect on the choice of medicine form depending on the remoteness of the patient.

Purpose of analysis

To compare the predicted and actual utilisation of ocrelizumab for relapsing remitting multiple sclerosis (RRMS) since it was PBS listed for this indication on 1 February 2018.

Background

Clinical situation

Multiple sclerosis (MS) is a progressive, chronic, autoimmune disease of the central nervous system in which the myelin sheath protecting axons is damaged resulting in distorted nerve signals and pathways. Multiple sclerosis is associated with a complex range of symptoms including visual disturbance, fatigue, pain, reduced mobility and coordination, cognitive impairment and mood changes.[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 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).[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]

Ocrelizumab is a monoclonal antibody that binds to the CD20 antigen on B lymphocytes. The resulting lymphocyte depletion modulates the immune response, but the exact mechanism of action of ocrelizumab in multiple sclerosis is currently uncertain.[4]

---

[1] Ocrelizumab Public Summary Document (PSD) November 2017 PBAC Meeting, https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2017-07/ocrelizumab-psd-july-2017
[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] https://www.nps.org.au/australian-prescriber/articles/ocrelizumab-for-multiple-sclerosis

Dosage and administration[5]

Ocrelizumab is administered as an IV infusion through a dedicated line under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion related reactions.

Ocrelizumab is administered by IV infusion as a 600 mg dose every 6 months. The initial 600 mg dose is administered as two separate IV infusions; one 300 mg infusion, followed by a second 300 mg infusion two weeks later. Subsequent doses thereafter are administered as a single 600 mg IV infusion every 6 months. (A minimum interval of 5 months should be maintained between each dose).

PBS listing details (Current as at 1 July 2020)

Item	Name, form & strength, pack size	Max. qty packs.	Max. qty units.	Rpts	DPMQ	Brand name and manufacturer
11237K	ocrelizumab 300 mg/10 mL injection, 10 mL vial, S100 HSD Private	2	2	0	$17,580.74	Ocrevus® Roche Products Pty Ltd
11242Q	ocrelizumab 300 mg/10 mL injection, 10 mL vial, S100 HSD Public	2	2	0	$17,533.00	Ocrevus® Roche Products Pty Ltd

Source: the PBS website. Special Pricing Arrangements apply.

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

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

Restriction

Multiple sclerosis

Treatment Phase: Initial treatment

Authority Required (STREAMLINED)

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

---

[5] OCREVU® (Ocrelizumab). Australian Approved Product Information. Roche Products Pty Limited. Approved 13 July 2017. Most recent revision 25 June 2020. Available from https:// https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-02089-1&d=202007201016933

- The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient,

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

Authority Required (STREAMLINED)

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

- 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

Ocrelizumab was listed as a Section 100 Highly Specialised Drug (HSD) on 1 February 2018. The public hospital item (11242Q) was Authority Required for initial treatment and Authority Required (STREAMLINED) for continuing treatment. The private hospital item (11237K) was Authority Required for both initial and continuing treatment.

Changes to listing

From 1 July 2018, the public hospital item (11242Q) changed from Authority Required to Authority Required (STREAMLINED) for initial treatment. From 1 October 2019, the private hospital item (11237K) changed from Authority Required to Authority Required (STREAMLINED) for both initial and continuing treatment.

Current PBS listing details are available from the PBS website.

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

July 2017

The PBAC recommended the listing of ocrelizumab for the treatment of relapsing-remitting multiple sclerosis 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).

The PBAC noted that ocrelizumab is a first-in-class medicine among currently PBS-subsidised treatments for multiple sclerosis. The PBAC noted the input from consumer comments and the consumer hearing that additional treatment options for multiple sclerosis are valued by patients and clinicians.

The PBAC accepted cost-minimisation on the basis that the annual treatment costs of ocrelizumab and fingolimod should be the same, at equi-effective doses of ocrelizumab 600 mg once every 24 weeks and fingolimod 500 micrograms daily and taking into account the cost of infusions for ocrelizumab.

The PBAC agreed that the nominated comparators of fingolimod, natalizumab and alemtuzumab were appropriate clinical comparators; however, considered that in practice, ocrelizumab would substitute for all PBS subsidised medicines for RRMS.

This submission was not considered by DUSC. The PBAC considered that the estimated PBS usage and financial implications presented in the submission and revised in the pre-sub-committee response (PSCR) and pre-PBAC response were highly uncertain due to:

- The submission assumed no overall growth in the multiple sclerosis market, which may not be reasonable as improvements in MRI technology allow earlier diagnosis of multiple sclerosis;
- The rapidly changing market for multiple sclerosis and uncertainty regarding the extent to which ocrelizumab may substitute for currently PBS listed medicines for RRMS;
- The potential that there may be leakage of use for primary progressive and secondary progressive multiple sclerosis.

The PBAC noted that the financial estimates would need to be revised to take into account the basis on which ocrelizumab was recommended for listing. The PBAC advised that a Risk Share Arrangement with annual expenditure caps was appropriate to mitigate the uncertainty in the utilisation and financial estimates.

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.

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.

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 multiple sclerosis refer to the Public Release Document from the October 2015 and February 2020 DUSC meetings.

Approach taken to estimate utilisation

The submission used a market share approach to estimate the utilisation and financial implications associated with the PBS listing of ocrelizumab. The assumptions were:

- Ocrelizumab will substitute a portion of currently listed RRMS therapies (predominantly the high efficacy treatments); alemtuzumab, natalizumab and fingolimod, which have comparable PBS restriction criteria. These substitution rates where estimated by the Sponsor's Advisory board and were claimed to be validated by uptake rates of previously listed disease modifying therapies (DMTs) such as dimethyl fumarate, fingolimod and natalizumab. The estimated substitution rates for alemtuzumab, natalizumab and fingolimod were 50%, 25% and 30% respectively in Year 1 and 50%, 25% and 35% respectively in Year 2.
- Ocrelizumab was not expected to increase the size of the current market and/or its growth rate, the estimated budget impact was derived only from costs and savings realised via the substitution of currently listed therapies by ocrelizumab.
- The numbers of patients treated were estimated from prescription volumes assuming that each patient had 13 prescriptions per year, expect for alemtuzumab where one prescriptions per year was assumed.
- Ocrelizumab was expected to substitute a small proportion (5% in each of Years 1 to 6) of 'other DMTs' (glatiramer acetate, dimethyl fumarate, teriflunomide, pegylated interferon beta 1a) which are priced lower than ocrelizumab resulting in a net increase in cost to government.; however, this increase is consistent with current RRMS market dynamics and is negligible relative to current government expenditure on RRMS therapies

There were a number of calculation errors in the submission that were corrected during the evaluation (e.g., the submission incorrectly estimated the number of patients treated annually on the average monthly patient number rather than the annual patient number for alemtuzumab). The PSCR presented revised financial estimates that accounted for these calculation errors and applied further updated PBS items data (to March 2017). The final estimates agreed between the Department and the Sponsor were used as the predicted values in the Predicted vs Actual section of this report.

Methods

The report examines the use of ocrelizumab for the treatment of MS in the context of the whole MS treatment market.

Prescriptions were extracted from the Services Australia prescription database for all PBS items that have an RRMS restriction (30 items, see Appendix A) from 1 January 2003 (the date from which allocation of PBS prescriptions to individual patients is considered reliable) until the end of June 2020 (based on date of supply). All these items are indication specific, so there was no need to use the Services Australia Authority approval database to clarify the indication of prescriptions.

Patient counts

Prevalent patient counts are normal calculated quarterly, however for this group of medicines annual counts were considered more appropriate. For a medicine that is normally re-supplied monthly, a quarterly count of prevalence of supply is a reasonable approximation to the number of patients on treatment. However, in the RRMS group of medicines there are two medicines whose re-supply frequency is more than monthly. The median time to re-supply for ocrelizumab and alemtuzumab is 6 and 12 months respectively (see Appendix B for the median time to re-supply of each of the RRMS medicines). A quarterly count of supply prevalence for these medicines will underestimate the number of patients on treatment. Thus in the analyses that follow, supply prevalence is calculated for 12 month periods. As the data are complete to the end of June 2020, the 12 month period chosen was financial years. Twelve months will provide a good approximation of the number of patients on treatment in each period, though the number of patients on alemtuzumab will still be slightly under-estimated because it is possible that a patient on treatment will not get a supply in a particular 12 month period (e.g. they may get a supply in June 2018 and July 2019 and so not be counted in 2018/19 even though they are still on treatment).

As these analyses use date of supply prescription data, there may be small differences compared with publicly available Services Australia PBS date of processing data[6] which only includes subsidised PBS and Repatriation PBS (R/PBS) prescriptions (i.e. prescriptions under the patient co-payment are not included). The Services Australia prescription database data used in this report includes under co-payment prescriptions from 1 April 2012.

Data manipulation was undertaken using SAS.

---

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

Results

Analysis of drug utilisation

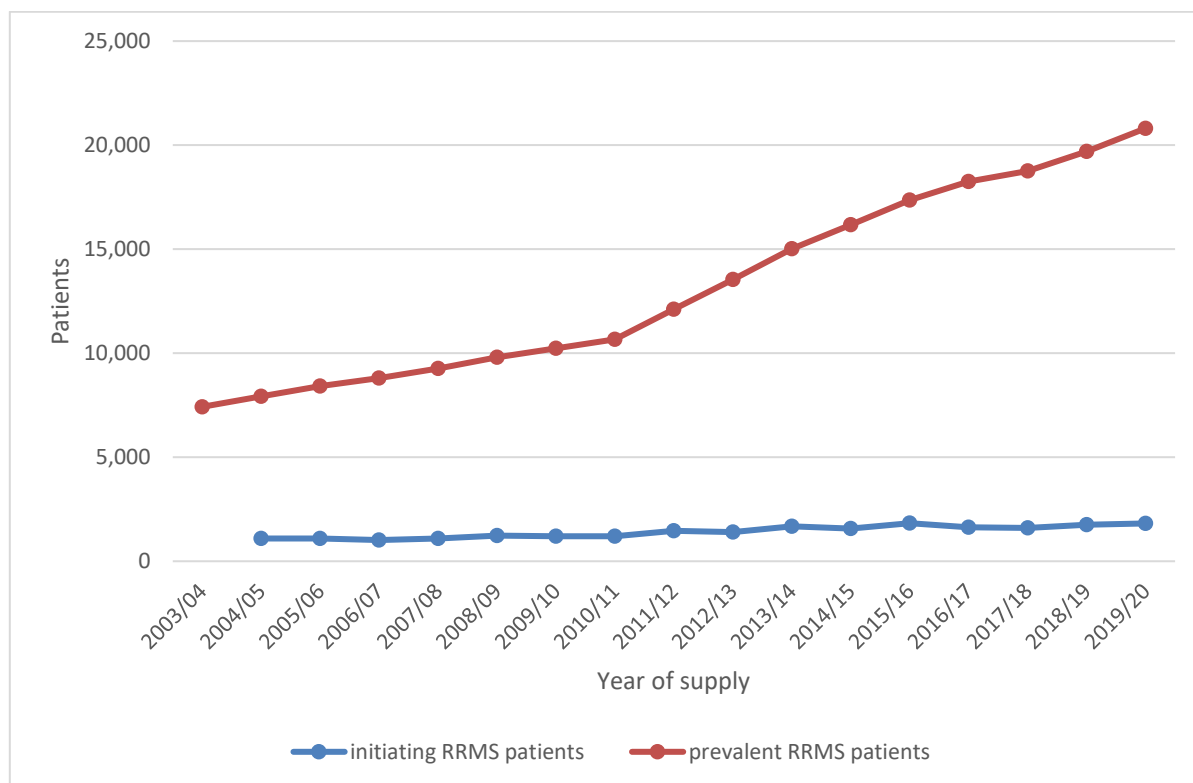### *Patient count and prescription utilisation*

Figure 1: Patients incident and prevalent to PBS RRMS therapy

The number of prevalent patients increased steadily from 2003/04 to 2010/11, after this the rate increased. This is most likely due to the listing and high uptake of fingolimod in 2011/12 (see Figure 2). The number of patients initiating RRMS therapy has increased very gradually over the period shown.
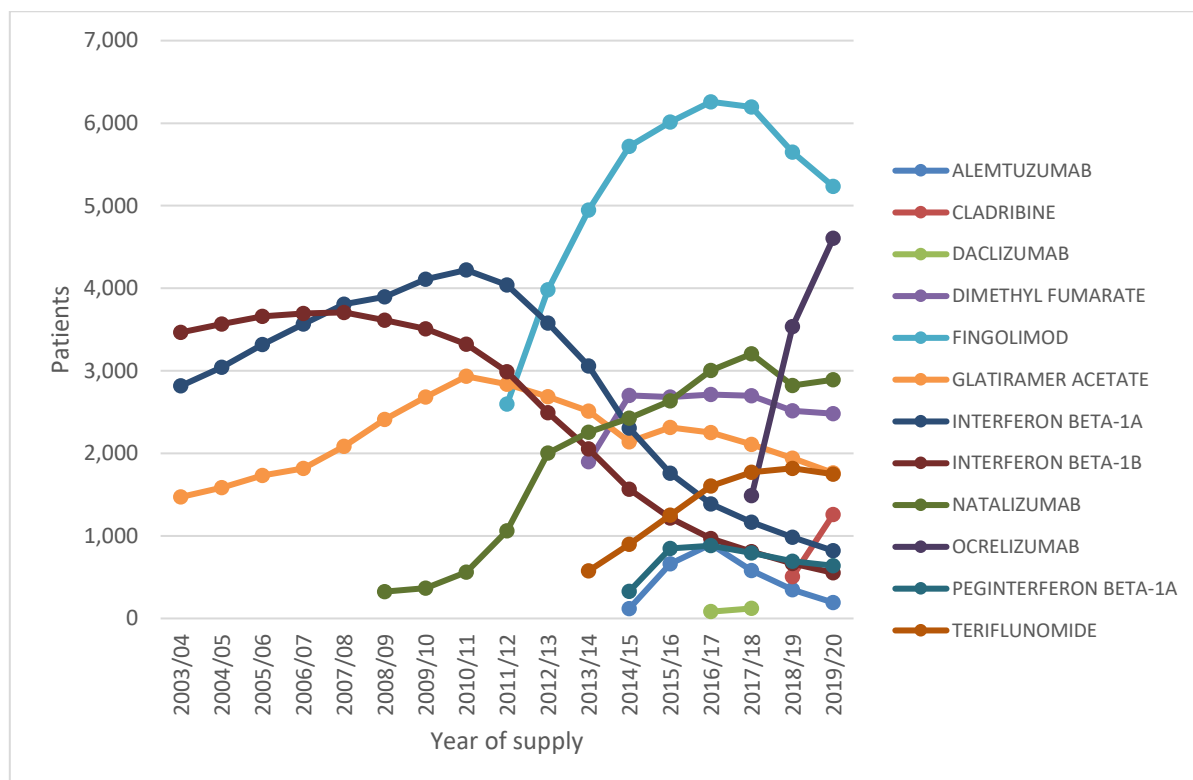
Figure 2: Patients prevalent to PBS RRMS medicines

Note: Daclizumab was delisted from the PBS on 31 May 2018. This followed the withdrawal of the product from the Australian market by the sponsor, Biogen, following cases of serious inflammatory brain disorders in Europe[7]. Also note that natalizumab (listed 1 July 2008) data are incomplete prior to July 2013 because it is a Highly Specialised Drug (HSD). Prescriptions for HSDs are incomplete in the Services Australia prescription database prior to July 2013 as some prescriptions were processed via an alternative system.

It can be seen that ocrelizumab was the second most commonly used medicine in 2019/20 and the number of patients on other medicines, except the recently listed cladribine (listed 1 January 2019), appear to be decreasing.

---

[7] https://www.tga.gov.au/alert/zinbryta-daclizumab#:~:text=Consumers%20and%20health%20professionals%20are,inflammatory%20brain%20disorders%20in%20Europe.
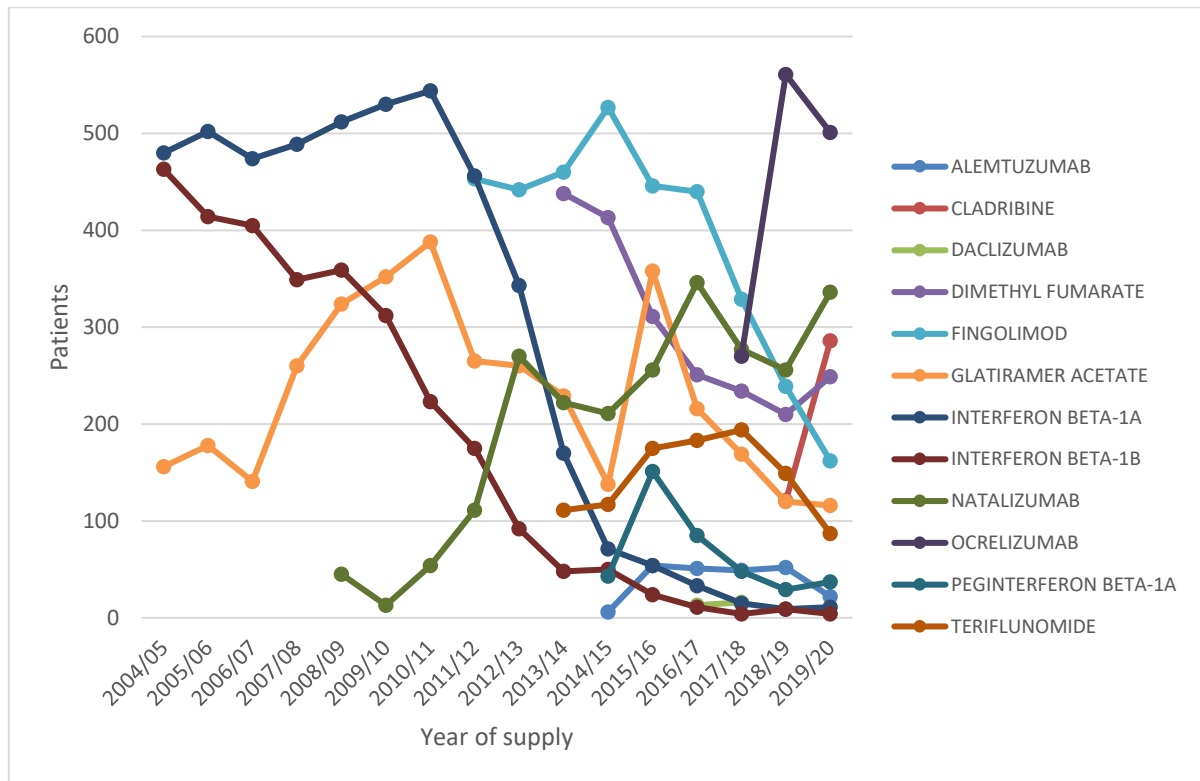
Figure 3: Patients initiating to PBS RRMS medicines

Figure 3 shows that ocrelizumab was the most commonly initiated medicine in both 2018/19 and 2019/20. The listing of cladribine in 2018/19 may have impacted the number of patients initiating on ocrelizumab in 2019/20.
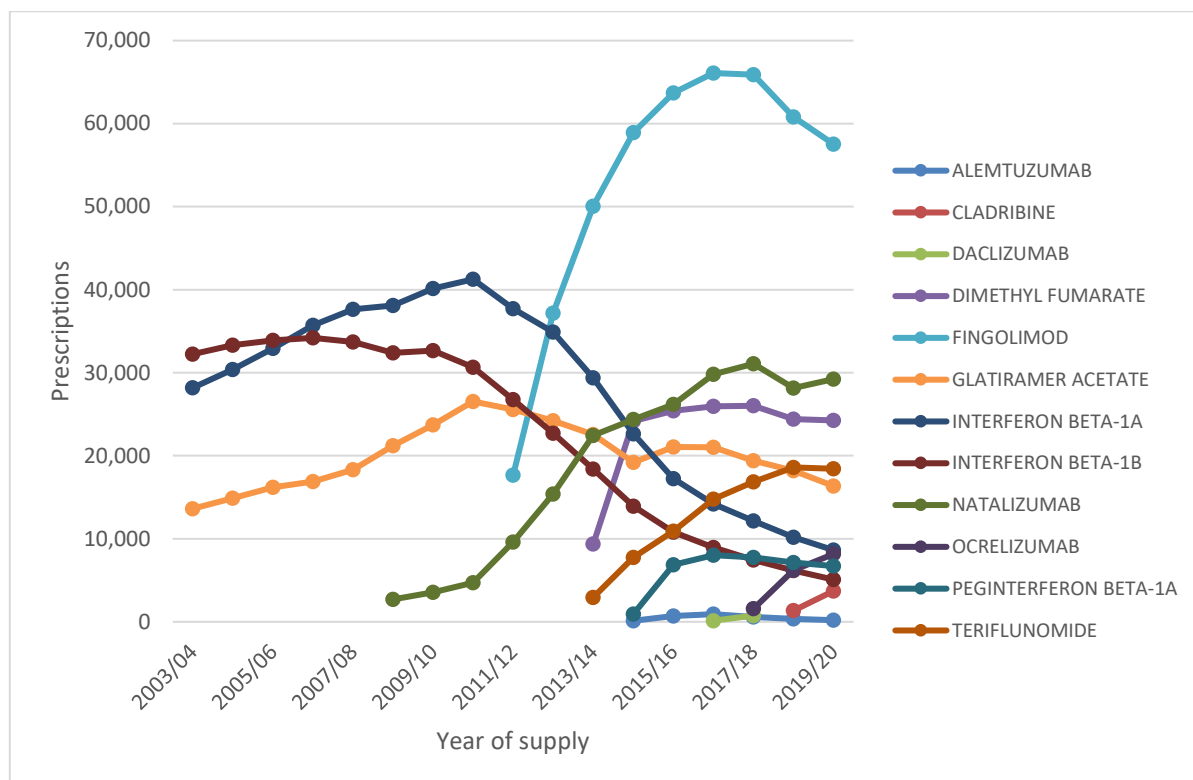
Figure 4: Prescriptions of PBS RRMS medicines

Figure 4 shows the number of ocrelizumab and alemtuzumab prescriptions are relatively low due to their low frequency of supply.

Analysis of predicted versus actual utilisation

Table 2: Predicted vs Actual analysis of ocrelizumab for RRMS

		Year 1	Year 2
		Feb 18 to Jan 19	Feb 19 to Jan 20
Treated patients	Predicted (P)	3,637	4,080
	Actual (A)	2,911	4,248
	% Difference (A-P)/P	-20%	+4%
Prescriptions	Predicted (P)	7,880	8,840
	Actual (A)	4,867	7,604
	% Difference (A-P)/P	-38%	-14%
Prescriptions per patient	Predicted (P)	2.17	2.17
	Actual (A)	1.67	1.79
	% Difference (A-P)/P	-23%	-17%

Source: predicted figures were sourced from the utilisation estimates model agreed with the sponsor, P17-12573 PBS Ocrelizumab vG 20171221.xlsx, sheet 2

In Table 2 the number of actual treated patients was 20% less than predicted in Year 1 and slightly more than predicted in Year 2. The number of actual prescriptions per patient was less than predicted. The predicted value of 2.17 was calculated in an attempt to allow for the fact based on the initial prescription is administered in two 300mg infusions two weeks apart and then the continuing infusion is 6 months after the second infusion. This means that the number of prescriptions in a year is on average $52 / (26 + 2) = 1.86$. Unfortunately this was miscalculated as $52 / (26 - 2) = 2.17$ in the estimates. The correct predicted value of 1.86 is closer to actual values in Table 2.

In addition, there was no "half-cycle correction" to allow for the fact that not all patients initiate treatment on the day of PBS listing. That is, the patients who initiated in the first 24 weeks of Year 1 should have had 2 prescriptions in Year 1 and the patients who initiated from weeks 25 to 52 of Year 1 should have had only 1 prescription in Year 1. Thus, the average will be 1.46 if the initiations are spread evenly throughout Year 1.

Other Analyses

Analysis of utilisation by medication form and remote area classification

In the October 2015 DUSC analysis of MS, DUSC suggested undertaking an analysis on whether the availability of oral RRMS therapy had improved access to treatment for patients in regional and remote areas.

The medications can be classified into three different forms:

- Infusion - alemtuzumab, natalizumab, ocrelizumab
- Oral - cladribine, dimethyl fumarate, fingolimod, teriflunomide
- Injection – daclizumab, glatiramer actetate, interferon beta-1a & 1b, peginterferon beta-1a

The number of patients by medicine form and year is shown in Figure 5.

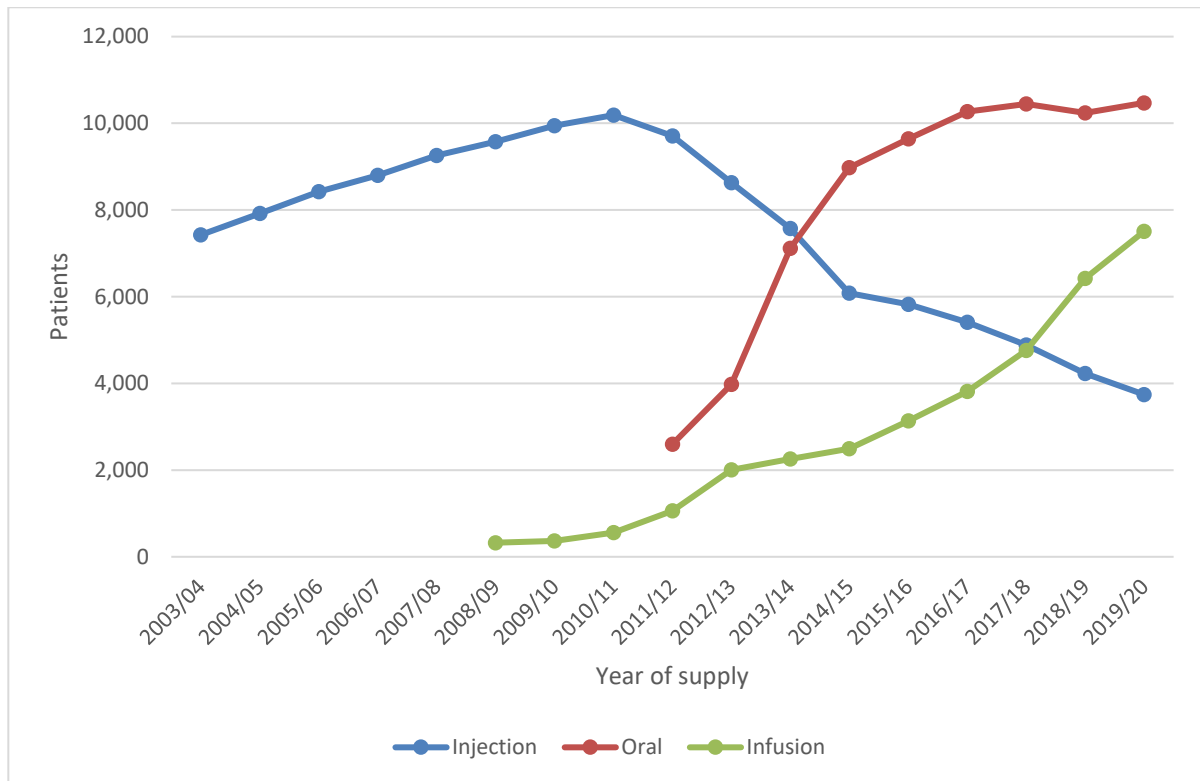**Figure 5: Patients prevalent to PBS RRMS medicines by medicine form**
Note: a patient can be counted in more than one form in a year

Figure 5 shows that most patients were treated by injection until 2014/15, after which oral treatment was the most common form. With the listing of ocrelizumab on 1 February 2018, infusion treatment became more common and was the second most common form in 2019/20.
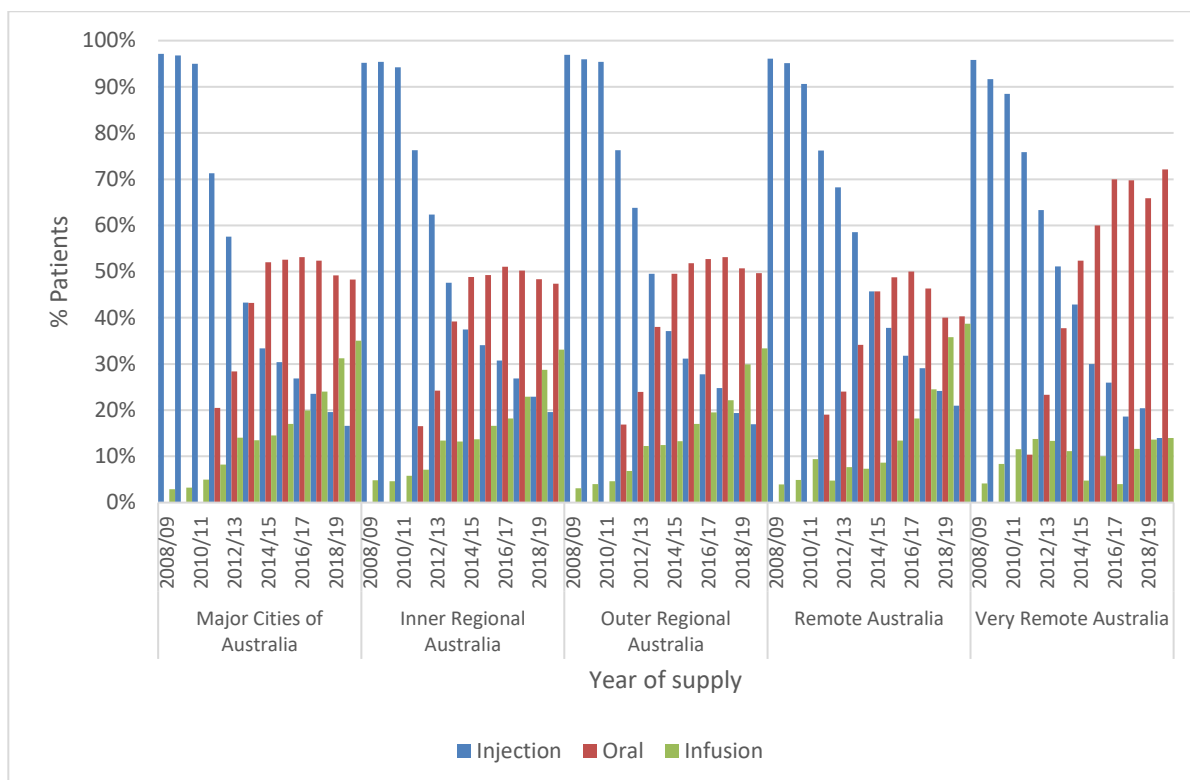
Figure 6: Patients prevalent to PBS RRMS medicines by medicine form and remote area classification.

Note: a patient can be counted in more than one form in a year. The remote area (RA) classification of a patient is the one associated with the first prescription in that year. The RA is based on the patient postcode at the time of prescription processing by Services Australia and uses the ABS Remoteness Structure 2018 (cat no. 1270.0.55.005)

Figure 6 shows the percentage of patients on each form is similar across time for the less remote areas. In Very Remote Australia oral treatment was by far the most common form of treatment (72%) in the most recent year (2019/20). In Remote Australia, oral and infusion treatment are equally common (approximately 39% each) in 2019/20. The distribution of forms is similar across the other less remote regions, with oral being the most common (approximately 49% of patients), infusion next most common (approximately 34%) and injection least common (approximately 17%) in 2019/20.

Sequence of drug initiation

Table 3 shows the drug sequence for patients who initiated MS therapy from January 2004 to the end of May 2020. Initiation to therapy was defined no prior MS medicine prescription back to 1 January 2003.

When a new medicine is initiated (indicated by ->), the analysis seeks to determine if the patient had been continuing (indicated by ->(cont)) on the previous treatment or had a break (indicated by ->(brk)) in the previous treatment at the time of the initiation of the new drug. A break was defined as more than 2 × median time to resupply (of the previous drug) to the supply of the new drug.

Table 3: Drug sequences for MS patients initiating therapy from 1 January 2004

Drug sequence	Patients	% Patients	Rank
fingolimod	2,196	9.42%	1
glatiramer acetate	1,549	6.64%	2
natalizumab	1,344	5.76%	3
ocrelizumab	1,303	5.59%	4
dimethyl fumarate	1,256	5.39%	5
interferon beta-1a	1,218	5.22%	6
interferon beta-1b	761	3.26%	7
teriflunomide	644	2.76%	8
cladribine	401	1.72%	9
interferon beta-1a(cont)->fingolimod	369	1.58%	10
interferon beta-1a(brk)->fingolimod	300	1.29%	11
glatiramer acetate(cont)->fingolimod	274	1.18%	12
natalizumab(cont)->ocrelizumab	235	1.01%	13
alemtuzumab	212	0.91%	14
interferon beta-1b(cont)->fingolimod	200	0.86%	15
peginterferon beta-1a	197	0.84%	16
natalizumab(brk)->ocrelizumab	197	0.84%	17
fingolimod(brk)->ocrelizumab	197	0.84%	18
interferon beta-1b(brk)->fingolimod	167	0.72%	19
glatiramer acetate(brk)->fingolimod	163	0.70%	20
interferon beta-1a(brk)->natalizumab	138	0.59%	21
interferon beta-1a(cont)->dimethyl fumarate	129	0.55%	22
interferon beta-1a(brk)->dimethyl fumarate	129	0.55%	23
glatiramer acetate(cont)->dimethyl fumarate	128	0.55%	24

Drug sequence	Patients	% Patients	Rank
interferon beta-1a(cont)->peginterferon beta-1a	116	0.50%	25
interferon beta-1a(brk)->glatiramer acetate	115	0.49%	26
interferon beta-1a(cont)->glatiramer acetate	111	0.48%	27
fingolimod(brk)->natalizumab	107	0.46%	28
fingolimod(cont)->natalizumab	103	0.44%	29
dimethyl fumarate(brk)->ocrelizumab	103	0.44%	30
glatiramer acetate(cont)->natalizumab	102	0.44%	31
glatiramer acetate(brk)->dimethyl fumarate	96	0.41%	32
interferon beta-1b(cont)->glatiramer acetate	96	0.41%	33
dimethyl fumarate(cont)->ocrelizumab	90	0.39%	34
interferon beta-1b(brk)->natalizumab	86	0.37%	35
fingolimod(cont)->ocrelizumab	86	0.37%	36
interferon beta-1a(cont)->teriflunomide	81	0.35%	37
interferon beta-1b(cont)->dimethyl fumarate	79	0.34%	38
glatiramer acetate(cont)->teriflunomide	78	0.33%	39
interferon beta-1a(brk)->teriflunomide	77	0.33%	40
glatiramer acetate(brk)->natalizumab	74	0.32%	41
interferon beta-1b(cont)->peginterferon beta-1a	71	0.30%	42
interferon beta-1b(brk)->glatiramer acetate	70	0.30%	43
fingolimod(brk)->cladribine	70	0.30%	44
dimethyl fumarate(cont)->natalizumab	70	0.30%	45
interferon beta-1b(brk)->dimethyl fumarate	69	0.30%	46
glatiramer acetate(brk)->teriflunomide	65	0.28%	47
natalizumab(cont)->alemtuzumab	63	0.27%	48
fingolimod(brk)->alemtuzumab	59	0.25%	49
dimethyl fumarate(cont)->fingolimod	58	0.25%	50
Other sequences	7,415	31.8%	
Total	23,317	100.0%	

Note: brk = break in treatment, cont = continuous treatment. A break was define as > 2 x standard coverage days (i.e. median time to resupply)

Table 3 shows that the most common transitions were from using interferon beta-1a and glatiramer acetate to fingolimod.

Table 4: Number of drug switches for MS patients initiating therapy from 1 January 2004

Number of drug switches	Patients	% Patients
0	11,082	47.5%
1	6,881	29.5%
2	3,385	14.5%
3	1,397	6.0%
4	448	1.9%
5	98	0.4%
>= 6	26	0.1%
Grand Total	23,317	100%

Table 4 shows that 47.5% of patients stayed on the same medicine they initiated therapy on (i.e. no switches).

A second sequence analysis was undertaken including only patients that initiated therapy after the listing of the first oral medicine for MS, fingolimod, to reflect more recent practice. Fingolimod was PBS listed on 1 September 2011 and the analysis will include patients initiating from 1 January 2012 (rather than 1 September 2011) to be more certain that the prescriber was aware of the option to use an oral agent.

Table 5: Drug sequences for MS patients initiating therapy from 1 January 2012

Drug sequence	Patients	% Patients	Rank
fingolimod	2,059	14.74%	1
ocrelizumab	1,303	9.33%	2
natalizumab	1,292	9.25%	3
dimethyl fumarate	1,256	8.99%	4
glatiramer acetate	840	6.01%	5
teriflunomide	644	4.61%	6
cladribine	401	2.87%	7
interferon beta-1a	240	1.72%	8
natalizumab(cont)->ocrelizumab	231	1.65%	9
alemtuzumab	212	1.52%	10
peginterferon beta-1a	197	1.41%	11
natalizumab(brk)->ocrelizumab	187	1.34%	12
fingolimod(brk)->ocrelizumab	185	1.32%	13
dimethyl fumarate(brk)->ocrelizumab	103	0.74%	14
glatiramer acetate(cont)->fingolimod	103	0.74%	15
fingolimod(brk)->natalizumab	101	0.72%	16
fingolimod(cont)->natalizumab	99	0.71%	17
dimethyl fumarate(cont)->ocrelizumab	90	0.64%	18
fingolimod(cont)->ocrelizumab	82	0.59%	19
glatiramer acetate(cont)->natalizumab	81	0.58%	20
interferon beta-1a(cont)->fingolimod	80	0.57%	21
glatiramer acetate(cont)->dimethyl fumarate	78	0.56%	22
dimethyl fumarate(cont)->natalizumab	70	0.50%	23
interferon beta-1b	67	0.48%	24
fingolimod(brk)->cladribine	63	0.45%	25
natalizumab(cont)->alemtuzumab	59	0.42%	26
dimethyl fumarate(cont)->fingolimod	58	0.42%	27
interferon beta-1a(cont)->dimethyl fumarate	54	0.39%	28
natalizumab(brk)->alemtuzumab	51	0.37%	29
glatiramer acetate(brk)->dimethyl fumarate	51	0.37%	30
teriflunomide(brk)->ocrelizumab	50	0.36%	31
fingolimod(brk)->alemtuzumab	50	0.36%	32
dimethyl fumarate(brk)->natalizumab	48	0.34%	33

Drug sequence	Patients	% Patients	Rank
glatiramer acetate(brk)->fingolimod	47	0.34%	34
fingolimod(cont)->alemtuzumab	45	0.32%	35
dimethyl fumarate(brk)->fingolimod	45	0.32%	36
natalizumab(cont)->fingolimod	44	0.32%	37
glatiramer acetate(cont)->teriflunomide	43	0.31%	38
fingolimod(brk)->dimethyl fumarate	42	0.30%	39
interferon beta-1a(cont)->peginterferon beta-1a	41	0.29%	40
dimethyl fumarate(brk)->cladribine	40	0.29%	41
teriflunomide(cont)->ocrelizumab	35	0.25%	42
natalizumab(brk)->fingolimod	35	0.25%	43
glatiramer acetate(cont)->ocrelizumab	31	0.22%	44
interferon beta-1a(brk)->dimethyl fumarate	31	0.22%	45
dimethyl fumarate(brk)->teriflunomide	30	0.21%	46
dimethyl fumarate(brk)->glatiramer acetate	30	0.21%	47
fingolimod(brk)->glatiramer acetate	30	0.21%	48
interferon beta-1b(cont)->fingolimod	29	0.21%	49
interferon beta-1a(brk)->fingolimod	29	0.21%	50
other sequences	2,856	20.4%	
total	13,968	100.0%	

Note: brk = break in treatment, cont = continuous treatment. A break was define as > 2 x standard coverage days (i.e. median time to resupply)

Table 5 shows that the most common switches for this cohort are from natalizumab, fingolimod and dimethyl fumarate to ocrelizumab.

Table 6: Number of drug switches for MS patients initiating therapy from 1 January 2012

Number of drug switches	Patients	% Patients
0	8,512	60.9%
1	3,713	26.6%
2	1,297	9.3%
3	361	2.6%
4	69	0.5%
>=5	16	0.1%
Total	13,968	100%

Table 6 shows that 61% of patients stayed on the same medicine they initiated therapy on (i.e. no switches).

Table 7 shows only drug sequences that include ocrelizumab

Table 7: Drug sequences for MS patients initiating therapy from 1 January 2012 that include ocrelizumab

Drug sequence	Patients	% Patients	Rank
ocrelizumab	1,303	41.5%	1
natalizumab(cont)->ocrelizumab	231	7.4%	2
natalizumab(brk)->ocrelizumab	187	6.0%	3
fingolimod(brk)->ocrelizumab	185	5.9%	4
dimethyl fumarate(brk)->ocrelizumab	103	3.3%	5
dimethyl fumarate(cont)->ocrelizumab	90	2.9%	6
fingolimod(cont)->ocrelizumab	82	2.6%	7
teriflunomide(brk)->ocrelizumab	50	1.6%	8
teriflunomide(cont)->ocrelizumab	35	1.1%	9
glatiramer acetate(cont)->ocrelizumab	31	1.0%	10
fingolimod(cont)->natalizumab(brk)->ocrelizumab	28	0.9%	11
glatiramer acetate(brk)->ocrelizumab	22	0.7%	12
natalizumab(brk)->fingolimod(brk)->ocrelizumab	18	0.6%	13
fingolimod(brk)->natalizumab(cont)->ocrelizumab	16	0.5%	14
fingolimod(cont)->natalizumab(cont)->ocrelizumab	16	0.5%	15
dimethyl fumarate(brk)->natalizumab(cont)->ocrelizumab	16	0.5%	16
fingolimod(brk)->natalizumab(brk)->ocrelizumab	15	0.5%	17
natalizumab(cont)->fingolimod(brk)->ocrelizumab	14	0.4%	18
dimethyl fumarate(cont)->natalizumab(cont)->ocrelizumab	13	0.4%	19
alemtuzumab(cont)->ocrelizumab	13	0.4%	20
peginterferon beta-1a(brk)->ocrelizumab	10	0.3%	21
fingolimod(cont)->dimethyl fumarate(cont)->ocrelizumab	9	0.3%	22
ocrelizumab(cont)->cladribine	8	0.3%	23
interferon beta-1a(brk)->ocrelizumab	8	0.3%	24
interferon beta-1a(cont)->dimethyl fumarate(brk)->ocrelizumab	8	0.3%	25
dimethyl fumarate(cont)->fingolimod(brk)->ocrelizumab	8	0.3%	26
interferon beta-1b(cont)->fingolimod(brk)->ocrelizumab	8	0.3%	27
fingolimod(cont)->dimethyl fumarate(brk)->ocrelizumab	8	0.3%	28
glatiramer acetate(cont)->natalizumab(cont)->ocrelizumab	8	0.3%	29

Drug sequence	Patients	% Patients	Rank
interferon beta-1a(cont)->fingolimod(brk)->ocrelizumab	8	0.3%	30
ocrelizumab(cont)->natalizumab	7	0.2%	31
dimethyl fumarate(cont)->fingolimod(cont)->ocrelizumab	7	0.2%	32
peginterferon beta-1a(cont)->ocrelizumab	7	0.2%	33
glatiramer acetate(cont)->fingolimod(brk)->ocrelizumab	7	0.2%	34
natalizumab(cont)->dimethyl fumarate(cont)->ocrelizumab	7	0.2%	35
dimethyl fumarate(brk)->natalizumab(brk)->ocrelizumab	7	0.2%	36
glatiramer acetate(cont)->dimethyl fumarate(cont)->ocrelizumab	6	0.2%	37
fingolimod(brk)->dimethyl fumarate(cont)->ocrelizumab	6	0.2%	38
teriflunomide(cont)->dimethyl fumarate(brk)->ocrelizumab	6	0.2%	39
fingolimod(brk)->glatiramer acetate(cont)->ocrelizumab	6	0.2%	40
glatiramer acetate(brk)->dimethyl fumarate(brk)->ocrelizumab	6	0.2%	41
natalizumab(cont)->fingolimod(cont)->ocrelizumab	6	0.2%	42
peginterferon beta-1a(cont)->fingolimod(brk)->ocrelizumab	<=5	0.2%	43
glatiramer acetate(cont)->natalizumab(brk)->ocrelizumab	<=5	0.2%	44
glatiramer acetate(cont)->dimethyl fumarate(brk)->ocrelizumab	<=5	0.2%	45
dimethyl fumarate(cont)->teriflunomide(brk)->ocrelizumab	<=5	0.2%	46
natalizumab(brk)->fingolimod(cont)->ocrelizumab	<=5	0.2%	47
fingolimod(brk)->dimethyl fumarate(brk)->ocrelizumab	<=5	0.2%	48
dimethyl fumarate(cont)->natalizumab(brk)->ocrelizumab	<=5	0.2%	49
fingolimod(cont)->glatiramer acetate(cont)->ocrelizumab	<=5	0.2%	50
other sequences	471	15.0%	
Total	3,140	100%	

Note: brk = break in treatment, cont = continuous treatment. A break was define as > 2 x standard coverage days (i.e. median time to resupply)

Table 7 shows that 41.5% of patients who have been treated with ocrelizumab initiated MS therapy on it and have not switched to any other medicine. There are only a few patients that have switched away from ocrelizumab (in the top 50 sequences). Eight patients have switched to cladribine and seven to natalizumab.

DUSC consideration

- DUSC agreed with the report findings that ocrelizumab and cladribine are rapidly substituting older medicines and that the listing of ocrelizumab has not substantially increased the rate of growth of the RRMS market.
- DUSC noted that COVID-19 may impact utilisation by medication form. DUSC considered that oral medications might be preferred during this time.
- DUSC noted the consumer input from MS Australia, which was that people with MS;
  - generally only see their specialist neurologist once a year and they are cautious about changing medicines;
  - are unlikely to change medicines unless something is going wrong e.g. no longer effective;
  - want the full spectrum of medicines available so that people have choice of what works for them.
  - adopt a healthy lifestyle;
  - also use allied health services to manage their MS;
  - living in remote locations may prefer infusion every six months to taking a daily tablet. They access infusions in a regional centre and stay for a few days to access other services, e.g. allied health services.
  - drift to live in the major cites of Sydney and Melbourne to access specialist and allied health services.

  MS Australia also noted that:

  - New medicines appeal to patients and are less intrusive to lifestyle.
  - Frequent injections are unpopular - oral treatments are more appealing particularly for those living in very remote locations.
  - The trend of rapid uptake of infusions for those in remote locations depends on access to regional services- a six-monthly infusion is more convenient than a regular injection or daily oral treatments.
  - The actual numbers of people with MS living in remote and very remote locations is very low compared to those with MS living in the large urban areas.
  - The less than expected number of patients for ocrelizumab could be due to a lag in neurologists' knowledge of newly PBS listed medicines and this could also explain why the second year of listing was close to the prediction.

DUSC also noted that:

- A QUM issue raised was that there was no restriction on first line treatment. This gives rise to personalised treatment pathways, due to specialist choice but also potentially patient preference.
- The drug sequence analysis in Table 7 showed that patients may initiate ocrelizumab after having a break from treatment or without a break (i.e. switching). DUSC suggested that a future analysis having regard to the length of breaks between drugs, in each line of treatment, would be of interest.

- The drug switching patterns were dependant on the starting point for the initiating patient cohort.

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

Roche Products Pty Ltd: The 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.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

Appendix A: PBS items indicated for the treatment of MS

Medicine	PBS Item Code	Form and Strength
ALEMTUZUMAB	10228H	Solution concentrate for I.V. infusion 12 mg in 1.2 mL
	10232M	Solution concentrate for I.V. infusion 12 mg in 1.2 mL
	10243D	Solution concentrate for I.V. infusion 12 mg in 1.2 mL
	10246G	Solution concentrate for I.V. infusion 12 mg in 1.2 mL
CLADRIBINE	11603Q	Tablet 10 mg
	11604R	Tablet 10 mg
	11611D	Tablet 10 mg
DACLIZUMAB	11101G	Injection 150 mg in 1 mL pre-filled pen
DIMETHYL FUMARATE	02896K	Capsule (modified release) 120 mg
	02943X	Capsule (modified release) 120 mg
	02966D	Capsule (modified release) 240 mg
FINGOLIMOD	05262Y	Capsule 500 micrograms (as hydrochloride)
	11818B	Capsule 250 micrograms (as hydrochloride)
GLATIRAMER ACETATE	08352N	Powder for subcutaneous injection 20 mg in single use vial and 1 ampoule diluent 1.1 mL
	08726G	Injection containing glatiramer acetate 20 mg in 1 mL single dose pre-filled syringe
	10416F	Injection containing glatiramer acetate 40 mg in 1 mL single dose pre-filled syringe
INTERFERON BETA-1A	08289G	Injection set comprising 1 vial powder for injection 30 micrograms (6,000,000 I.U.) with diluent
	08403G	Injection 44 micrograms (12,000,000 I.U.) in 0.5 mL single dose pre-filled syringe
	08805K	Injection 30 micrograms (6,000,000 I.U.) in 0.5 mL single dose pre-filled syringe
	08968B	Injection 44 micrograms (12,000,000 I.U.) in 0.5 mL single dose autoinjector
	09332E	Solution for injection 132 micrograms in 1.5 mL multidose cartridge
INTERFERON BETA-1B	08101J	Injection set including 1 vial powder for injection 8,000,000 I.U. (250 micrograms) and solvent
NATALIZUMAB	09505G	Solution concentrate for I.V. infusion 300 mg in 15 mL
	09624M	Solution concentrate for I.V. infusion 300 mg in 15 mL
OCRELIZUMAB	11237K	Solution concentrate for I.V. infusion 300 mg in 10 mL
	11242Q	Solution concentrate for I.V. infusion 300 mg in 10 mL
PEGINTERFERON BETA-1A	10212L	Single use injection pen containing 125 micrograms in 0.5 mL
	10218T	Pack containing single use injection pens containing 63 micrograms in 0.5 mL and 94 micrograms in 0.5 mL
	10220X	Single use injection pen containing 125 micrograms in 0.5 mL
TERIFLUNOMIDE	02898M	Tablet 14 mg

Appendix B: Days to re-supply of each of the RRMS medicines

Medicine	Mean	Mode	Median
FINGOLIMOD	32	28	29
NATALIZUMAB	31	28	28
GLATIRAMER ACETATE	36	28	29
INTERFERON BETA-1A	33	28	29
DIMETHYL FUMARATE	33	28	29
INTERFERON BETA-1B	37	28	32
TERIFLUNOMIDE	32	28	28
PEGINTERFERON BETA-1A	32	28	28
OCRELIZUMAB	181	182	183
CLADRIBINE	68	28	28
ALEMTUZUMAB	373	364	366
DACLIZUMAB	31	28	30