Multiple sclerosis: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2015

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 the oral therapies, dimethyl fumarate, teriflunomide and fingolimod.

Date of PBS listing of oral therapies

- Fingolimod – 1 September 2011.
- Dimethyl fumarate – 1 December 2013.
- Teriflunomide – 1 December 2013.

Data Source / methodology

Prescription data from the Department of Human Services (DHS). Data was extracted from January 2002 to the most currently available data (March 2015). Prescription data was based on the date of supply.

The medicines included in the analysis were interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate and teriflunomide.

Key Findings

- 13,648 patients were treated with a PBS medicine for RRMS in 2014. Both the number of people starting treatment for the first time and the total number of people receiving treatment with PBS RRMS medicines has increased.
- There has been a significant rise in the number of prevalent patients since the introduction of oral RRMS therapy. The entry of dimethyl fumarate and teriflunomide appears to have grown the market, as the rate of growth of existing RRMS therapy has declined while the overall RRMS market has increased its rate of growth above that observed prior to the listing of these new oral therapies.
- Fingolimod is the most widely used drug when taking account of all patients on treatment. Dimethyl fumarate is the most frequently prescribed drug for patients new

to RRMS therapy and in patients switching from prior RRMS therapy or returning to therapy after a treatment break.

- Patients appear to persist longer on oral compared to injectable therapy based on a length of treatment analysis of fingolimod. However, a median time on treatment had not been reached for fingolimod and a longer period of data is required to confirm this.
- In their first year of listing the utilisation of dimethyl fumarate has been higher than predicted while the usage of teriflunomide was substantially lower than expected.
- Instances of potential co-administered RRMS therapies were found to be negligible (<1%).
- Expenditure on RRMS medicines has continued to grow. This was mainly driven by an increasing utilisation of the oral therapies fingolimod and dimethyl fumarate with a decline in the use of injectable therapy.

Purpose of analysis

To examine the utilisation of PBS listed medicines for relapsing-remitting multiple sclerosis (RRMS), including an assessment of the predicted versus actual use of the oral therapies, dimethyl fumarate, teriflunomide and fingolimod.

Clinical situation

Multiple sclerosis is a progressive, chronic disease of the central nervous system. The disease damages the myelin sheath which protects nerve axons causing changes to nerve pathways and signals. Relapsing-remitting multiple sclerosis is the most common form of disease, characterised by acute clinical attacks (relapses) followed by variable recovery and periods of clinical stability. Symptoms of multiple sclerosis include impaired mobility and coordination, cognitive impairment, pain, fatigue and visual disturbance.

Background

The PBAC requested a 12 month review of the utilisation of dimethyl fumarate and teriflunomide, which were recommended for listing in July 2013. This review examines the predicted versus actual utilisation of dimethyl fumarate and teriflunomide for their first year of listing (1 December 2013 to 30 November 2014).

The DUSC, when considering the 12 month predicted versus actual analysis of fingolimod (June 2013), recommended another utilisation analysis of fingolimod when a further 12 months of data was available. Noting that dimethyl fumarate and teriflunomide were expected to substitute for other RRMS therapies including fingolimod, this subsequent review was deferred until 12 months of data for dimethyl fumarate and teriflunomide were available to assess the impact of the three oral medicines on the overall RRMS market.

As at August 2015, there were nine drugs which were PBS listed for RRMS (Table 1).

Table 1. PBS-listed RRMS drugs as at 1 August 2015

Drug	Route	Dosage	Frequency	PBS listing date
Immunomodulators (ABCR therapy)				
interferon beta-1b (Betaferon®)	SC	8 million IU	on alternate days	November 1996
interferon beta-1a (Avonex®)	IM	6 million IU	weekly	February 1999
interferon beta-1a (Rebif®)	SC	12 million IU	3 times weekly	May 2000
glatiramer acetate (Copaxone®)	SC	20 mg	daily	May 2004
Newer therapies				
natalizumab (Tysabri®)	IV	300 mg over 1 hour	every 4 weeks	July 2008
fingolimod (Gilenya®)	oral	0.5 mg	daily	September 2011
Dimethyl fumarate (Tecfidera®)	oral	120 mg starting dose for first 7 days. 240 mg maintenance dose.	twice a day	December 2013
teriflunomide (Aubagio®)	oral	14 mg	daily	December 2013
peginterferon beta-1a (Plegridy®)	SC	125 µg	Every 2 weeks	March 2015
alemtuzumab (Lemtrada®)	IV	12 mg per day	Two treatment courses. Over 5 days for initial treatment and over 3 days 12 months after initial treatment.	April 2015

Source: Administration, dosage and frequency information was sourced from the respective drug's Product Information from the Therapeutic Goods Administration website at https://www.ebs.tga.gov.au/.

The immunomodulators are often termed 'ABCR therapy', which refers to the first initials of the trade names of these products (Avonex, Betaferon, Copaxone and Rebif).

The current listings are summarised in Appendix A. A chronology of PBS listings is provided in Appendix B. The approved indications for each RRMS medicine are listed in Appendix C.

At the time of this report, peginterferon beta-1a and alemtuzumab were recent listings (from 1 March 2015 and 1 April 2015, respectively) for RRMS.[1,2] As such these listings have not been included as part of analyses of the overall RRMS market.

[1] Alemtuzumab Public Summary Document November 2014. Accessed on 18 August 2015 at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/alemtuzumab-psd-11-2014

[2] Peginterferon beta -1a Public Summary Document November 2014. Accessed on 18 August 2015 at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/peginterferon-beta-1a-psd-11-2014

Previous reviews by DUSC

This is the first review of dimethyl fumarate and teriflunomide.

The utilisation of drugs to treatment RRMS was reviewed by DUSC at its June 2013 meeting. DUSC noted that the number of people supplied with a disease modifying treatment for relapsing-remitting multiple sclerosis 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 would potentially increase the number of people with multiple sclerosis treated with a disease modifying treatment.

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 disease modifying treatments are used in practice. Patient experience is likely to inform use in practice including uptake rates and duration of treatment.

A 12 month predicted vs. actual review of fingolimod was also considered by DUSC in June 2013. Utilisation of fingolimod was slightly higher than expected in the first year of PBS listing. DUSC considered that the rapid uptake of fingolimod observed in the first few months of PBS listing was likely due to patients moving from a compassionate use program to PBS supply.

The 12 month review of fingolimod, considered by DUSC in June 2013, was not able to derive the median length of time on this drug due to insufficient data. The preliminary data from this 2013 review indicated that the submission's assumption that fingolimod would have the same discontinuation rates as other ABCR therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b and glatiramer acetate) may not be reasonable. The median length of treatment was examined in this report for ABCR therapy and fingolimod. A concern was also raised in the 2013 DUSC review about the potential coadministration of fingolimod with other RRMS therapies. Coadministration among RRMS therapies was examined as part of this report.

PBS listing details

A summary of all current PBS listings for relapsing remitting multiple sclerosis is provided at Appendix A. A chronology of listings for multiple sclerosis is summarised in Appendix B. The PBS maximum quantities for all of the medicines provide sufficient therapy for 28 days, except interferon beta-1b which provides for 30 days, and the 120mg strength of teriflunomide which provides 7 days of treatment as a starting dose.

Abridged Restrictions for RRMS medicines

Natalizumab is listed as a Section 100 Highly Specialised Drug (HSD), as Authority Required for private hospital prescriptions and as Authority Required (STREAMLINED) for public

hospital prescriptions. The other RRMS drugs are Section 85 Authority Required listings with separate authority codes for initial and continuing therapy.

All current PBS listings for RRMS DMTs require:

- at least two documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding two years;
- 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.

Unlike the other RRMS listings, the S100 public and private restrictions for natalizumab:

- stipulate that it must be prescribed by a neurologist;
- state that patients must be 18 years of age or older; and
- do not include a statement that authorities will be limited to the maximum quantity and number of repeats indicated in the schedule which is included in all other RRMS listings.

The full version of the restrictions for RRMS medicines are available from the PBS website at the following addresses:
Alemtuzumab - http://www.pbs.gov.au/medicine/item/10228H-10232M-10243D-10246G
Dimethyl fumarate - http://www.pbs.gov.au/medicine/item/2896K-2943X-2966D
Fingolimod - http://www.pbs.gov.au/medicine/item/5262Y
Glatiramer acetate - http://www.pbs.gov.au/medicine/item/10416F-8726G
Interferon beta-1a - http://www.pbs.gov.au/medicine/item/8289G-8403G-8805K-8968B-9332E
Interferion beta-1b - http://www.pbs.gov.au/medicine/item/8101J
Natalizumab - http://www.pbs.gov.au/medicine/item/9505G-9624M
Peginterferon beta-1a - http://www.pbs.gov.au/medicine/item/10212L-10218T-10220X
Teriflunomide - http://www.pbs.gov.au/medicine/item/2898M

The RRMS items have been included in a post-market review of Authority Required PBS listings which is being conducted by the Department of Health. Further details about this review are available on the PBS website at the following address:
http://www.pbs.gov.au/info/reviews/authority-required-listings

Relevant aspects of PBAC consideration of oral RRMS therapy

Dimethyl fumarate

The PBAC (July 2013) recommended the listing of dimethyl fumarate on a cost-minimisation basis to ABCR therapies.[3] The PBAC considered that the submission had underestimated the utilisation of dimethyl fumarate and noted that a re-estimation of the prescriptions and costs should be based on the revised growth rates for fingolimod as recommended in the evaluation.[3] The PBAC considered that as fingolimod is more expensive than ABCR therapy, the extent of substitution of fingolimod could have substantial cost implications for the PBS. The PBAC noted the submission's estimates for the substitution of existing listings of [redacted] of ABCR therapy and [redacted] of fingolimod.[3]

Teriflunomide

The PBAC (November 2012) rejected the initial submission for teriflunomide seeking an Authority Required listing for the initial and continuing treatment of clinically definite relapsing-remitting multiple sclerosis (RRMS) in ambulatory patients. In its recommendation, the PBAC raised the following main concerns with the submission's approach to estimating the utilisation of teriflunomide: the exclusion of fingolimod and glatiramer from the uptake assumptions; and the assumption of full compliance when interferon therapy is associated with a substantial number of discontinuations.[4]

The PBAC (July 2013) recommended teriflunomide 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 β-1a and interferon β-1b.[5] The PBAC noted that there was the potential for teriflunomide to be cost saving if it substituted for fingolimod or natalizimab which were more expensive than the submission's proposed price for teriflunomide. However, the PBAC considered that the submission's claimed cost-savings from substitution of RRMS medication were not clearly substantiated.[5]

Fingolimod

The PBAC (March 2011) recommended listing fingolimod on the PBS as an Authority Required benefit for the initial and continuing treatment of clinically relapsing-remitting multiple sclerosis.[6]

The preliminary data from the 12 month review of fingolimod conducted in 2013 indicated that the submission's assumption that fingolimod would have the same discontinuation

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[3] Public Summary Document for dimethyl fumarate, July 2013. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/dimethyl-fumarate

[4] Public Summary Document for teriflunomide, November 2012. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-11/teriflunomide

[5] Public Summary Document for teriflunomide, July 2013. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/teriflunomide

[6] Public Summary Document for fingolimod, March 2011. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-03/pbac-psd-fingolimod-march11

rates as other ABCR therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b and glatiramer acetate) may not be reasonable.

Approach taken to estimate utilisation for dimethyl fumarate and teriflunomide

Dimethyl fumarate

A market share approach was used to model the financial impact of listing dimethyl fumarate. The historical number of scripts for fingolimod for the period September 2011 to August 2012 was used for the base year (18,701).

The RRMS market growth assumptions were derived from the growth in supplies for interferon-1a, interferon-1b and glatiramer acetate over the first four years of their listing, as shown in Table 2. These growth rate assumptions were applied to the base year script volume for fingolimod to project the number of fingolimod supplies over a five year forward estimates period (Table 2).

Table 2. Projected estimates for fingolimod used to derive dimethyl fumarate use

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Annual growth rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To estimate the number of patients treated with dimethyl fumarate, a flat assumption ([redacted]) was used for the uptake of dimethyl fumarate relative to fingolimod for each listing year. DUSC (June 2013) considered that the uptake of dimethyl fumarate could be higher due to the expansion of the McDonald criteria in 2010 for the diagnosis of multiple sclerosis (MS) which may increase the incidence of MS. Further, DUSC noted that concerns raised over the cardiac side effects associated with fingolimod may lead to clinicians switching patients to an alternative oral therapy.

The starting dose for dimethyl fumarate is 120 mg over 7 days with an ongoing maintenance dose of 240 mg. The projected number of supplies for the 120 mg and 240 mg strengths was then derived by multiplying the respective patient number estimate by the annual number of packs (1 for 120 mg and 13.04 for 240 mg), as shown in Table 3.

Table 3. Projected utilisation for dimethyl fumarate

Listing year	Year 1	Year 2	Year 3	Year 4	Year 5
Projected patients treated with fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative uptake from the fingolimod patient population	[redacted]				
Treated patient population					
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prescriptions					
120 mg pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 mg pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DUSC (June 2013) considered that the treated population with dimethyl fumarate was underestimated as:

- the actual number of patients (2,882) supplied with fingolimod in its first listing year was more than estimated by the submission. As such the projected use of dimethyl fumarate was underestimated as it was based on the forecast of fingolimod use; and
- oral therapies will eventually dominate the RRMS market.

The estimated substitution effects were [redacted] of interferon beta-1a and [redacted] of fingolimod. On the basis of the cost offsets from these assumptions, the listing of dimethyl fumarate was anticipated to be cost saving. DUSC (June 2013) considered that there would not just be substitution within the existing market. Noting that the 2013 MS review indicated an unmet need for therapy, DUSC considered that the addition of dimethyl fumarate would grow the market and that the cost offsets were overestimated.

Teriflunomide

A market share approach was used to project the financial estimates for teriflunomide.

The projected eligible population was derived by taking the monthly average number of prescriptions for all potential comparators at the time of the submission (interferon beta-1a, interferon beta-1b, glatimer acetate, natalizumab and fingolimod) and applying the average population growth rate sourced from the ABS (1.36%, divided by 12 to obtain a monthly growth rate). DUSC (June 2013) considered that the market would grow at a higher rate than the general population growth because, as mentioned above, of the revision to the McDonald MS diagnosis criteria and the 2013 MS review finding of a potential unmet need. The number of patients was estimated by dividing the number of prescriptions for each RRMS medicine by its average number of packs per year, adjusted for compliance and discontinuation. The compliance and discontinuation assumptions are presented in Table 4.

Table 4. Compliance and discontinuation assumptions

	Compliance rate [a]	Discontinuation rate
Teriflunomide	91.20%[b]	10.91% [c]
Interferon beta-1a	87.53%	21.78% [c]
Interferon beta-1b	81.58%	21.78% [c]
Glatiramer acetate	86.08%	4.00% [d]
Fingolimod	91.20%	6.21% [e]
Natalizumab	91.76%	2.39% [f]

Note:
[a] Based on the outcomes of a Treatment Compliance Report provided in the submission.
[b] Assumption based on the compliance to another oral therapy, fingolimod.
[c] Sourced from the TENERE study.
[d] Johnson et al. (1995).
[e] Cohen et al. (2010); Kappos et al. (2010).
[f] Polman et al. (2006).

Table 5 presents the estimated utilisation of teriflunomide. These figures were adjusted by an assumption, based on a treatment practice survey undertaken by the sponsor, that 6.64% of patients would not otherwise have received treatment. In deriving the average number of prescriptions per patient, the compliance rate was based on an assumption of 91.20% and the discontinuation rate was assumed to be 10.91% based on the TENERE study.

Table 5. Projected utilisation for teriflunomide

	Year 1	Year 2	Year 3	Year 4	Year 5
Total projected scripts for all RRMS listings	146,181	148,182	150,210	152,265	154,349
Number of eligible patients	15,276	15,485	15,697	15,912	16,130
Teriflunomide market share	7.5%	12.5%	15.0%	17.5%	20.0%
Proportion of teriflunomide patients previously receiving no treatment	6.64%	6.64%	6.64%	6.64%	6.64%
Treated population	1,227	2,073	2,522	2,983	3,455
Average prescriptions per patient	10.59	10.59	10.59	10.59	10.59
Number of prescriptions	12,998	21,960	26,712	31,591	36,598

The listing of teriflunomide was predicted to be cost saving through achieving cost offsets from substitution for fingolimod, natalizumab and ABCR therapy. Based on a treatment practice survey, the sponsor assumed that teriflunomide would mainly substitute for fingolimod (27.06%) and interferon beta-1a (27.65%), with the saving largely driven from replacing the more expensive oral fingolimod therapy. DUSC considered that safety concerns in relation to the cardiac effects of fingolimod may lead clinicians to switch patients to teriflunomide as an alternative oral therapy. A lower relative uptake was expected for interferon beta-1b (14.56%), glatiramer acetate (16.77%) and natalizumab (6.35%).

Methods

All analyses were undertaken using SAS Enterprise Guide version 5.1.

PBS/RPBS prescription data for the RRMS therapies were extracted from the Department of Human Services Prescription database for the period from January 2002 to March 2015 inclusive, based on the date that the prescription was supplied. The data differs from that available from the DHS (Medicare) PBS statistics website which is based on the date of processing.[7]

An analysis of the number of incident and prevalent patients taking RRMS therapies was undertaken using the DHS Prescription database. Patient counts were based on de-identified unique patient identification numbers (PINs) from the prescription data. Initiations were calculated during the period 1 December 2013 to 30 November 2014, the period corresponding to the first year of listing for dimethyl fumarate and teriflunomide. Three groups of initiators were analysed:

1. Patients initiating on any PBS/RPBS RRMS drug for the first time.
2. Treatment experienced patients who initiated on a new therapy between 1 December 2013 and 30 November 2014.
3. Patients who recommenced on RRMS therapy between 1 December 2013 and 30 November 2014 after a treatment break of more than 12 months.

Patients were identified as being prevalent if they had received at least one dispensing of any of the RRMS therapies in a calendar year. The DHS Prescriptions database data for the S100 Highly Specialised Drugs data first became available from July 2010 and was not fully complete until July 2013. As such, the total number of prevalent patients is under reported prior to July 2013 due to incomplete data for the S100 public hospital listing for natalizumab. Refer to Appendix E for the methods used to estimate the number of prevalent patients receiving natalizumab.

Length of treatment and co-administration analyses were performed using the DHS Prescription database data using the methodology described in Appendix D. Co-administration was investigated for ABCR therapy, natalizumab and fingolimod. Patients initiating RRMS therapy between March to August 2014 were analysed to allow at least seven months of follow up to the end of the analysis period (31 March 2015).

For the predicted versus actual comparisons of dimethyl fumarate and teriflunomide the modelled estimates were obtained from the financial estimates models that were agreed with the sponsors of these agents. Part-year adjustments were applied to the estimates to align the figures with the listing date in order to compare them with the actual figures.

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

Results

Utilisation for the overall RRMS market

Number of patients

Table 6 presents three groups of initiating patients: (1) those who are new to RRMS therapy ('New to any PBS RRMS therapy'); (2) those who are experienced with RRMS treatment who start another RRMS therapy for the first time ('switched from another PBS RRMS drug'); and (3) patients recommencing after a break from treatment of more than 12 months ('returning from a break in PBS therapy'). The figures are for patients initiating therapy during the period 1 December 2013 to 30 November 2014 to align with the first listing year for dimethyl fumarate and teriflunomide.

Table 6. Number of initiations[1] to each RRMS drug between 1 December 2013 and 30 November 2014

Drug	Group 1 N (%) new to any PBS RRMS therapy[2]	Group 2 N (%) switched from another PBS RRMS drug[3]	Group 3 N(%) returning from a break in PBS therapy of >12 months
Glatiramer acetate	182 (10%)	46 (2%)	60 (7%)
IFN beta-1a	101 (6%)	26 (1%)	40 (5%)
IFN beta-1b	43 (2%)	12 (0.4%)	27 (3%)
Fingolimod	481 (26%)	620 (22%)	129 (16%)
Dimethyl fumarate	641 (35%)	1,482 (53%)	332 (41%)
Teriflunomide	166 (9%)	367 (15%)	173 (21%)
Natalizumab	209 (11%)	255 (9%)	53 (7%)
All RRMS drugs	1,823	2,808	814

Source: DHS prescriptions data
Note:
[1] Including patients who were new to RRMS treatment, initiated on a new RRMS drug after a switch from a prior RRMS drug or recommencing after a treatment break of over 12 months.
[2] A first time initiator to PBS RRMS therapy was identified as having a first prescription for any RRMS drug since 1 January 2002.
[3] Excludes patients who were identified as having a treatment break of more than 12 months.

Referring to Table 6, the majority of new patients commenced on dimethyl fumarate and fingolimod. Only a relatively small proportion (18%) of patients received ABCR as their first RRMS therapy (Table 6).

For the patients who switched their therapy, Table 7 presents the number of prior therapies received and Table 8 profiles the last drug received before a new RRMS drug was supplied between 1 December 2013 and 30 November 2014.

Table 7. Number of prior therapies by patients switching to a new RRMS therapy between 1 December 2013 and 30 November 2014

Number of prior RRMS drugs	Count	Proportion
1	1596	56.8%
2	832	29.6%
3	295	10.5%
4	77	2.7%
5	8	0.3%

Table 8. Profile of last RRMS received before a patient switched to a new RRMS therapy between 1 December 2013 and 30 November 2014

RRMS switched from	Count	Proportion
Dimethyl fumarate	44	1.6%
Fingolimod	465	16.6%
Glatiramer acetate	546	19.4%
Interferon beta-1a	822	29.3%
Interferon beta-1b	537	19.1%
Natalizumab	379	13.5%
Teriflunomide	15	0.5%

For patients who switched to a new RRMS therapy in the first year that dimethyl fumarate and teriflunomide were available, only a small proportion (11%) had used more than two prior drugs (Table 7) and most (68%) switched from an ABCR therapy (Table 8). Most patients who switched from fingolimod received dimethyl fumarate (55%) and natalizumab (29%).

There has been a strong growth in the number of incident and prevalent patients since the introduction of oral RRMS therapy (Table 9, Figure 1).

Table 9. Number of initiating and prevalent patients on PBS-listed RRMS therapy by calendar year

Calendar year	Number of initiating patients[2]	Number of prevalent patients (without correction for natalizumab)	Number of prevalent patients (Adjusted with an estimate of natalizumab Public patients prior to July 2013)[1]
2006	1,025	8,630	8,630
2007	1,043	9,042	9,042
2008	1,176	9,595	9,858
2009	1,215	10,025	10,861
2010	1,232	10,492	11,615
2011	1,327	11,534	12,899
2012	1,351	12,647	14,203
2013	1,470	14,073	14,892
2014	1,765	15,704	15,704

[1] Highly Specialised Drugs data for Section 100 listings is incomplete in the DHS prescriptions database prior to July 2013. These figures are adjusted with an estimate of the number of S100 public patients receiving natalizimab before July 2013. Refer to Appendix E for the methods used to estimate these additional patients.
[2] A first time initiator to RRMS therapy was identified as having a first prescription for any RRMS drug since 1 January 2002.

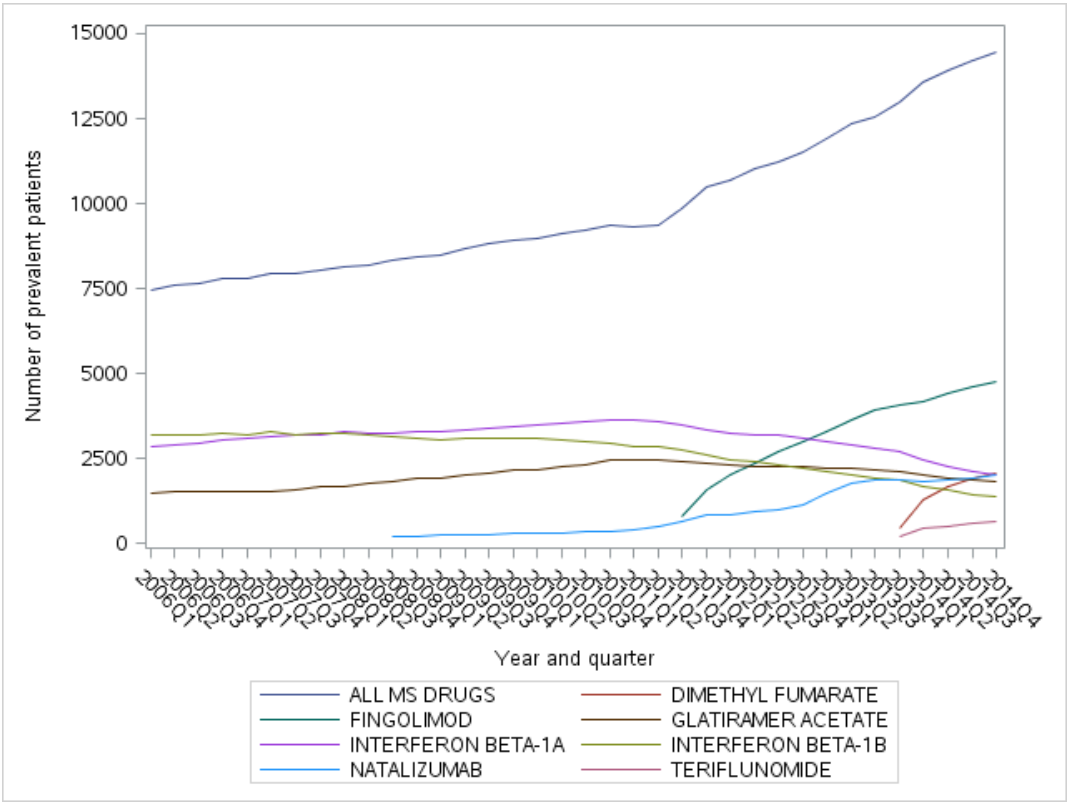

Figure 1: Prevalent patients by RRMS therapy by quarter of supply
Source: DHS Prescription database data
Note: PBS public hospital DHS Prescription database data has only been fully available since July 2013. Prior to this time the patient counts are incomplete for natalizumab.

Number of prescriptions

Consistent with the increase in the growth in the number of prevalent patients (Figure 1), the number of prescriptions for the overall RRMS market has grown steadily since the introduction of oral therapy (fingolimod, dimethyl fumarate and to a lesser extent teriflunomide), (Figure 2, Figure 3). There was no indication that growth in the RRMS market will attenuate in the near future.

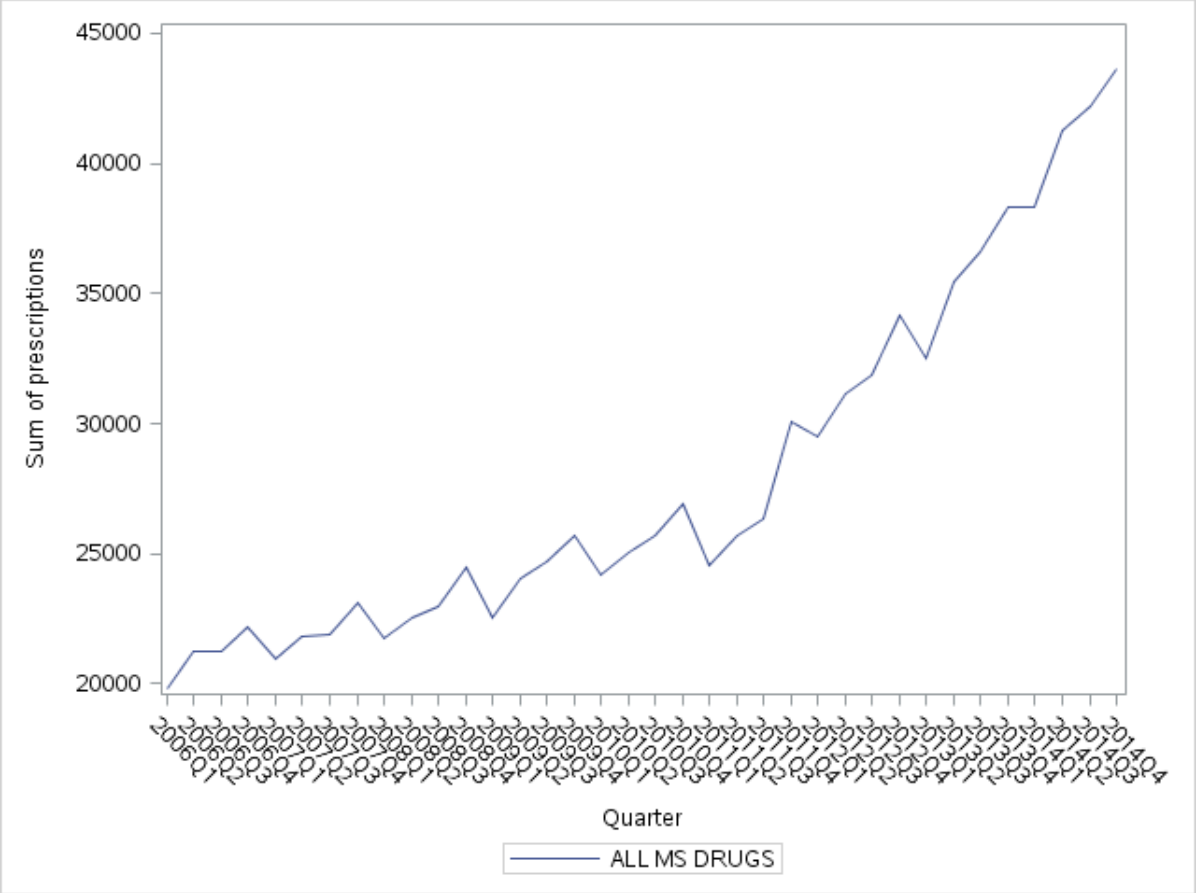

Figure 2. Prescriptions for all PBS-listed RRMS therapy
Source: DHS prescriptions data.

The utilisation of prescriptions for the individual RRMS medicines by quarter of supply is presented in Figure 3.

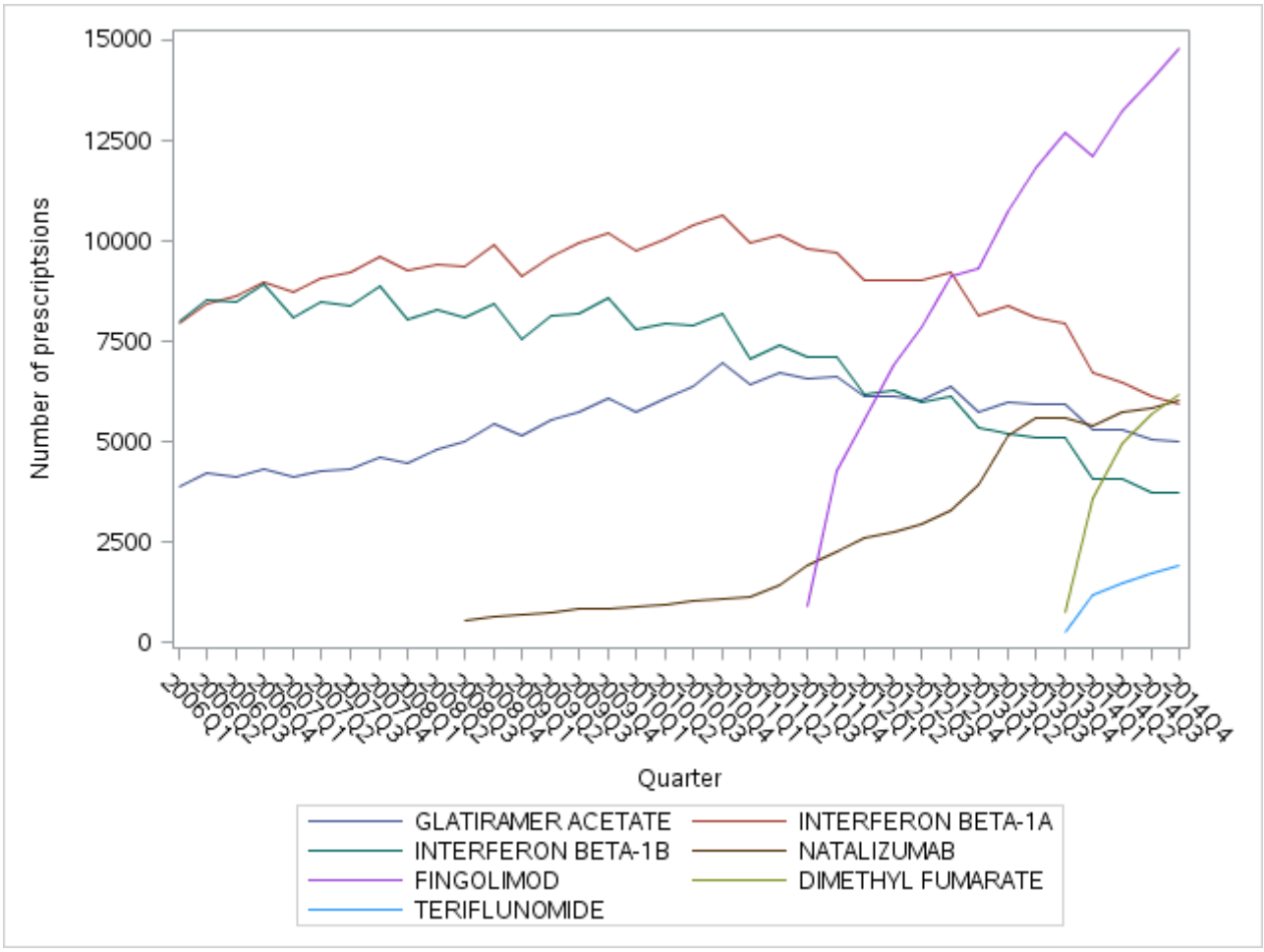

Figure 3. Prescriptions for all PBS-listed products in the RRMS market by quarter of supply
Source: DHS prescriptions data.

The number of prescriptions for natalizumab shown in Figure 3 is underrepresented as the Highly Specialised Drugs data is incomplete in the DHS prescriptions database prior to July 2013. The utilisation of natalizumab in terms of the number of packs is shown in Figure 4 which includes the full S100 Public component.

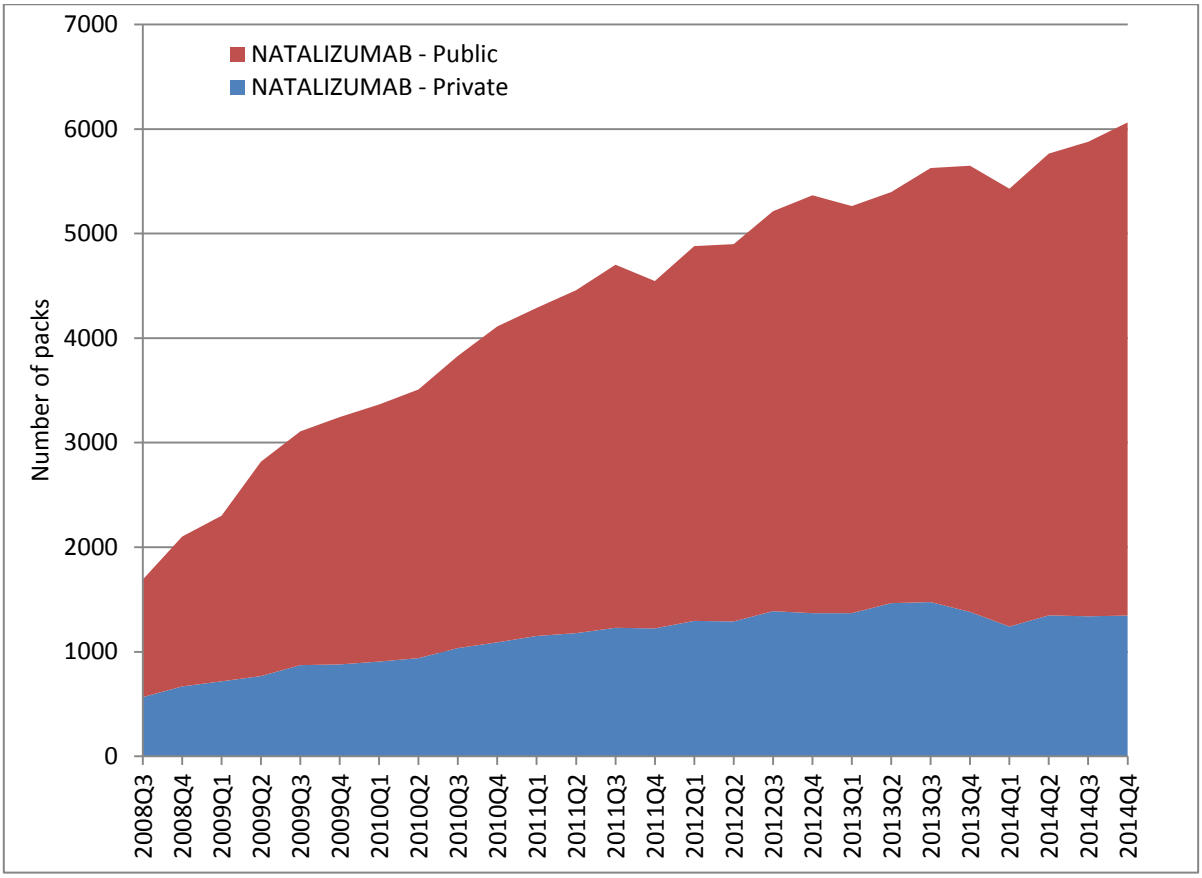

Figure 4. Number of packs of natalizumab by quarter of supply
Source: Highly Specialised Drugs database.

Oral RRMS is taking an increasing market share from the ABCR therapies (interferon beta-1a, interferon beta-1b and glatiramer acetate) and natalizumab (Figure 3). The uptake of dimethyl fumarate had reached a similar quarterly script volume compared to natalizumab by the December 2014 fourth quarter, teriflunomide had less market penetration than dimethyl fumarate over their first year of listing (Figure 3).

In modelling the utilisation of dimethyl fumarate and teriflunomide it was assumed that these medicines would take market share from fingolimod and natalizumab, as described under section 'Approach taken to estimate utilisation for dimethyl fumarate and teriflunomide' above. There has been a further decline in the growth of the ABCR therapies and fingolimod since the 2013 DUSC review after the introduction of further oral therapies (Table 10).

Table 10. Comparison of RRMS annual market growth for prescriptions

Drug	Prior year 2: Dec11-Nov12 (number of prescriptions)	Prior year 1: Dec12-Nov13 (number of prescriptions)	Current period: Dec13-Nov14 (number of prescriptions)	Annual Growth: Prior year 1 vs. prior year 2 (%)	Annual Growth: Current vs. prior year 1 (%)
ALL RRMS (excluding NATALIZUMAB[1])	114,370	121,253	140,867	6%	14%
DIMETHYL FUMARATE	NA	NA	18,906	NA	NA
FINGOLIMOD	27,884	43,361	53,309	36%	19%
GLATIRAMER ACETATE	24,808	23,811	20,955	-4%	-14%
INTERFERON BETA-1A	36,619	33,056	25,813	-11%	-28%
INTERFERON BETA-1B	25,059	21,025	16,005	-19%	-31%
TERIFLUNOMIDE	NA	NA	5,879	NA	NA

Source: DHS prescriptions data. Prescription volumes are based on the date of supply.

[1] Excluding natalizumab as data for this agent is incomplete in the DHS prescriptions database prior to July 2013. Including estimates for the total number of natalizumab scripts for the periods Prior Year 1 and Prior Year 2 (18,360 and 17,202, respectively) and the actual number of natalizumab scripts in December 2013 to November 2014 (22,800) had only a minor impact on the overall RRMS growth rates (5% for annual growth Prior Year 1 vs. Prior Year 2 and 14% for the annual growth Current vs Prior Year 1). See Appendix E for the methods used to derive the estimated prescriptions for natalizumab,

A slowing in the growth of natalizumab is seen when comparing the number of packs supplied over the last three years based on Quarter 4 to Quarter 3 figures, as shown in Table 11.

Table 11. Natalizumab growth based on the number of packs supplied

	2011 Q4-2012 Q3	2012 Q4-2013 Q3	2013 Q4 - 2014 Q3	Growth: Period 1 vs Period 2	Growth: Period 2 vs Period 3
NATALIZUMAB	19,539	21,653	22,721	10%	5%

Benefits

The net cost to Government for RRMS therapy based on their published prices are provided in Table 12.

Table 12. Net cost to the Commonwealth based on the published prices for the RMSS therapies

	2006	2007	2008	2009	2010	2011	2012	2013	2014
Published cost ($m)	$91.0	$93.4	$95.4	$106.6	$110.0	$114.2	$181.6	$194.7	$288.4

Note: Figures are based on the date of processing and are net of patient contributions

Utilisation for dimethyl fumarate

The submission assumed that dimethyl fumarate would capture [redacted] of the fingolimod market share in its first listing year. For the 12 month period prior to the listing of dimethyl fumarate (1 December 2012 to 30 November 2013) 68% of first time RRMS users received fingolimod. In its first year of listing dimethyl fumarate captured 53% of first time initiators (Table 6). When compared to the prior period (December 2012 to November 2013) fingolimod's market share for first time initiators fell by 42%.

For the period December 2013 to November 2014, 52% of patients switching to a new RRMS therapy and 41% of patients returning from a treatment break of more than 12 months were supplied with dimethyl fumarate. During the same period a substantially lower proportion of switchers to a new RRMS therapy and patients returning from a treatment break received fingolimod (21% and 16%, respectively). Of the 548 patients who switched from fingolimod (Table 8), 55% switched to dimethyl fumarate. Overall, dimethyl fumarate captured a large market share from fingolimod in its first listing year but not to the 70% uptake level predicted by the submission.

DUSC (June 2013) considered that the entry of dimethyl fumarate would act to grow the market rather than substitute for existing ABCR therapy and fingolimod. Referring to Tables 10 and 11 above, following the entry of dimethyl fumarate and teriflunomide declining growth was seen in the existing RRMS listings whereas the growth in the overall RRMS market increased by 8% (ie. from 6% to 14%) suggesting that the new oral RRMS therapies acted to expand the market.

DUSC (June 2013) considered that the submission had underestimated the use of dimethyl fumarate. DUSC noted that the submission's estimate of treated patients relied on the projected number of fingolimod patients and that the submission's patient estimate for fingolimod in its first listing year was less than the actual number of patients supplied with fingolimod. DUSC considered that the incidence of RRMS would likely increase from a change in the McDonald diagnosis criteria. As shown in Table 13, compared to actual figures the submission had substantially underestimated the use of dimethyl fumarate for its first listing year. The expenditure figures provided in Table 13 are based on the published prices for the 120 mg and 240 mg strength and are net of patient contributions.

Table 13. Predicted vs. Actual comparison for dimethyl fumarate

		Utilisation of all strengths Dec13 to Nov14	120 mg pack Dec13 to Nov14	240 mg pack Dec13 to Nov14
Treated patients	Predicted	[redacted]		
	Actual	2,534		
	Difference	[redacted]		
Number of prescriptions	Predicted	[redacted]	[redacted]	[redacted]
	Actual	18,906	2,468	16,438
	Difference	[redacted]	[redacted]	[redacted]
Drug cost to the PBS and RPBS	Predicted	[redacted]	[redacted]	[redacted]
	Actual	$31,648,779	$1,555,272	$30,093,506
	Difference	[redacted]	[redacted]	[redacted]

Note: All expenditure figures are for date of supply and are based on published prices and are net of patient co-payments. Dimethyl fumarate has a special pricing arrangement and government expenditure may be less than presented here.
The predicted estimates were agreed between the Sponsors and the Department post PBAC recommendation to list. Part-year corrections have been applied to account for the listing date to allow a comparison to the actual figures. An adjustment of 0.08 (i.e. 1 month/12 months) and 0.5 (i.e. 6 months/12 months) are applied to predicted figures for Years 1 and 2, as was done for the original modelling.
The actual figures were sourced from the Department of Human Services PBS Prescriptions Database accessed July 2015. These figures are based on the date of prescription supply.

Utilisation for teriflunomide

Based on a Treatment Practice Survey undertaken by the sponsor it was assumed that 6.64% of patients who would not have otherwise received a RRMS would be eligible for teriflunomide. Teriflunomide was predicted to grow the market through capturing an untreated population. As discussed under 'Utilisation of dimethyl fumarate' above, while a 3% increase in growth in the RRMS market occurred after the entry of the new oral RRMS this was mainly attributed to dimethyl fumarate. Only a low proportion (3%) of first-time initiators received teriflunomide. Teriflunomide may have been used in patients who may not have previously sought treatment for RRMS, however the impact of this appears minimal.

Comparisons of the predicted versus actual utilisation and expenditure for teriflunomide is presented in Table 14. The drug costs presented in Table 14 are based on the published price of teriflunomide and are net of patient contributions.

Table 14. Predicted vs Actual comparison for teriflunomide

		Utilisation Dec13 to Nov14
Treated patients	Predicted	1,134
	Actual	765
	Difference	-369 (-32.5%)
Number of prescriptions	Predicted	12,019
	Actual	5,879
	Difference	-6,140 (-51.1%)
Drug cost to the PBS and RPBS	Predicted	$21,924,379
	Actual	$10,614,946
	Difference	-$11,309,433 (-51.6%)

Note: All expenditure figures are based on published prices and are net of patient co-payments. Teriflunomide has a special pricing arrangement and government expenditure may be less than presented here. The predicted estimates were agreed between the Sponsors and the Department post PBAC recommendation to list. Part-year corrections have been applied to account for the listing date to allow a comparison to the actual figures. An adjustment of 0.08 (i.e. 1 month/12 months) and 0.5 (i.e. 6 months/12 months) are applied to predicted figures for Years 1 and 2, as was done for the original modelling.
The actual figures were sourced from the Department of Human Services PBS Supplied Prescriptions Database accessed July 2015. These figures are based on the date of prescription supply.

As a consequence of competing with dimethyl fumarate the predicted use of teriflunomide was overestimated.

Length of treatment analysis for fingolimod, natalizumab and ABCR therapy

As dimethyl fumarate and teriflunomide have only been listed from 1 December 2013 there was insufficient data to include these drugs in the length of treatment analyses.

The analysis included 4,680 patients who initiated their first PBS RRMS therapy on either fingolimod, natalizumab or ABCR therapy since the listing of fingolimod from 1 September 2011.

A patient was defined as having a break in treatment if there was no re-supply during a period that was three times the standard coverage days of treatment . That is, a gap between scripts of more than three times the median days to re-supply (see Appendix D for details).

The Kaplan-Meier estimates for time on the first episode of RRMS therapy are presented in Figure 4 and Table 18.

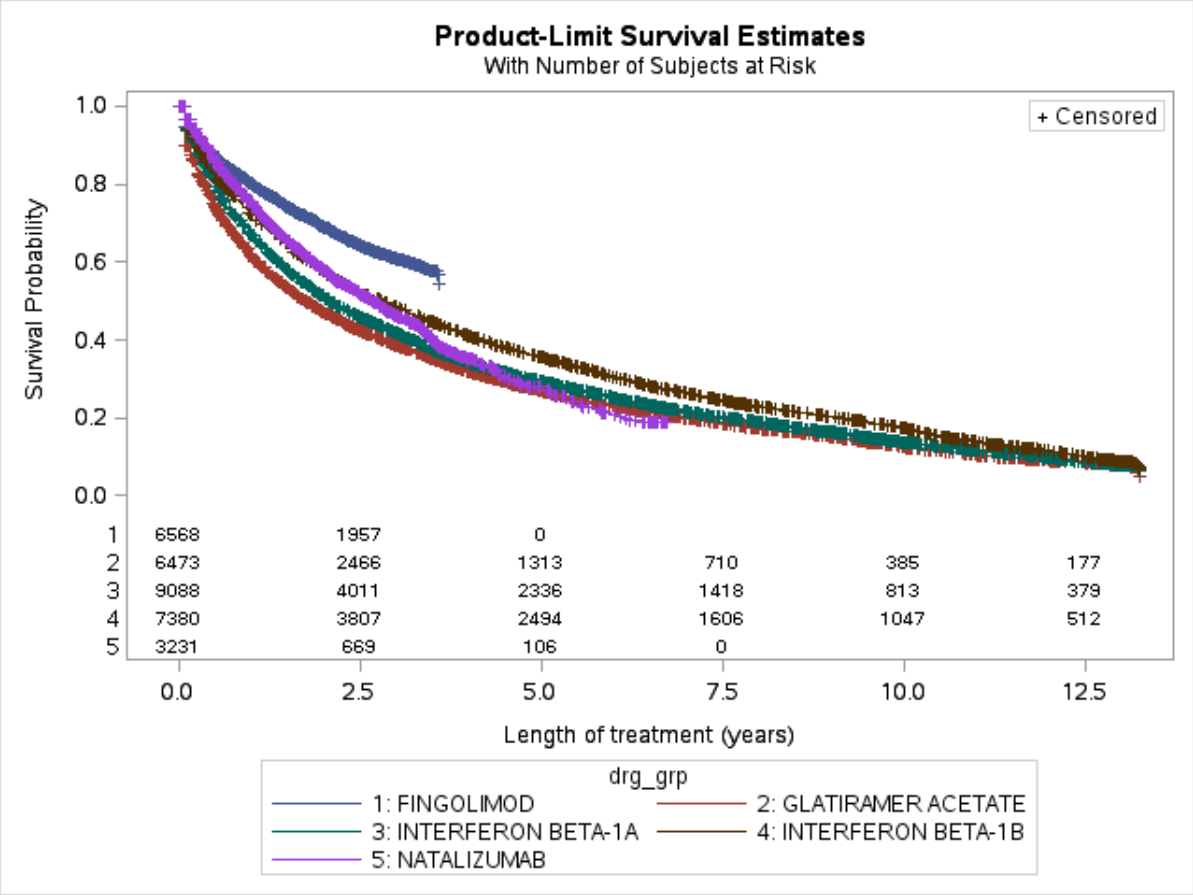

Figure 4. Kaplan-Meier survival estimates for fingolimod, ABCR therapy and natalizumab
Source: DHS prescriptions data.
Note: For the first episode of treatment. See Appendix D.

Fingolimod had not reached a median treatment time as at March 2015 (Figure 4). The median treatment times for ABCR therapy and natalizumab for the first episode of treatment and all episodes of treatment, including and excluding treatment breaks, are provided in Table 15.

Table 15: Median and mean time on the first episode of RRMS treatment in years

	First episode Median (95% CI) (years)	All episodes including treatment breaks Median (95% CI) (years)	All episodes excluding treatment breaks Median (95% CI) (years)
Fingolimod[1]	At least 3.5 years	At least 3.5 years	At least 3.5 years
Glatiramer acetate	1.8 (1.7, 1.9)	3.3 (3.0, 3.4)	2.6 (2.5, 2.8)
Interferon beta-1a	2.2 (2.1, 2.3)	3.3 (3.2, 3.4)	2.9 (2.8, 3.0)
Interferon beta-1b	2.7 (2.6, 2.8)	4.3 (4.1, 4.4)	3.7 (3.5, 3.8)
Natalizumab	2.7 (2.5, 2.8)	3.7 (3.5, 4.0)	3.5 (3.4, 3.7)

Source: DHS PBS supplied prescription database for prescriptions supplied from January 2002 to March 2015 inclusive.

[1] A median value had not been reached since the listing of fingolimod in September 2011 to the time of the analysis (March 2015)

Investigation of co-administration of RRMS therapies

The 2013 review of RRMS therapy identified potential coadministration of fingolimod with other RRMS therapy.

Co-administration was investigated for ABCR therapy, natalizumab and fingolimod. Patients initiating RRMS therapy between March to August 2014 were analysed to allow at least six months of follow up to the end of the analysis period (31 March 2015).

The results are presented in Tables 16 to 20 for the respective drugs. Overall instances of potential coadministration were found to be negligible (<1%).

Table 16. Use of fingolimod as monotherapy and cases of potential co-supply of another RRMS therapy

Drug regimen	Proportion of all regimens
FINGOLIMOD	99.2%
FINGOLIMOD+NATALIZUMAB	0.3%
FINGOLIMOD+GLATIRAMER ACETATE	0.2%
FINGOLIMOD+INTERFERON BETA-1B	0.2%
FINGOLIMOD+INTERFERON BETA-1A	0.1%

Note: Based on RRMS therapy estimated drug regimen in the week beginning 25 February 2015.

Table 17. Use of glatiramer acetate as monotherapy and cases of potential co-supply of another RRMS therapy

Drug regimen	Proportion of all regimens
GLATIRAMER ACETATE	99.2%
FINGOLIMOD+GLATIRAMER ACETATE	0.7%
GLATIRAMER ACETATE+INTERFERON BETA-1A	0.1%

Note: Based on the RRMS therapy estimated drug regimen in the week beginning 25 February 2015.

Table 18. Use of interferon beta-1a as monotherapy and cases of potential co-supply of another RRMS therapy

Drug regimen	Proportion of all regimens
INTERFERON BETA-1A	99.4%
FINGOLIMOD+INTERFERON BETA-1A	0.4%
INTERFERON BETA-1A+NATALIZUMAB	0.1%
GLATIRAMER ACETATE+INTERFERON BETA-1A	0.1%

Note: Based on the RRMS therapy estimated drug regimen in the week beginning 25 February 2015.

Table 19. Use of interferon beta-1b as monotherapy and cases of potential co-supply of another RRMS therapy

Drug regimen	Proportion of all regimens
INTERFERON BETA-1B	99.3%
FINGOLIMOD+INTERFERON BETA-1B	0.6%
INTERFERON BETA-1B+NATALIZUMAB	0.1%

Note: Based on the RRMS therapy estimated drug regimen in the week beginning 25 February 2015.

Table 20. Use of natalizumab as monotherapy and cases of potential co-supply of another RRMS therapy

Drug regimen	Proportion of all regimens
NATALIZUMAB	99.2%
FINGOLIMOD+NATALIZUMAB	0.6%
INTERFERON BETA-1A+NATALIZUMAB	0.1%
INTERFERON BETA-1B+NATALIZUMAB	0.1%

Note: Based on the RRMS therapy estimated drug regimen in the week beginning 25 February 2015.

Discussion

DUSC (June 2013) considered that the number of patients on RRMS therapy would increase mainly from: (1) revisions to the McDonald criteria[8] which have simplified the diagnosis of multiple sclerosis which may lead to a greater and earlier diagnosis of the disease; and (2) the availability of further oral treatment options for patients where injectable therapy is unsuitable. Consistent with this the RRMS market has continued to grow at a steady rate, largely driven by the uptake of fingolimod, dimethyl fumarate and, to a lesser extent, teriflunomide (Figures 1 to 3). There was also a substantial negative growth in the use of injectable therapy (Table 10).

A slowing in the growth of fingolimod was observed since the introduction of dimethyl fumarate and teriflunomide (Table 10). As previously noted by DUSC (June 2013) in its consideration of teriflunomide, the adverse cardiac effects of fingolimod may lead some clinicians to prescribe the alternative oral therapies.

[8] Polman, C.H. et al. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria; ANN NEUROL 2011;69:292–302

The entry of dimethyl fumarate and teriflunomide has appeared to increase the size of overall RRMS market rather than directly substituting for existing therapy, however the effect is small (3% change in year-on-year growth) (Table 10). This is inferred from an overall growth in the market with a declining rate of growth in the use of ABCR, natalizumab and fingolimod.

During the first year of listing for the new oral therapies the majority of previously untreated patients initiated on dimethyl fumarate (35%), around one-quarter received fingolimod and 29% initiated on injectable therapy (Table 6). Similarly for patients switching to a new RRMS therapy or returning from a treatment break longer than 12 months, most were initiated on an oral therapy. This is consistent with DUSC's (June 2013) previous view that around 50% of the RRMS market could be oral therapy within five years of the listing of dimethyl fumarate and teriflunomide.

The uptake of dimethyl fumarate was substantially more than teriflunomide (Figure 3). A review of therapy for multiple sclerosis published in the Medical Journal of Australia (Broadly et al., 2015) suggested that there could be a preference among clinicians for dimethyl fumarate as teriflunomide was considered to have less efficacy. There are varying results of post hoc analyses reported in the literature comparing the efficacy of dimethyl fumarate versus teriflunomide. For example, on the basis of indirect comparison Hutchinson et al. (2014) found that dimethyl fumarate achieved a significantly greater reduction in the annualised relapse rate (ARR) compared to the 14 mg strength of teriflunomide. However Freedman et al. (2014) reported comparable effect sizes for dimethyl fumarate 240 mg and teriflunomide 14 mg on relapse based on the number needed to treat. The interpretation of the available evidence is difficult as the results are subject to bias from the indirect nature of the analyses and the potential impact of heterogeneity among the included trials, such as differences in disease severity and event rates.

DUSC (June 2013) previously observed that patients may persist for longer on oral compared to injectable therapy given the adverse effects and more complicated dosing regimens required with injectable therapy. As previously recommended by the DUSC, the look-back period for the length of treatment analyses was extended to January 2002 to allow for the long periods of stability between attacks and treatment breaks which can occur with the multiple sclerosis. However, this analysis was unable to confirm whether there was a significant difference in the treatment durations between oral therapy, ABCR and natalizumab. Fingolimod had not reached a median treatment time by the data cut-off date for this reporting (31 March 2015) and there was insufficient data to undertake an analysis of the treatment times for dimethyl fumarate and teriflunomide. The Kaplan-Meier results presented in Figure 4 suggest that patients may persist longer on fingolimod compared to ABCR and natalizumab.

The previous predicted versus actual analysis of fingolimod conducted in 2013 identified the possible co-administration of this agent with other RRMS therapy. DUSC (June 2013) considered that this finding could reflect the co-supply of drug around the point of transition to a new therapy rather than a persistent co-administration of therapy. Patients initiating to ABCR therapy, natalizumab and fingolimod between March to August 2014,

with a look-back period to January 2002 to identify no previous use of RRMS therapy, were followed up to 31 March 2015. The instances of potential coadministration for these RRMS therapies was negligible (<1%, see Tables 16 to 20).

DUSC consideration

DUSC noted that the usage of RRMS therapy had increased with the availability of oral therapy. DUSC considered that this indicated a greater willingness of patients to receive treatment with the oral medicines; as such the utilisation of RRMS therapy appeared to be appropriate. DUSC noted the response to the report from MS Australia which considered that the rise in prevalent patients since the introduction of oral medicines indicated that there was a significant unmet need for these treatments. MS Australia also considered that the longer persistence on oral medicines was likely to improve treatment outcomes.

DUSC noted that it was unknown whether better patient outcomes were being realised from the greater utilisation of RRMS therapy since the introduction of oral medicines.

DUSC suggested undertaking an analysis on whether the availability of oral RRMS therapy has improved access to treatment for patients in regional and remote areas.

DUSC noted that the number of cases of potential co-administration among the RRMS therapies included in the analysis was negligible. DUSC suggested that when more mature data are available for alemtuzumab that its potential use in combination with other RRMS medicines is assessed.

DUSC actions

The DUSC requested that the report be provided to the PBAC for information.

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

Bayer Australia Pty Ltd:

The sponsor has no comment.

Biogen Idec Australia Pty Ltd:

The sponsor has no comment.

Merck Serono Australia Pty Ltd:

The sponsor has no comment.

Novartis Pharmaceuticals Australia Pty Limited:

The sponsor has no comment.

sanofi-aventis Australia Pty Ltd:

The sponsor has no comment.

Teva Pharma Australia 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.

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Public Summary Document for teriflunomide, November 2012. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-11/teriflunomide

Public Summary Document for teriflunomide, July 2013. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/teriflunomide

Appendix A – Summary of PBS listings for multiple sclerosis

Drug	Brand name	ATC5	Item	First listing date	Form and strength	Pack size	Max qty	Rpts	DPMQ
Alemtuzumab	Lemtrada	L04AA34	10228H	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	5	0	$56,970.00
Alemtuzumab	Lemtrada	L04AA34	10232M	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	3	0	$34,182.00
Alemtuzumab	Lemtrada	L04AA34	10243D	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	5	0	$57,016.76
Alemtuzumab	Lemtrada	L04AA34	10246G	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	3	0	$34,228.75
Dimethyl fumarate	Tecfidera	N07XX09	02896K	1 Dec 2013	Capsule (modified release) 120 mg	14	14	0	$491.31
Dimethyl fumarate	Tecfidera	N07XX09	02943X	1 Dec 2013	Capsule (modified release) 120 mg	14	14	0	$491.31
Dimethyl fumarate	Tecfidera	N07XX09	02966D	1 Dec 2013	Capsule (modified release) 240 mg	56	56	5	$1,880.00
Fingolimod	Gilenya	L04AA27	05262Y	1 Sep 2011	Capsule 500 micrograms (as hydrochloride)	28	28	5	$2,313.32
Glatiramer	Copaxone	L03AX13	08726G	1 May 2004	Injection containing glatiramer acetate 20 mg in 1 mL single dose pre-filled syringe	28	28	5	$1,092.99
Interferon beta-1a	Avonex	L03AB07	08289G	1 Feb 1999	Injection set comprising 1 vial powder for injection 30 micrograms (6,000,000 I.U.) with diluent	4	4	5	$1,057.11
Interferon beta-1a	Rebif 44	L03AB07	08403G	1 May 2000	Injection 44 micrograms (12,000,000 I.U.) in 0.5 mL single dose pre-filled syringe	12	12	5	$1,057.11
Interferon beta-1a	Avonex	L03AB07	08805K	1 Apr 2005	Injection 30 micrograms (6,000,000 I.U.) in 0.5 mL single dose pre-filled syringe	4	4	5	$1,057.11
Interferon beta-1a	Rebif 44	L03AB07	08968B	1 May 2011	Injection 44 micrograms (12,000,000 I.U.) in 0.5 mL single dose autoinjector	12	12	5	$1,057.11
Interferon beta-1a	Rebif 44	L03AB07	09332E	1 May 2010	Solution for injection 132 micrograms in 1.5 mL multidose cartridge	4	4	5	$1,057.11

Drug	Brand name	ATC5	Item	First listing	Form and strength	Pack	Max	Rpts	DPMQ
Interferon beta-1b	Betaferon	L03AB08	08101J	1 Nov 1996	Injection set including 1 vial powder for injection 8,000,000 I.U. (250 micrograms) and solvent	15	15	5	$1,001.15
Natalizumab	Tysabri	L04AA23	09505G	1 Jul 2010	Solution concentrate for I.V. infusion 300 mg in 15 mL	1	1	5	$1,568.04
Natalizumab	Tysabri	L04AA23	09624M	1 Jul 2008	Solution concentrate for I.V. infusion 300 mg in 15 mL	1	1	5	$1,614.80
Peginterferon beta-1a	Plegridy	L03AB13	10212L	1 Mar 2015	Single use injection pen containing 125 micrograms in 0.5 mL	2	2	4	$1,057.11
Peginterferon beta-1a	Plegridy	L03AB13	10218T	1 Mar 2015	Pack containing single use injection pens containing 63 micrograms in 0.5 mL and 94 micrograms in 0.5 mL	1	1	0	$1,057.11
Peginterferon beta-1a	Plegridy	L03AB13	10220X	1 Mar 2015	Single use injection pen containing 125 micrograms in 0.5 mL	2	2	5	$1,057.11
Teriflunomide	Aubagio	L04AA31	02898M	1 Dec 2013	Tablet 14 mg	28	28	5	$1,847.26

Appendix B – Chronology of PBS listings for multiple sclerosis

Drug	Brand name	ATC5	Item code	First listing date	Form and strength	Pack size	Max qty	Rpts	DPMQ
Interferon beta-1b	Betaferon	L03AA11	08101J	1 Nov 1996	Injection set comprising 1 vial powder for injection providing a final dose of 8,000,000 I.U. and 1 vial solvent 2 mL	15	15	5	$1,448.04
Interferon beta-1a	Avonex	L03AA11	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	4	4	5	$1,169.84
Glatiramer acetate	Copaxone	L04AA07	08352N	1 Nov 1999	Powder for subcutaneous injection 20 mg in single use vial and 1 ampoule diluent 1.1 mL	28	28	5	$1,112.14
Interferon beta-1a	Rebif 22	L03AB07	08402F	1 May 2000	Injection 22 micrograms (6,000,000 I.U.) in 0.5 mL single dose pre-filled syringe	12	12	5	$1,060.44
Interferon beta-1a	Rebif 44	L03AB07	08403G	1 May 2000	Injection 44 micrograms (12,000,000 I.U.) in 0.5 mL single dose pre-filled syringe	12	12	5	$1,359.57
Glatiramer acetate	Copaxone	L03AX13	08726G	1 May 2004	Injection 20 mg in 1 mL single dose pre-filled syringe	28	28	5	$1,090.89
Interferon beta-1a	Avonex	L03AB07	08805K	1 Apr 2005	Injection 30 micrograms (6,000,000 I.U.) in 0.5 mL single dose pre-filled syringe	4	4	5	$1,090.93
Natalizumab	Tysabri	L04AA23	09624M	1 Jul 2008	Solution concentrate for I.V. infusion 300 mg in 15 mL	1	1	0	$2,038.46
Interferon beta-1a	Rebif 44	L03AB07	09332E	1 May 2010	Solution for injection 132 micrograms in 1.5 mL multidose cartridge	4	4	5	$1,056.77
Natalizumab	Tysabri	L04AA23	09505G	1 Jul 2010	Solution concentrate for I.V. infusion 300 mg in 15 mL	1	1	5	$2,038.46
Interferon beta-1a	Rebif 44	L03AB07	08968B	1 May 2011	Injection 44 micrograms (12,000,000 I.U.) in 0.5 mL single dose autoinjector	12	12	5	$1,056.77
Fingolimod	Gilenya	L04AA27	05262Y	1 Sep 2011	Capsule 500 micrograms (as hydrochloride)	28	28	5	$2,312.98
Dimethyl fumarate	Tecfidera	N07XX	02896K	1 Dec 2013	Capsule (modified release) 120 mg	14	14	0	$491.18
Dimethyl fumarate	Tecfidera	N07XX	02943X	1 Dec 2013	Capsule (modified release) 120 mg	14	14	0	$491.18
Dimethyl fumarate	Tecfidera	N07XX	02966D	1 Dec 2013	Capsule (modified release) 240 mg	56	56	5	$1,879.87
Teriflunomide	Aubagio	L04AA	02898M	1 Dec 2013	Tablet 14 mg	28	28	5	$1,847.13
Peginterferon beta-1a	Plegridy	L03AB	10212L	1 Mar 2015	Single use injection pen containing 125 micrograms in 0.5 mL	2	2	4	$1,057.11
Peginterferon beta-1a	Plegridy	L03AB	10218T	1 Mar 2015	Pack containing single use injection pens containing 63 micrograms in 0.5 mL and 94 micrograms in 0.5 mL	1	1	0	$1,057.11
Peginterferon beta-1a	Plegridy	L03AB	10220X	1 Mar 2015	Single use injection pen containing 125 micrograms in 0.5 mL	2	2	5	$1,057.11
Alemtuzumab	Lemtrada	L01XC04	10228H	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	5	0	$56,970.00
Alemtuzumab	Lemtrada	L01XC04	10232M	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	3	0	$34,182.00
Alemtuzumab	Lemtrada	L01XC04	10243D	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	5	0	$57,016.76
Alemtuzumab	Lemtrada	L01XC04	10246G	1 Apr 2015	Solution concentrate for I.V. infusion 12 mg in 1.2 mL	1	3	0	$34,228.75

Appendix C – Therapeutic Goods Administration (TGA) approved indications

Drug	Date of registration	Approved indication
Alemtuzumab (Lemtrada)	18 Dec 2013	Alemtuzumab is indicated for the treatment of relapsing forms of multiple sclerosis (MS) for patients with active disease defined by clinical or imaging features to slow the accumulation of physical disability and reduce the frequency of clinical relapses.
Dimethyl fumarate (Tecfidera)	11 Jul 2013	Dimethyl fumarate is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability
Fingolimod (Gilenya)	1 Feb 2011	Fingolimod is indicated for the treatment of Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse. Safety and efficacy of GILENYA beyond 2 years are unknown.
Glatiramer (Copaxone)	17 Dec 2003	Glatiramer is indicated for the reduction of the frequency of relapses in patients with Relapsing Remitting Multiple Sclerosis. Reduction of the frequency of relapses in patients with Relapsing Remitting Multiple Sclerosis. Treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent MRI lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded.
Interferon beta-1a (Avonex, Rebif 44)	31 Aug 2001	Interferon beta-1a (Avonex): For the treatment of relapsing forms of multiple sclerosis. Also for use in patients who have experienced a single demyelinating event and are at risk of developing clinically definite multiple sclerosis based on the presence of brain MRI abnormalities characteristic of MS. Interferon beta-1a (Rebif 44): Treatment of: Patients with a single demyelinating event in the central nervous system with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. High risk can be inferred from cerebral MRI with 2 or more lesions suggestive of demyelination; Ambulatory patients with multiple sclerosis who have experienced two or more relapses within the last 2 years. Rebif 44 therapy should not be initiated in secondary progressive MS patients who no longer experience relapses.
Interferon beta-1b (Betaferon)	9 Aug 2002	Interferon beta-1b is indicated for the treatment of: - Ambulatory patients with relapsing-remitting multiple sclerosis (MS) characterised by at least two attacks of neurologic dysfunction over a two year period followed by complete or incomplete recovery. - Betaferon is also indicated for the reduction of frequency and severity of clinical relapses, and for the slowing of progression of disease in patients with secondary progressive multiple sclerosis. - The treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent

Drug	Date of registration	Approved indication
		magnetic resonance imaging (MRI) lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded.
Natalizumab (Tysabri)	1 Nov 2006	Natalizumab is indicated as monotherapy for the treatment of patients with relapsing remitting multiple sclerosis (MS) to delay the progression of physical disability and to reduce the frequency of relapse.
Peginterferon beta-1a (Plegridy)	10 Nov 2014	Peginterferon beta-1a is indicated for the treatment of relapsing forms of Multiple Sclerosis.
Teriflunomide (Aubagio)	14 Nov 2012	Teriflunomide is indicated for the treatment of patients with relapsing forms of Multiple Sclerosis to reduce the frequency of clinical relapses and to delay the progression of physical disability.

Source: Australian Register of Therapeutic Goods. Accessed on 21 July 2015 at: https://www.ebs.tga.gov.au/

Appendix D

Methodology for Kaplan Meier length of treatment analyses

A break in treatment is defined as a gap of 2 x Standard Coverage Days (SCD) in drug coverage which is equivalent to 3 x SCDs between prescription supply. An episode is defined as the time from the first prescription to the last prescription before a break plus one SCD (i.e. the coverage of the last prescription). The SCDs are equal to the median time to re-supply of prescriptions calculated at the drug level. The table below shows the SCDs used in this analysis.

Drug	Median time to re-supply by any item of the specified drug = SCD (days)
FINGOLIMOD	28
GLATIRAMER ACETATE	29
INTERFERON BETA-1A	28
INTERFERON BETA-1B	30
NATALIZUMAB	28

The data period used in the length of treatment analysis was from January 2002 to March 2015 inclusive (based on date of supply). A patient was deemed to be continuing treatment (i.e. censored for the purposes of the Kaplan-Meier analysis) at the end of the data period if the supply of their last prescription was within 3 x SCDs (which is equivalent to the item coverage end date being within 2 x SCDs) of the end of the data period (i.e. 31 March 2015). Three lengths of treatment were calculated:

- the first episode of treatment (i.e. up to the first break in treatment);
- all treatment excluding breaks (i.e. the sum of all episodes); and
- all treatment including breaks (i.e. the time from the first prescription of the first episode to the last prescription of the last episode plus one SCD which is the coverage of the last prescription).

When two different strengths (i.e. PBS items) of the same drug were supplied on the same day it was assumed that these strengths were taken concurrently (i.e. were necessary to achieve the prescribed dose). This was not considered to be stockpiling.

Stockpiling

Non-same day stockpiling is when a patient gets the next supply of a drug earlier than expected (i.e. before the median time to re-supply). This most commonly occurs late in the calendar year when a patient is on the PBS Safety Net. By not allowing for this a break in treatment may be imputed for a patient early in the calendar year when the patient is simply consuming the stockpiled drug. Allowing for non-same day stockpiling could result in a patient consistently having less than the median time to re-supply (e.g. because they have a high prescribed dose) and so the imputed coverage end date gets to be significant further than the real coverage end date. This means a break in treatment may be missed. In this Kaplan-Meier analysis, non-same-day stockpiling was not allowed for because the risk of stockpiling of these drugs was considered low.

Same day stockpiling is deemed to have occurred when there are multiple supplies of the same PBS item on the same day. Supplies of different strengths on the same day is deemed to be necessary for the supply of the prescribed dose and so is not considered to be stockpiling. Multiple supplies of the same strength on the same day are most likely due to stockpiling (i.e. if such a quantity were required for the prescribed dose then the prescriber should have requested an increased maximum quantity). Same day stockpiling is taken into account in this analysis.

Methodology to estimate co-administration

Co-administration was estimated from the data in the following way:

Step 1: Determine the estimated medication coverage days for each drug or drug group. This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode of treatment for each drug or drug group.

Step 2: Determine the estimated medication coverage days across all drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every week in the data period.

Similar methods have been used for assessing medicine use in Australian populations.[9,10] Hallas[11] describes the method and provides references to early variants.

Drug treatment regimens were estimated from prescription supply dates. The estimated medication coverage days for each drug were determined. This involved detecting breaks in treatment. The outcome was the start and estimated end date for each episode for each drug or drug group.

If the medication coverage start date falled in a particular calendar week (for prevalent patient analysis) or week since initiation (for initiation analysis) then the medication was deemed to cover that week. The same rule was applied to the medication coverage end date.

Once estimated drug regimens were determined for every week, transitions between drugs were computed. These are useful for determining patient behaviour upon initiation of a drug; e.g. A→A+B (adding to existing therapy), A→B (switching) or None→A (starting therapy).

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[9] Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P 2011 "Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: a self-controlled case-series analysis in an Australian health care claims database" Drug Saf. 34(7):567-75. doi: 10.2165/11588470-000000000-00000.

[10] Vitry AI, Roughead EE, Preiss AK, Ryan P, Ramsay EN, Gilbert AL, Caughey GE, Shakib S, Esterman A, Zhang Y, McDermott RA 2010 "Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study" PLoS One. 5(11):e14024. doi: 10.1371/journal.pone.0014024.

[11] Hallas J. 2005 "Drug utilization statistics for individual-level pharmacy dispensing data" Pharmacoepidemiol Drug Saf. 14:455–463. doi: 10.1002/pds.1063.

The transitions can be:
A. previous drug regimen →drug regimen at week x, or
B. drug regimen at week -1 →drug regimen at week x

Option A has the advantage that it can be calculated at any week, whereas Option B can only be calculated after initiation (i.e. from week 0). The main advantages of Option B are that it can easily be used to adjust the drug regimen in the first few weeks after initiation to allow for switching when the prior medication is not fully used. That is, if a patient switches from A to B, in the first few weeks after initiation to drug B the drug regimen may be incorrectly estimated to be A+B if the patient still has drug A “on hand” (i.e. some is unused) when drug B is initiated.

The regimen transitions are adjusted so that if a regimen transition corresponding to a switch (e.g. A→B) is detected within the first X weeks after initiation (e.g. at week Y), then all weeks between the initiation (i.e. week 0) and week Y are modified to the switch transition (i.e. A-B). This means some instances of "A→A+B" (apparent co-administration after a switch) are modified to "A→B" from week 0 to week Y (where $Y \leq X$). The value of X is the 1 week + SCD (expressed in weeks) for the drug or drug group that is being substituted.

If a drug A was supplied 1 day before an initiation to drug B and then there were no further supplies of drug A, then there would be apparent co-administration of A and B from week 0 to week X-1 and in week X the drug regimen would be drug B only and considered a switch. Thus the regimens from weeks 0 to X-1 would be modified to be drug B only. If a switch is first detected in week X +1 then the A script would have been supplied in week 0 (i.e. at or after initiation to drug B) and this would mean that the transition was not a switch but an addition. Thus the logic is only applied to weeks 0 to X.

A transition was considered a switch if a drug in the regimen prior to initiation (the week=-1 regimen) was not in the regimen post initiation (i.e. the week=0 regimen). After this transition adjustment, the drug regimens can were adjusted by using the regimen after the arrow in the adjusted regimen transition. That is, if a transition got adjusted from A→A+B to A→B in week Y then the adjusted drug regimen for week Y changed from A+B to B. Thus even though the drug regimen is calculated first, its adjustment is dependent on both the regimen transition and adjusted regimen transition. The sequence of calculation steps was:
1. drug regimens
2. drug regimen transitions around initiation
3. adjusted drug regimen transitions
4. adjusted drug regimens

The above adjustment process considers drug initiations. If the analysis is for prevalent drug regimens only (i.e. regimens by calendar week and not relative to an initiation date) then the above adjustments were not possible. This was considered to have a minor impact as the overestimation of co-administration (e.g. A→A+B instead of A→B) would be greatest in the month after initiation. In a prevalent patient analysis, patient initiations (to any and

all drugs) are spread out in time (i.e. all patients do not generally initiate in the same week), and so the overestimation is also spread out over time and so minimised. In the initiating patient analysis, all overestimations occurred at the same time (as time is relative to the initiation week) and so the overestimation is significant and so needs to be adjusted for. For the prevalent patient analysis, it would have been possible to do an initiation analysis for every drug and find adjusted drug regimens that could then be re-expressed in calendar weeks. In practice this was considered to be too resource intensive and would be unlikely to be make a significant difference to the prevalent patient drug regimens.

Stockpiling may occur towards the end of the calendar year when a Safety Net card holder fills prescriptions more frequently than expected so as to stockpile the medicine and avoid a higher co-payment in the next calendar year when they lose Safety Net eligibility. Stockpiling can also occur at other times of the year. Higher rates of breaks in episodes around February could occur from the stockpiling effect and not due to genuine breaks in treatment. Thus the rule to estimate the prescription coverage end date was modified to be the greater of:

- the predicted coverage end date of the previous prescription plus the standard coverage days (SCD); or
- the actual refill date of the previous prescription plus the SCD.

This way of calculating the prescription coverage end date takes into account medication stockpiling (i.e. early supply). The logic of the break rule remained unchanged, that is a break was where a prescription was supplied 2 x SCD or more after the coverage end date of the previous prescription for the same drug or drug group. Application of this refinement reduces the extent of seasonality in the number of breaks in episodes.

If multiple prescriptions of the same drug (but not the same strength) are supplied on the same day, it was assumed that these were necessary for the prescribed dose for the SCD and not for an extension of coverage. If multiple prescriptions of the same drug are supplied it is generally for two different strengths to enable the prescribed dose to be administered. If two prescriptions for the same strength (as opposed to increased quantity for a single script) are supplied, the method assumes this is similar to stockpiling (i.e. same day stockpiling) and the predicted coverage end date is extended to be the greater of:

- the predicted coverage end date of the previous prescription plus n x SCD; or
- the actual refill date of the previous prescription plus n x SCD

where n = number of prescriptions on the same day.

A special case of multiple prescriptions being supplied on the same day is Regulation 24 prescriptions. If the original and repeat prescriptions were supplied under Regulation 24 on the same day, this was assumed to extend the coverage period (i.e. coverage period = prescriptions x SCD).

The stockpiling rule could result in the script coverage end date getting considerably ahead of the script supply date. To correct for this, the script coverage rule was changed so that if the script coverage period for drug A included the initiation date for drug B, then the stockpiling rule would not apply to the drug A script (i.e. its coverage would be from its

supply date to the supply date + SCD). The rationale for this change was that even if the patient has a lot of drug A on hand, the decision by the prescriber to initiate a new drug means that a switch could have occurred.

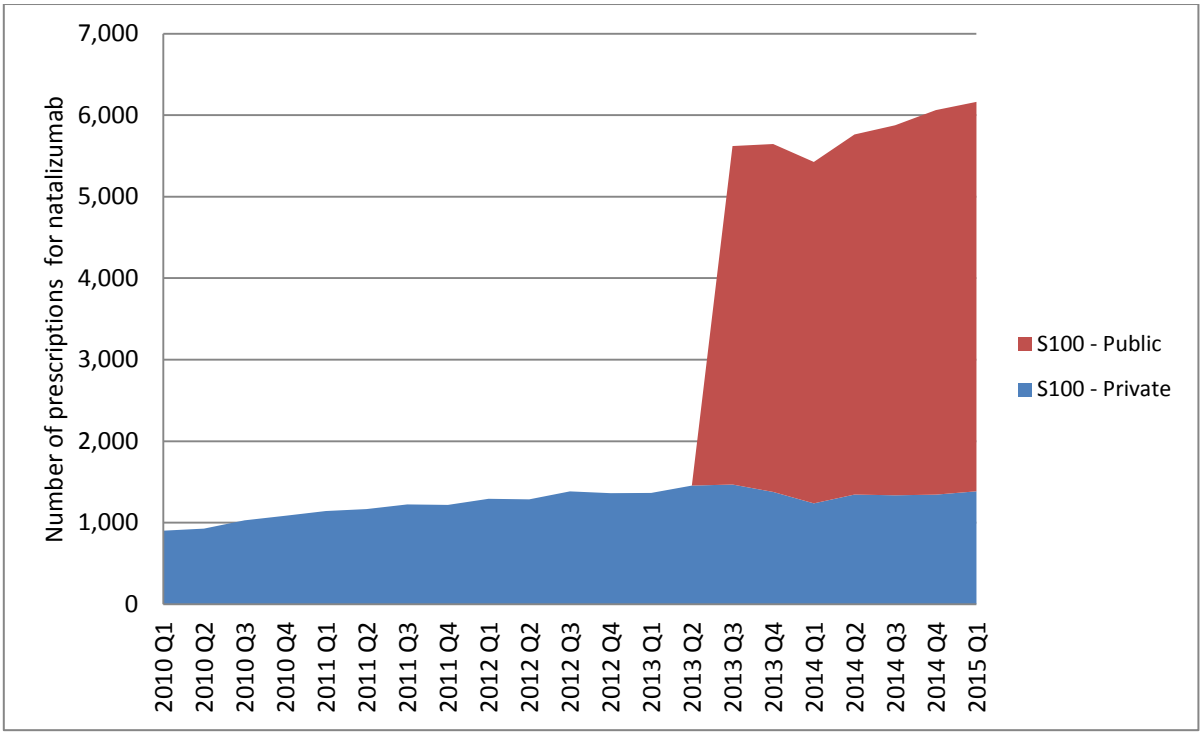
If the last script in a patients script history is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period (i.e. the episode coverage end date is set to the end date of the data period). Otherwise the treatment episode is estimated to have stopped and the episode coverage end date is equal to If the last script in a patients script history plus 1 x SCD.

The standard coverage days used in this analysis are summarised in the table above under 'Methodology for Kaplan Meier length of treatment analyses'.

Appendix E

Methodology to estimate prevalent patients receiving natalizumab

Highly Specialised Drugs data for public hospital supplies only became fully available from July 2013, as shown in the following figure for natalizumab:



Source: DUSC database, August 2015

The following methods were used to estimate the number of patients accessing the S100 Public listing of natalizumab to provide indicative figures for the total number of patients using RRMS therapy.

Step 1: Derivation of the number of scripts per patient for the S100 public listing for natalizumab in 2014 as the assumption of scripts per patient before July 2013.

An analysis of the PBS DHS Prescription database data identified 1,842 patients received 17,775 S100 public prescriptions. This gave an average of 9.6 scripts per patient.

Step 2: Public vs private splits for natalizumab based on the utilisation of packs was obtained.

Script type	2008	2009	2010	2011	2012	2013 (to 30 June)
Private	33%	28%	27%	27%	26%	27%
Public	67%	72%	73%	73%	74%	73%

Source: Highly Specialised Drugs database.

Step 3: The number of prescriptions for public patients based on the actual number of prescriptions for S100 private patients was estimated.

Step 3a – The number of S100 private prescriptions for natalizumab per calendar year was calculated (2013 is a part year to 30 June as actual public data became available from July 2013).

Step 3b – Using the assumption of 77% of total prescriptions for natalizumab being public from Step 2, the estimated number of prescriptions for the S100 public listing of natalizumab was calculated. The formula was:

Estimated Public natalizumab = Actual Private scripts x proportion S100 Public / proportion S100 Private.

The results are shown in the following table:

	2008	**2009**	**2010**	**2011**	**2012**	**2013 (to 30 June 2013)**
Public (estimated)	2,524	8,022	10,781	13,107	14,938	7,865
Private (actual)	1,223	3,179	3,948	4,744	5,317	2,847

Step 4: The number of prevalent patients accessing S100 Public natalizumab was estimated.

The number of estimated S100 natalizumab prescriptions was divided by the average number of scripts for S100 public natalizumab in 2014 (9.6, from Step 1) to estimate the number of prevalent Public patients, as shown in the following table.

	2008	**2009**	**2010**	**2011**	**2012**	**2013 (to 30 June)**
Estimated Public scripts	2,524	8,022	10,781	13,107	14,938	7,865
Average scripts for patient	9.6					
Estimated Public patients	263	836	1,123	1,365	1,556	819