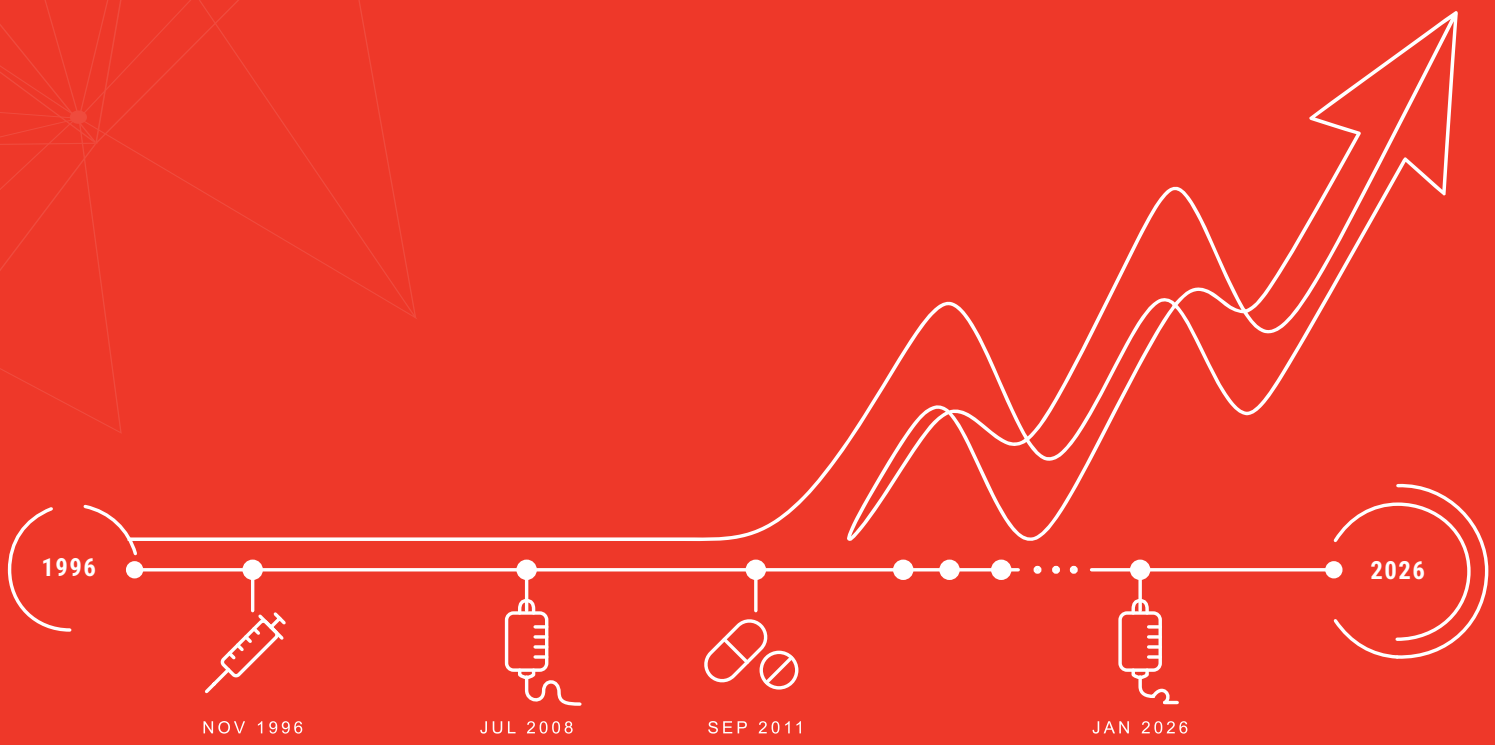
MS AUSTRALIA

Assessing the value of 30 years of disease-modifying therapies for multiple sclerosis in Australia

NOVEMBER 2026



About THEMA Consulting

THEMA Consulting Pty Ltd is an independent health economics consultancy based in Sydney, Australia. Founded in 2006, THEMA provides health technology assessment and health economics and outcomes research services in Australia and internationally. Its work includes supporting pharmaceutical reimbursement applications to the Pharmaceutical Benefits Advisory Committee (PBAC), medical device reimbursement applications to the Medical Services Advisory Committee (MSAC), and health economics projects for pharmaceutical and medical device companies, patient advocacy organisations, charities and industry associations.

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Independence and disclosure

MS Australia determined the scope and objectives of the project and commissioned THEMA Consulting to undertake the work. THEMA Consulting independently undertook the evidence review, analysis and economic modelling described in the report.

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Abbreviations

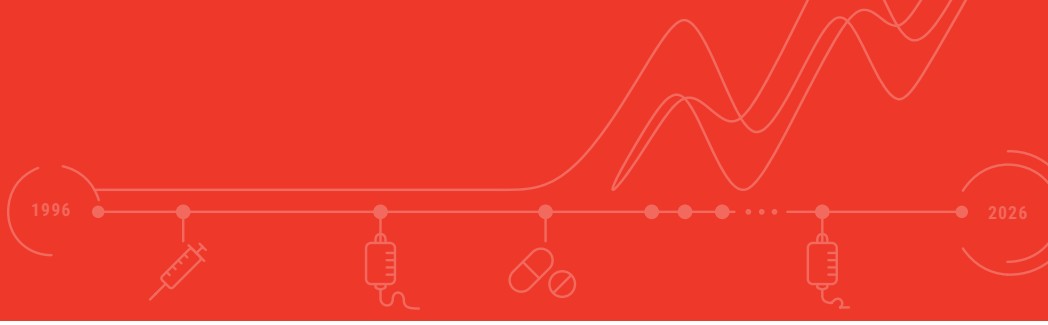
Abbreviation	Definition
ABCR	Avonex, Betaferon, Copaxone and Rebif
ABN	Association of British Neurologists
AEs	Adverse events
aHSCT	Autologous haematopoietic stem cell transplantation
AIHW	Australian Institute of Health and Welfare
ALE	Alemtuzumab
ANZCTR	Australian New Zealand Clinical Trials Registry
AQoL	Assessment of Quality of Life
AR-DRG	Australian Refined Diagnosis Related Group
ARR	Annualised relapse rate
ARTG	Australian Register of Therapeutic Goods
ATC	Anatomical Therapeutic Chemical
AVO	Avonex
BCMS	British Columbia Multiple Sclerosis database
BET	Betaferon
BID	Twice a day
BPF	Brain parenchymal fraction
BSC	Best supportive care
BTK	Bruton's tyrosine kinase
CAR T-cell therapy	Chimeric antigen receptor T-cell therapy
cCDP	Composite confirmed disability progression
CEA	Cost-effectiveness analysis
CIS	Clinically isolated syndrome
CLA	Cladribine
CMA	Cost-minimisation analysis
CNS	Central nervous system
COP	Copaxone
CUA	Cost-utility analysis
CUR	Cured
DAC	Daclizumab

Abbreviation	Definition
DAEs	Adverse events leading to discontinuation
DHODH	Dihydroorotate dehydrogenase
DIR	Diroximel fumarate
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy
DPMQ	Dispensed price maximum quantity
DUSC	Drug Utilisation Sub-Committee
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	EuroQol five-dimension questionnaire
FDA	Food and Drug Administration
FIN	Fingolimod
FNB	First new brand
GA	Glatiramer acetate
Gad/Gd	Gadolinium
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFN-β	Interferon beta
IM	Intramuscular
ITC	Indirect treatment comparison
IV	Intravenous
LAQ	Laquinimod
MD	Mean difference
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MS	Multiple sclerosis
MSBase	Multiple Sclerosis Base registry
MSC	Mesenchymal stem cell
NAT	Natalizumab
NCT	National Clinical Trial number
NEDA	No evidence of disease activity

Abbreviation	Definition
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
Nurr1	Nuclear receptor-related 1
OCR	Ocrelizumab
OIA	Office of Impact Analysis
OMB	Ofatumumab
OPC	Oligodendrocyte precursor cell
OR	Odds ratio
OOS	Out-of-session
OZA	Ozanimod
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PBS	Pharmaceutical Benefits Scheme
PEG	Peginterferon beta-1a
PFS	Pre-filled syringe
PIRA	Progression independent of relapse activity
PK	Pharmacokinetics
PMR	Post-Market Review
PMS	Progressive multiple sclerosis
PON	Ponesimod
PPMS	Primary progressive multiple sclerosis
PRL	Paramagnetic rim lesion
PSD	Public Summary Document
QALY	Quality-adjusted life year

Abbreviation	Definition
R22	Rebif 22
R44	Rebif 44
RCT	Randomised controlled trial
RIS	Radiologically isolated syndrome
RMS	Relapsing multiple sclerosis
ROM	Ratio of means
RPBS	Repatriation Pharmaceutical Benefits Scheme
RR	Rate ratio
RRMS	Relapsing-remitting multiple sclerosis
RRR	Relative risk reduction
RSA	Risk-sharing arrangement
SAE	Serious adverse event
SC	Subcutaneous
SDP	Sustained disability progression
SIP	Siponimod
SMR	Standardised mortality ratio
SoC	Standard of care
SPA	Special Pricing Arrangement
SPMS	Secondary progressive multiple sclerosis
SPR	Statutory price reduction
TGA	Therapeutic Goods Administration
tolDC	Tolerogenic dendritic cell
Treg	Regulatory T cell
UTX	Ublituximab
VEP	Visual evoked potential

1. Introduction



1.1. Background

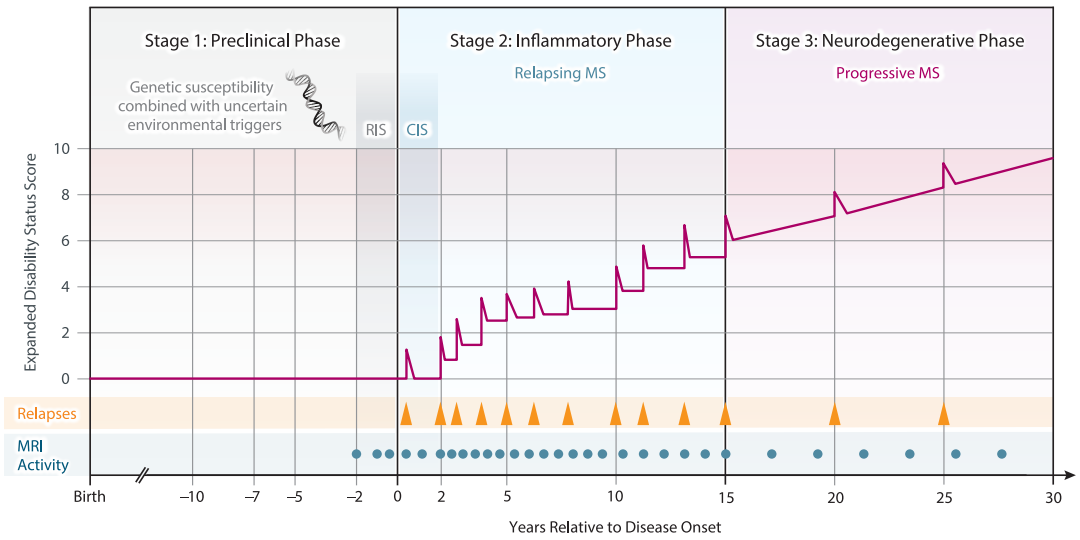
Multiple sclerosis (MS) is a progressive, chronic, immune-mediated neurological disease characterised by an inflammatory attack on myelin, the protective sheath surrounding nerve fibres in the central nervous system (CNS). Damage to myelin disrupts the efficient transmission of electrical signals, resulting in a wide range of neurological symptoms including visual disturbance, fatigue, pain, reduced mobility and coordination, cognitive impairment and mood changes as well as impairments to quality of life. Over time, ongoing inflammation and tissue injury can lead to axonal damage, scar formation, and irreversible neurological dysfunction and disability[1, 2].

Relapsing-remitting multiple sclerosis (RRMS) is the most common MS phenotype, accounting for approximately 85–90% of cases at diagnosis; a smaller proportion of people present with a progressive phenotype, primary progressive MS (PPMS). RRMS is characterised by episodes of acute neurological dysfunction, or relapses, followed by periods of partial or complete recovery. Over time, some people with RRMS transition to secondary progressive MS (SPMS), in which disability accumulates gradually and increasingly independently of relapse activity[3].

The burden of MS in Australia has increased substantially over recent decades. In 2024, an estimated 37,756 Australians were living with MS, compared with 25,607 in 2017 and 21,238 in 2010[4, 5]. Beyond its clinical consequences, MS imposes a considerable economic burden on individuals, carers, the healthcare system and broader society, with annual costs in Australia estimated to exceed $3 billion in 2024[5]. This burden is amplified by the age at which RRMS commonly affects individuals, with treatment initiation most frequent among those aged 40–44 years, with a predominance towards females (73.4%) (DUSC PBS utilisation analysis, February 2022[6]). As a result, MS contributes not only to substantial healthcare costs, but also to productivity losses during key working years.

The subsidisation of interferon beta-1b as the first disease-modifying therapy (DMT) for RRMS on the Pharmaceutical Benefits Scheme (PBS) in November 1996 marked a significant milestone in the treatment of MS in Australia. The advent of DMTs has fundamentally transformed the disease course and evolution of MS (Figure 1). In the pre-DMT era, one-third to one-half of people experienced progressive neurological disability within 15 years of onset and treatment was largely reactive, focusing on symptom control and rehabilitation[7-11]. Since the introduction of DMTs, and in particular high-efficacy DMTs, outcomes for people with MS have improved substantially, with fewer and less severe relapses, slower disease progression, reduced conversion to SPMS, and improvements in quality of life and life expectancy[12-15]. Consequently, modern and high-efficacy DMTs are now a cornerstone of MS management, with approximately two-thirds of individuals with MS receiving treatment during the course of their disease[5].

A The Traditional Model



B New Concepts in the Current Treatment Era

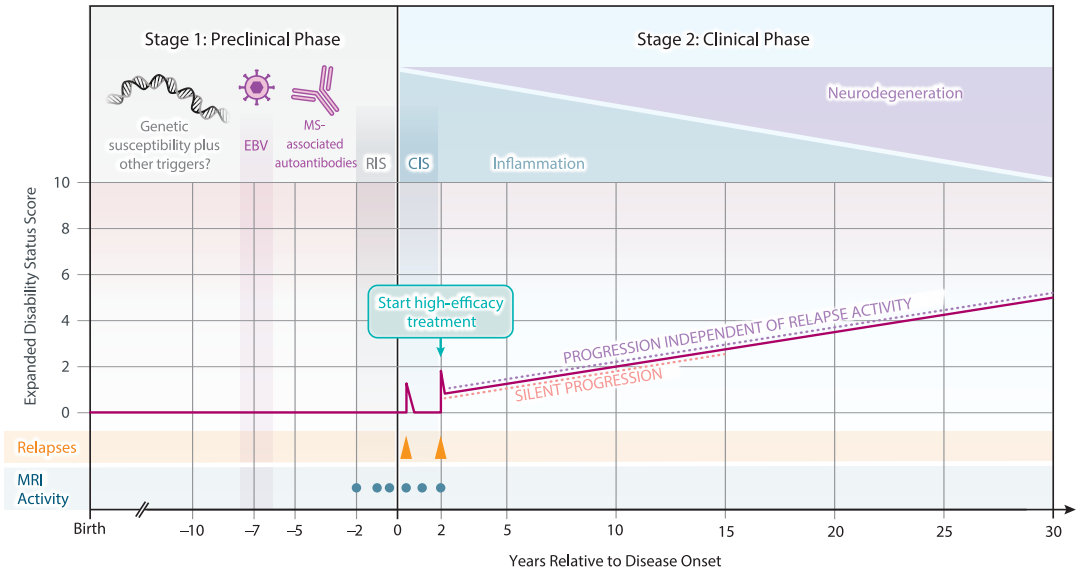


Figure 1: Evolving natural history / disease course of MS

Abbreviations: CIS, clinically isolated syndrome; EBV, Epstein-Barr virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; RIS, radiologically isolated syndrome

Notes: **Left panel=**Traditional concepts of the natural history of RRMS before the era of highly effective DMT. In the traditional model, disability accumulation was thought to result entirely from incomplete recovery from relapses, until clinically significant relapse-independent disability (SPMS) supervened, on average 15 to 16 years after clinical onset. Less commonly, PPMS developed without earlier relapses. **Right panel=**Most recent concepts of the disease course of MS in the current DMT era. With early treatment, attacks are prevented in most patients, but insidious progression independent of relapse activity (PIRA) or silent progression is now evident during the relapsing phase, which reveal that both inflammation and neurodegeneration are present throughout the disease course. In addition, the time to reach permanent disability milestones and SPMS is substantially lengthened.

Source: Hauser 2026[16] Figure 1

Over the past 30 years, people living with MS in Australia have gained subsidised access to an expanding range of DMTs through the PBS, reflecting substantial public investment in improving outcomes for people living with MS. During this period, 18 DMTs have been made available on the PBS for the treatment of MS, three of which have subsequently been delisted. The availability of multiple agents with differing mechanisms of action, efficacy profiles, safety considerations, and administration requirements has created a complex and evolving treatment landscape, whilst recognising the complex individual needs of people with MS.

This report was commissioned by MS Australia to mark 30 years since the first PBS-subsidised DMT became available in Australia. Over that period, access to DMTs has transformed outcomes for many people living with MS, changing expectations regarding disease progression, disability and quality of life. Beyond the benefits experienced by individuals, these advances have also had important impacts on families, carers, the health system and Australian society more broadly.

> “The thing I reflect on most is how different this is from the experience people with MS had ten-plus years ago. That high-efficacy medications like this exist at all is remarkable, and that they’re offered first-line in Australia, rather than only after years of damage, is something I don’t take for granted. Starting on a strong treatment early has given me stability that an earlier generation simply didn’t have access to.”
>
> **JODI MARTIN**
> **PERSON LIVING WITH MS**

Together, the increasing burden of MS, the substantial public investment in DMTs, and the growing complexity of treatment selection provide a strong rationale for evaluating the broader value of DMT availability in Australia. This assessment is particularly timely in light of the rapid Post-Market Review (PMR) of PBS medicines for MS initiated by the Pharmaceutical Benefits Advisory Committee (PBAC) in July 2026, which underscores the need to understand how current access arrangements, utilisation patterns and public expenditure align with clinical evidence and cost-effectiveness upon which reimbursement decisions were based. This report therefore examines how access and availability to PBS-subsidised DMTs have transformed clinical outcomes, economic impacts and societal value over time.

1.2 Project objectives

This study aims to assess the clinical, economic and societal value of DMTs for MS in Australia. The key objectives were to:

1. Demonstrate the importance of the availability and accessibility of DMTs in transforming outcomes for people with MS in Australia.
2. Assess how clinical, social and economic outcomes for people with MS have improved over time following the introduction and expansion of DMTs.
3. Examine the role of Government investment and reimbursement in enabling access to DMTs, and the returns generated from that investment.
4. Identify areas where unmet clinical and societal need remains, and consider implications for future treatment pathways, policy and investment.

2. MS treatment availability and supporting evidence



KEY POINTS

- The introduction of DMTs has transformed MS from a disease managed primarily through symptom control and rehabilitation into a treatable disease whose inflammatory activity and long-term course can be modified.
- The treatment landscape for MS has expanded from a small number of broadly comparable injectable therapies to a diverse range of oral, injectable and infusion DMTs with distinct mechanisms, efficacy, safety and administration profiles.
- Contemporary MS management is increasingly personalised, with treatment choice guided by disease phenotype, activity and prognosis, comparative efficacy and safety, administration and monitoring requirements, reproductive considerations, access and patient preferences.
- As incremental improvements in efficacy between DMTs have become apparent with newer-generation therapies, clinical guidance has shifted towards classifying therapies according to two- or three-tier efficacy frameworks; the most recent Australian and New Zealand consensus recommendations adopt a three-tier system of low-, intermediate- and high-efficacy DMTs. Current guidelines increasingly support early use of high-efficacy DMTs, particularly for people with active RRMS or poor prognostic features.
- Across clinical and radiological outcomes, DMTs reduce relapse activity, delay disability progression, suppress MRI lesion activity and brain volume loss, and increase the likelihood of achieving no evidence of disease activity (NEDA); newer high-efficacy therapies generally produce larger treatment effects than first-generation DMTs, yet no single DMT is optimal across all outcomes.
- Evidence and treatment options remain comparatively limited for progressive MS and progression independent of relapse activity (PIRA), reflecting the ongoing unmet need for therapies to address the underlying mechanisms driving progressive disease activity in MS.

Management of MS encompasses a range of therapeutic approaches, including treatment of relapses, management of symptoms and complications, rehabilitation, and therapies aimed at modifying the underlying disease course. Guidelines recommend corticosteroids for the treatment of moderate to severe relapses, while symptomatic management and rehabilitation remain important components of supportive care to help maintain quality of life. However, altering the trajectory of the disease itself was only made possible with the introduction of DMTs in the late 1990s, representing a fundamental shift in the management of MS.

The key goal of DMTs is to minimise disease activity and, where possible, achieve ‘no evidence of disease activity’ (NEDA), a composite measure indicating the absence of relapses, disability progression and new MRI lesion activity. As this report focuses on three decades of DMT availability in Australia, this section examines how treatment recommendations evolved in response to the expanding landscape, and how increasing therapeutic choice modified approaches to treatment selection and overall patient outcomes.

2.1 Evolution of treatments for management of MS

2.1.1. Pre-1990s: prior to the introduction of DMTs

For most of the 20th century, management of MS was limited to symptom control and rehabilitation, as no therapies had demonstrated an ability to modify the underlying disease course[17, 18]. The introduction of corticosteroids as a treatment in the 1960s provided additional benefit in terms of accelerating recovery following relapses, however corticosteroids had minimal effect on future relapses or disability progression[18]. Consequently, treatment goals centred on managing the consequences of disease rather than altering its trajectory.

Experimental approaches to disease modification were investigated throughout this period, but evidence remained insufficient to support routine clinical use, and guidelines in the late 1980s and early 1990s continued to distinguish established relapse and rehabilitative care from experimental immunomodulatory therapies – consistently viewing these therapies with caution. This attitude was illustrated by guidance noting that many MS researchers themselves said that *"they could not be prepared to be randomised into trials of immunosuppression or treatment with interferon"*, reflecting the considerable uncertainty surrounding the efficacy and clinical use of these emerging therapies[19].

Thus, prior to the introduction of DMTs, MS was largely viewed as an untreatable disease, whose long-term progression could not be prevented.

2.1.2 The 1990s to early 2000s: emergence of DMTs

The emergence of DMTs in the early 1990s fundamentally changed the treatment landscape by demonstrating that disease activity and relapse frequency could be modified. Following Food and Drug Administration (FDA) approval of interferon beta-1b in 1993, guideline recommendations increasingly reflected the growing confidence in immunomodulatory treatment, describing interferon beta as a well-tolerated therapy capable of reducing relapses and slowing disability[20]. Interferon beta-1b received Australian regulatory approval by the Therapeutic Goods Administration (TGA) in 1995 and was subsequently listed on the PBS in 1996, marking the introduction of subsidised access to DMTs into Australian MS care (see Section 3.2 for PBS listing timelines).

Interferon beta-1b was soon followed by additional first-generation DMTs, including interferon beta-1a and glatiramer acetate, overtaking standard of care for MS and establishing a small but expanding treatment landscape for RRMS[21]. Notably, interferon beta was also recommended for SPMS by the European Medicines Agency (EMA) in 1999, reflecting the first treatment capable of delaying the neurological deterioration associated with the disease[21, 22]. By 1999, guidelines stated that, based on Phase III trial evidence for these first-generation DMTs, *"MS is considered to be a treatable disease"*, representing a marked shift from the 1978 guidance, which described treatment as focused on minimising the effects of MS rather than modifying its course[17, 23].

Standard of care remained relatively stable throughout this period, with interferons and glatiramer acetate becoming established as the principal DMTs for RRMS[24]. These therapies were generally considered to have comparable efficacy, and treatment recommendations placed relatively little emphasis on selecting one therapy over another. In the case of treatment failure, switching between interferons and glatiramer acetate was recommended, reflecting a treatment paradigm that valued the therapies to be broadly equivalent in terms of benefit and associated risk[25]. The mid-2000s would see the emergence of DMTs with greater efficacy, that would not only expand treatment availability, but influence the way treatments were selected, and that would improve overall disease outcomes.

2.1.3. Mid-2000s to present: efficacy-based classification of DMTs

A second major shift in MS management emerged during the late 2000s as higher-efficacy therapies became available. The emergence of natalizumab in 2004 (the first monoclonal antibody to receive FDA approval for MS), followed by fingolimod, cladribine and other highly effective agents, introduced meaningful differences in efficacy between available therapies; and with several

additional high-efficacy therapies (e.g., alemtuzumab, daclizumab, ocrelizumab) undergoing investigation through clinical trials, this increasingly challenged the assumption that all DMTs should be considered broadly equivalent[26, 27].

This expansion of the treatment landscape prompted growing consideration of treatment selection and sequencing. Initial recommendations typically positioned higher-efficacy therapies as second-line treatments within escalation strategies, reserving them for people with ongoing disease activity despite treatment with established first-line therapies (i.e., first-generation DMTs with lower efficacy)[28].

Importantly, this increasing clinical differentiation was not always reflected in reimbursement settings. For example, when natalizumab was considered for PBS listing in 2006–07, imposing restrictions requiring prior treatment failure were not accepted, as the clinical evidence was derived from treatment-naïve populations and such requirements would *"unnecessarily dictate clinical practice in an area where a standard treatment algorithm has not been established"*[29, pg. 7]. Further distinctions between clinical guidance and reimbursement policy are explored in Section 3.3.

As evidence accumulated and the availability of DMTs increased, treatment selection began to move beyond a simple distinction between first- and second-line therapy. Some guidelines began to support the use of higher-efficacy therapies from disease outset, particularly in people with active disease or poor prognostic markers to combat disease progression earlier in the disease course[28]; and disease activity, prognosis and relative treatment efficacy became increasingly influential determinants of treatment choice[30].

The Australian and New Zealand expert consensus review published in 2014 captured this transition, highlighting substantial differences in efficacy between available DMTs (Figure 2). The recommendations retained an escalation approach to treatment selection, with interferons, glatiramer acetate and teriflunomide recommended as initial options for active RRMS and escalation to higher-efficacy therapies (i.e., fingolimod, dimethyl fumarate, natalizumab or alemtuzumab) recommended in the presence of ongoing disease activity. However, higher-efficacy treatment could also be considered from disease outset in people with poor prognostic indicators[30].

Drug[ref]	β-interferon 1a IM[70, 71]	Laquinimod[23]	Azathioprine[72]	Glatiramer acetate[73, 74]	β-interferon 1b S/C[75, 76]	Teriflunomide[3]	β-interferon 1a S/C[77, 78]	Fingolimod[79]	Dimethyl fumarate[9, 80]	Natalizumab[81, 82]	Alemtuzumab*[15, 16]
Year of study	1993	2010	1993	1992	1990	2008	1995	2009	2010	2004	2012
ARR (placebo)	0.82	0.30	0.43	0.84	1.27	0.54	1.28	0.40	0.36	0.73	0.67
Relapses (ARR RRR)	18%	23%	23%	29%	34%	32%	32%	55%	53%	68%	67%
Disability (3m SDP RRR)	37%	36%	42%	12%	25%	30%	29%	30%	38%	54%	52%
New Gad Lesions (RRR)	52%	37%		33%	43%	80%	88%	82%	90%	92%	94%
New T2 Lesions (RRR)	33%	30%		31%	63%	77%	78%	75%	85%	83%	83%
Brain Atrophy (BPF RRR)	18%	30%		11%†	21%‡	25%	32%	36%	21%#	2%	57%

Key	0-19%	20-39%	40-59%	60-79%	80-100%

Figure 2: Comparison of 2-year efficacy for treatments for RRMS in an Australian review (2014)

Abbreviations: ARR, annualised relapse rate; BPF, brain parenchymal fraction; Gad, Gadolinium-enhancing; m, months; IM, intramuscular; RRMS, relapsing-remitting multiple sclerosis; RRR, relative risk reduction; SC, subcutaneous; SDP, sustained disability progression

Source: Adapted from Broadley 2014[31]

The growing differentiation in treatment efficacy is also reflected in how clinical guidelines classified DMTs. As the number of available therapies increased, efficacy-based categorisation became an increasingly common feature of international treatment recommendations (Table 1). Early frameworks by the Association of British Neurologists (ABN) generally distinguished between moderate- and high-efficacy therapies, reflecting that some DMTs produced substantially greater reductions in disease activity than first-generation DMTs[32]. Other guidelines simply named treatments which were grouped to be more efficacious than others (e.g., American Academy of Neurology, Arabian Gulf expert consensus, etc.), highlighting the increasing recognition of these broader efficacy categories. However, as additional therapies emerged and differences in efficacy became increasingly apparent, some guidelines adopted three-level classifications to better characterise the expanding range of treatment options. For example, the German Neurological Society guidelines classify DMTs into three efficacy categories based on their effects on relapse rate, MRI activity and relapse-related progression[33].

By the 2020s, three-level efficacy classifications were appearing more frequently within clinical guidance, although the specific therapies included within each category varied between frameworks. The most recent Australian and New Zealand clinical practice guidelines similarly distinguish between low-, intermediate- and high-efficacy DMTs, reflecting the increasing use of a three-tier approach to DMT classification in Australian practice[34].

Table 1: Differentiation of DMT efficacy in local and international treatment guidelines

Year	Guideline/consensus	Efficacy classification
2014	Australia and New Zealand expert consensus review	Higher efficacy: fingolimod, DMF, natalizumab, alemtuzumab.
2015	Association of British Neurologists	Drugs of moderate efficacy: IFN-β, GA, teriflunomide, DMF, fingolimod Drugs of high efficacy: alemtuzumab, natalizumab
2018	American Academy of Neurology	Higher efficacy: alemtuzumab, natalizumab, fingolimod and ocrelizumab Compared to previously approved self-injectable DMTs (IFN, GA, etc)
2018	Brazilian Academy of Neurology and Brazilian Committee on Treatment and Research in Multiple Sclerosis	Higher-potency drugs: alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab
2020	Arabian Gulf expert consensus	Platform DMTs: IFN-β, GA, teriflunomide, DMF Agents of higher-efficacy: cladribine, DMF, fingolimod, natalizumab, ocrelizumab, alemtuzumab
2021	German Neurological Society (*Deutsche Gesellschaft für Neurologie*)	Efficacy category 1: IFN-beta, DMF, GA, teriflunomide Efficacy category 2: cladribine, fingolimod, ozanimod Efficacy category 3: alemtuzumab, ocrelizumab, rituximab, natalizumab
2021	Multiple sclerosis therapy consensus group	Mild/moderate: IFN-β, GA, DMF, teriflunomide, *azathioprine* Highly-active (first/second-line): alemtuzumab, cladribine, ocrelizumab, natalizumab, ofatumumab, fingolimod, ozanimod, ponesimod
2025	Australia and New Zealand consensus recommendations	Low-efficacy therapy: NR Intermediate-efficacy therapy: NR High-efficacy therapy: natalizumab, ocrelizumab, ofatumumab, cladribine

Year	Guideline/consensus	Efficacy classification
2025	Switzerland Delphi Study	Low efficacy: glatiramer acetate, interferon beta, teriflunomide Medium efficacy: fumarates, S1P modulators, cladribine High efficacy: alemtuzumab, anti-B-cell therapy, natalizumab
2025	Canadian consensus recommendations	Lower-efficacy agents: fingolimod, ozanimod, ponesimod, IFN-β-1a, teriflunomide, and other lower-efficacy oral agents Higher-efficacy DMTs: natalizumab, ocrelizumab, ofatumumab, alemtuzumab, cladribine
2026	Australian Therapeutic Guidelines	Lower-efficacy: DMF, diroximel fumarate, teriflunomide, IFN-β-1b, peginterferon beta-1a, GA High-efficacy: alemtuzumab, natalizumab, ocrelizumab, ofatumumab, fingolimod, ozanimod, siponimod, cladribine

Abbreviations: DMF, dimethyl fumarate; DMTs, disease-modifying therapies; GA, glatiramer acetate; IFN-β, interferon beta; NR, not reported

Source: Broadley 2014[30]; Scolding 2015[32]; Rae-Grant 2018[35]; Marques 2018[36]; Alroughani 2020[37]; Bayas 2021[33]; Wiendl 2021[28]; Shipley 2025[34]; Yaldizli 2025[38]; Freedman 2025[39]; Therapeutic Guidelines 2025[40]

Similarly, the wider literature is beginning to adopt three-level classifications of DMTs. A review of high efficacy therapy strategies implemented in people with MS in the US stratifies DMTs into low-, moderate-, and high-efficacy categories based on impact on relapse rates[41]; a Swiss registry analysis investigating the effect of escalation of DMTs uses low-, medium- and high-efficacy classifications[42]; and a retrospective case-control study using machine learning to model disease progression in MS categorises therapies by low-, intermediate- and high-efficacy tiers[43].

The increasing adoption of efficacy-based classifications reflects a broader shift in MS management. As the number of available DMTs expands and differences in treatment efficacy have become more apparent, DMTs are no longer considered clinically interchangeable. Consequently, treatment selection has become increasingly personalised, with efficacy considered alongside factors such as disease activity, prognosis, safety and preference when determining the most appropriate treatment strategy[34].

2.1.4. Differences between international and Australian treatment availability

Several DMTs are funded or available internationally but not within Australia. Ponesimod is recommended by NICE (National Institute for Health and Care Excellence) for adults with active RRMS and is funded in the UK; however, is not PBS-listed in Australia. Although ponesimod received TGA approval on 11 March 2022, its Australian registration was subsequently cancelled by the Sponsor (Janssen-Cilag Pty Ltd) in March 2026. Monomethyl fumarate is FDA-approved in the US for relapsing forms of MS, including RRMS and active SPMS, but is not registered in Australia, though other fumarates are available. Ocrelizumab is recommended by NICE for early PPMS with imaging features of inflammatory activity and has been funded for the same indication in New Zealand since September 2023. However, despite being registered for PPMS in Australia, it is not PBS-subsidised, with PBAC submissions seeking PBS listing being unsuccessful in November 2017 and July 2020. Notably, there are currently no subsidised treatments for PPMS in Australia, representing a significant unmet clinical need and a longstanding gap between Australian and international treatment availability.

"There are currently no subsidised treatments for PPMS in Australia, representing a significant unmet clinical need and a longstanding gap between Australian and international treatment availability"

2.2. Current treatment recommendations in Australia

Current Australian clinical guidance emphasises early diagnosis, timely treatment initiation, and ongoing management of relapses, symptoms and lifestyle factors. DMTs are recommended to reduce disease activity and limit relapse and disability progression. As the number of available DMTs has expanded, treatment decision-making has become increasingly individualised. Contemporary management is no longer focused solely on whether a person should receive a DMT, but rather which therapy is most appropriate for an individual's disease characteristics, prognosis and treatment goals. Treatment selection therefore involves balancing expected efficacy against treatment-related risks, route and frequency of administration, monitoring requirements, accessibility, reproductive considerations, and patient preferences.

The following sections summarise the principal factors influencing treatment selection in contemporary Australian practice, as outlined in the Australian and New Zealand expert consensus recommendations[34, 44], and the Therapeutic Guidelines for MS [40].

2.2.1. Disease phenotype

Disease phenotype is one of the first considerations in treatment selection, as the clinical course of MS varies between RRMS, SPMS, PPMS, and the earlier disease states of clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS).

In Australia, most currently available DMTs are indicated for relapsing forms of MS, while interferons and ocrelizumab are additionally indicated for progressive forms of MS (SPMS and PPMS, respectively), and siponimod is indicated for SPMS alone. However, evidence supporting DMT use in progressive MS, particularly PPMS, remains more limited than in relapsing disease. Consequently, current guidance recommends careful consideration of the likelihood of slowing disability progression relative to treatment-related risks when making treatment decisions for these individuals. Notably, despite TGA registration, ocrelizumab is not currently subsidised through the PBS for PPMS.

Disease phenotype also influences treatment decisions early in the disease course. DMTs such as glatiramer acetate, interferon beta, and teriflunomide have demonstrated efficacy in reducing the risk of clinically definite MS for people with CIS and at least two T2 lesions. Thus, individuals experiencing a first demyelinating event suggestive of MS should be considered for DMTs where MRI findings or other clinical characteristics indicate a high risk of future disease activity. Although no DMT is currently subsidised through the PBS specifically for CIS, interferon beta and glatiramer acetate are TGA-registered for use in selected high-risk people with CIS.

Individuals with RIS are not currently recommended for treatment with DMTs, with the benefit of DMT-intervention for this population currently under investigation. Although recent studies have demonstrated some benefit with DMT use in extending the time to a first clinical demyelinating event in people with RIS, the evidence remains limited, and there are no registered nor subsidised DMTs for this group. Thus, guidelines recommend that people with RIS be monitored for the development of clinical manifestations and new demyelinating lesions on MRI at least annually for at least five years, and that advice from MS specialist neurologists be sought in treatment decisions.

2.2.2. Approaches to treatment initiation

As discussed in the previous section, two broad treatment initiation strategies are recognised: escalation and induction. Escalation involves commencing treatment with a lower-efficacy therapy and transitioning to a more effective agent if disease activity persists; whereas induction involves initiating treatment with a high-efficacy therapy from the outset.

Treatment initiation decisions involve balancing the greater efficacy associated with early high-efficacy treatment against the increased monitoring requirements, adverse effects and potential long-term risks associated with these therapies. However, as increasing evidence suggests that neurological damage accumulates earlier in the disease course and may only be partially reversed once established, guidance has shifted towards the induction approach to prevent disease activity and disability accumulation earlier in the disease course.

Reflecting this evidence, current Australian and New Zealand consensus recommendations favour early use of high-efficacy DMTs for people with RRMS, particularly those with features associated with poor prognosis[34]. High-efficacy therapies identified in the recommendations include natalizumab, ocrelizumab, ofatumumab and cladribine; with evidence suggesting that early use of these therapies provides greater protection against relapse and disability progression than escalation approaches. However, lower- and intermediate-efficacy therapies remain appropriate in selected circumstances following consideration of the balance between efficacy, safety, and most importantly, patient preference.

2.2.3. Switching, sequencing and discontinuation of DMTs

Treatment decision-making in MS extends beyond treatment initiation. Ongoing monitoring of disease activity, treatment tolerability and personal circumstances means that DMT selection is increasingly viewed as an ongoing process throughout the disease course. Treatment is reassessed following initiation after being on and adherent to a DMT for a sufficient time for it to be fully effective. Switching to an alternative DMT may be recommended where there is lack of treatment efficacy, evidence of breakthrough clinical or radiological disease activity, unacceptable adverse effects, changing reproductive considerations, or emerging safety concerns that alter the balance of benefit and risk.

The choice of subsequent therapy depends on the reason for switching, prior treatment exposure, comparative efficacy and safety, and the potential for rebound disease activity when some therapies are discontinued. A washout period may be needed when switching therapies to reduce the risk of toxicity, particularly for DMTs with prolonged immunological effects.

In terms of discontinuation, there is insufficient evidence with existing DMTs regarding the risk-benefit of discontinuing ongoing therapy. Discontinuation may be associated with an increased risk of relapse, disability progression, and radiological disease activity in people with RRMS; thus, continuation of treatment is recommended in people who are clinically stable and not experiencing any significant adverse effects. However, in older people or those with progressive disease, the balance between treatment benefit and adverse effects may change and the discontinuation or de-escalation of their DMT regimen may be considered on an individual basis with continued clinical and radiological monitoring.

2.2.4. Autologous haematopoietic stem cell transplantation

The position of autologous haematopoietic stem cell transplantation (aHSCT) within current treatment guidelines highlights the trade-off underlying MS treatment decision-making: maximising treatment efficacy and disease control while minimising treatment-related harm.

aHSCT involves the collection of a person's haematopoietic stem cells, administration of conditioning chemotherapy, and reinfusion of the stem cells to reconstitute the immune system. Although aHSCT is widely regarded as a highly effective approach for achieving sustained disease control and NEDA, its use is limited by the substantial risks associated with intensive immune suppression. These risks may include infection, secondary autoimmune disease, secondary malignancy, endocrine dysfunction, infertility, cardiovascular disease and rarely, death[34].

Consequently, current Australian recommendations reserve aHSCT for carefully selected patients with RRMS and highly active inflammatory disease who continue to experience clinical or radiological disease activity despite treatment with high-efficacy DMTs. To date, over 120 people with MS have received aHSCT in Australian teaching hospitals. Current guidance recommends referral of appropriate patients for review by the Australian aHSCT Committee.

2.2.5. Summary

Collectively, current Australian and international treatment recommendations reflect a shift towards increasingly personalised management of MS. Treatment selection is no longer based solely on disease diagnosis, but rather on the combination of disease phenotype, disease activity, prognostic

indicators, comparative efficacy and safety considerations, administration factors, monitoring requirements, and patient preference.

The growing availability of DMTs with differing efficacy and safety profiles has expanded opportunities for individualised treatment while simultaneously increasing the complexity of clinical decision-making. Current guidance recommends shared decision-making between clinicians and people with MS, recognising the need to balance treatment efficacy against treatment-related risks and individual preferences. Consequently, treatment strategies aim not only to reduce relapses and delay disability progression, but also to preserve neurological function, maintain quality of life and support long-term treatment adherence.

2.3. Clinical rationale and evidence supporting DMT use

The primary goal of DMTs is to minimise disease activity, delay disability accumulation and preserve neurological function over the course of the disease. Given the large and evolving evidence base for the increasing number of available DMTs, this section draws primarily on recent systematic reviews and network meta-analyses to provide an overview of the clinical rationale supporting DMT use.

2.3.1. Outcomes used to assess DMT benefit

The effectiveness of DMTs has to date, been assessed using a range of clinical and radiological outcomes that capture different aspects of disease activity and progression. Relapses, disability progression, MRI lesion activity, and quality of life form the principal outcome measures used in clinical trials to evaluate treatment response in MS[45].

Rate of relapse and the Expanded Disability Status Scale (EDSS) have been the most widely used measures in MS for evaluating the comparative efficacy of DMTs to date. Relapses reflect episodes of inflammatory disease activity; however, their evaluation is limited by the relative rarity of events and variation in how relapses are defined across studies[45]. Relapse-based outcomes are also less informative in progressive forms of MS. In contrast, EDSS is applicable across disease phenotypes and provides an indication of long-term disability accumulation and disease progression. However, EDSS is strongly driven by walking ability, and therefore largely underrepresents upper-extremity function and neuropsychological disability impacts of MS.

Additional outcomes are often used alongside relapse and disability measures to provide a more comprehensive assessment of disease activity. MRI outcomes (including new or enlarging T2 lesions and contrast-enhancing lesions) are important markers of inflammatory activity and can identify subclinical disease progression that may not be evident through clinical assessment alone. The timed 25-foot walk test (T25FW) is useful for quantifying changes in walking ability over time and has an important role in evaluating disease progression in progressive forms of MS. Similarly, the nine hole peg test (9HPT) may provide additional information on upper-limb function, particularly in people with advanced disability where walking-based measures are less informative.

As no single outcome fully captures disease activity, composite measures have been developed and are supported by clinical guidelines for use in the evaluation of DMTs[40]. The most widely recognised composite outcome is NEDA, particularly NEDA-3, which combines the absence of relapses, disability progression, and new MRI lesions. NEDA is increasingly used to assess overall disease control and treatment effectiveness. More recent frameworks, such as NEDA-4, additionally incorporate brain volume loss, although these approaches remain less widely adopted.

The following sections focus on relapse activity, disability progression, MRI activity, and NEDA as the principal outcomes informing efficacy of DMTs.

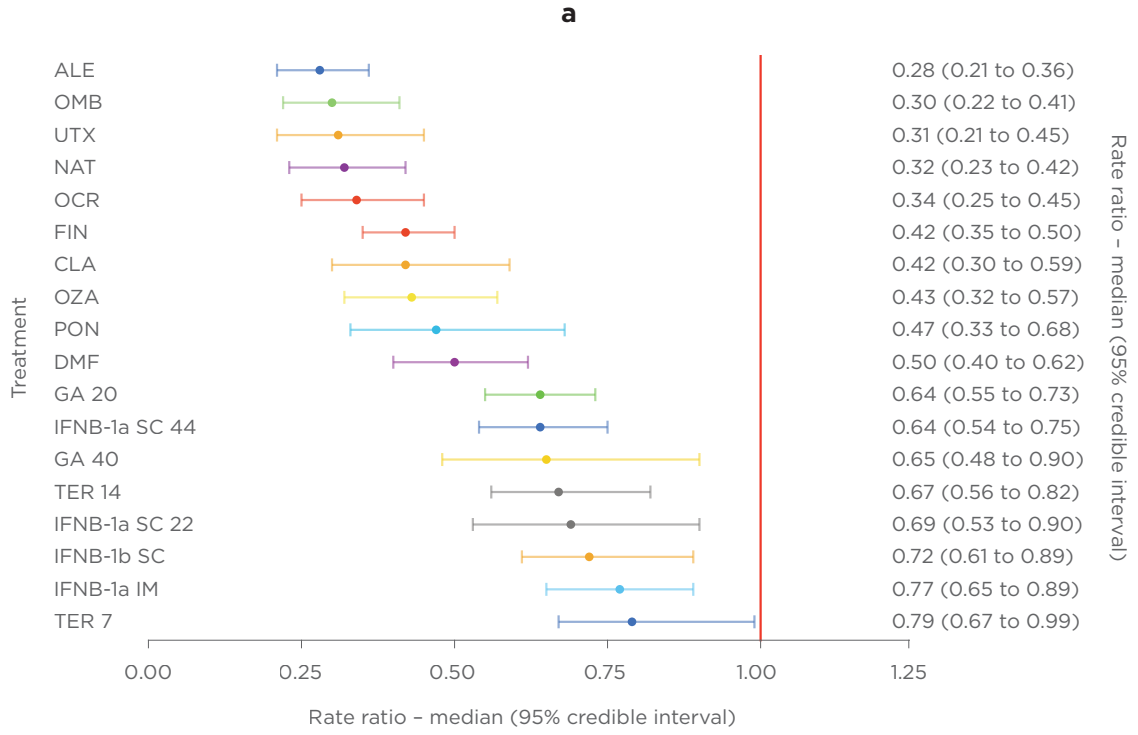
2.3.2. Comparative efficacy of DMTs in relapsing MS

RELAPSE

A substantial body of clinical evidence demonstrates that DMTs modify the course of relapsing MS, reducing relapse activity and delaying the accumulation of disability. A systematic literature review and Bayesian network meta-analysis (NMA) by Samjoo[12] compared up to 19 DMTs based on annualised relapse rate (ARR) and 3-month and 6-month confirmed disability progression (CDP), incorporating up to 39 RCTs in total. The NMA found that treatment effects consistently and significantly favoured active DMTs over placebo for ARR, with rate ratios (RRs) ranging from 0.28 for alemtuzumab to 0.79 for teriflunomide 7 mg. Monoclonal antibody therapies generally produced the largest reductions in relapse frequency, with alemtuzumab, ofatumumab and ublituximab ranked among the three most efficacious treatments for ARR (RRs ranging from 0.28 to 0.31). Importantly, while first-generation DMTs such as interferons and glatiramer acetate remained effective at reducing relapses relative to placebo (RRs ranging from 0.64 to 0.79), they generally demonstrated smaller treatment effects than many subsequently developed therapies (Figure 3a).

These findings were consistent with the ICER[46] NMA of 20 RCTs, in which all the DMTs evaluated were significantly more effective than placebo in reducing ARR. The monoclonal antibody therapies demonstrated broadly similar treatment effects and were among the most efficacious therapies assessed, reducing ARR by approximately 70% relative to placebo. Greater variation was observed among oral DMTs, although these therapies also reduced ARR by approximately 50% on average, with ponesimod demonstrating the largest treatment effect among the oral therapies evaluated (RR: 0.46). Overall, the analysis supported high efficacy of monoclonal antibody therapies and intermediate efficacy of oral DMTs in terms of reducing relapse activity. Notably, the most recently introduced therapy within each class, ublituximab among monoclonal antibodies and ponesimod among oral DMTs, demonstrated the largest treatment effect within its respective class, consistent with incremental gains in efficacy as newer therapies have entered the treatment landscape [46] (Figure 3c).

The variation observed among oral DMTs was examined more closely by Zhao[47], a NMA of 15 RCTs (n=14,869) focusing on DMTs by oral route of administration. Across ARR, most oral therapies demonstrated larger estimated treatment effects than glatiramer acetate and interferon beta-1a, with the exception of siponimod 0.5 mg, which was assessed at a dose below the standard maintenance dose, and laquinimod, which is not registered for use in Australia but is widely accepted as a low- to moderate-efficacy DMT (Figure 3b). Together, these findings suggest that, although disease modification is a consistent feature across DMTs, meaningful differences in efficacy have emerged as the treatment landscape has expanded.



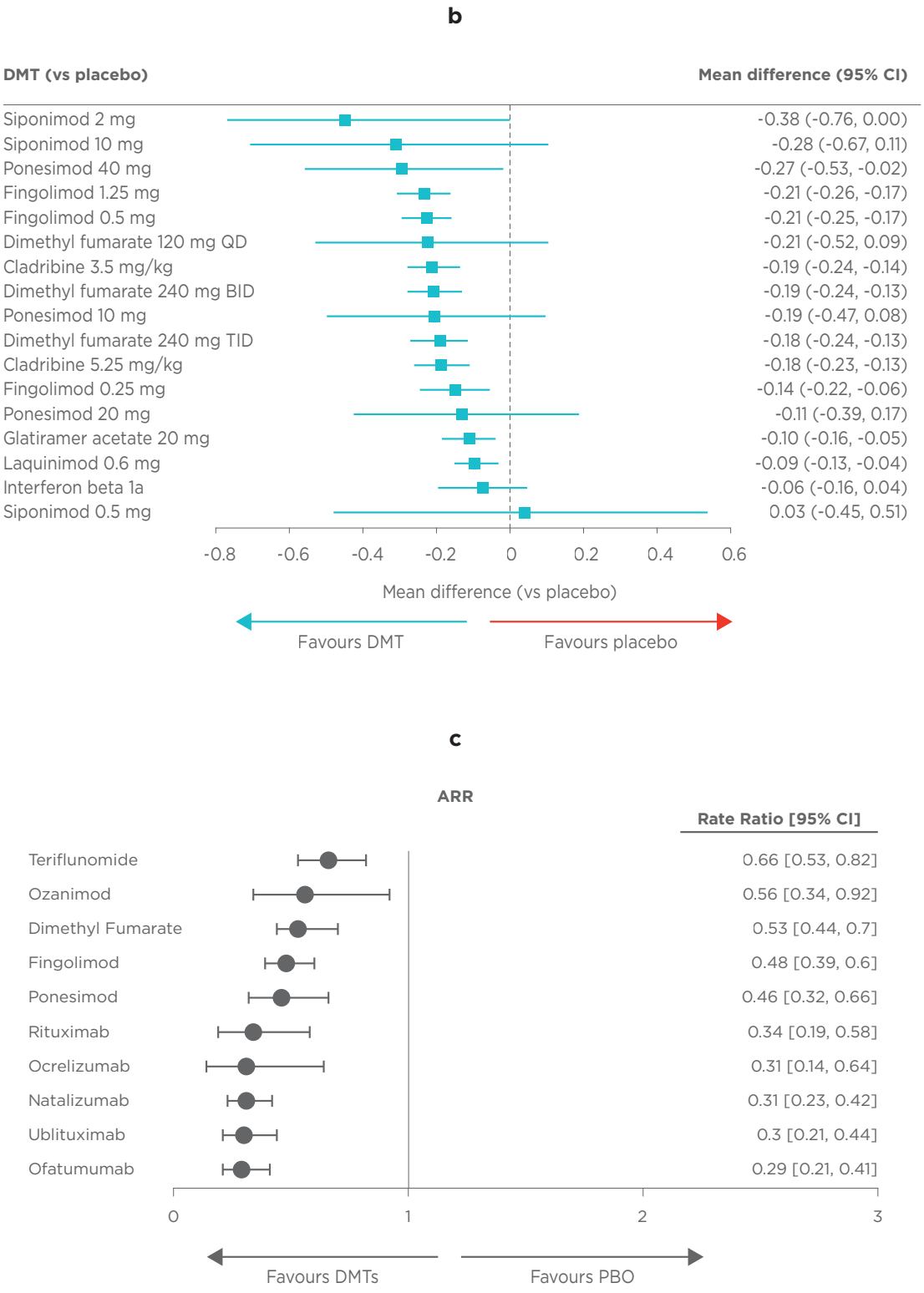


Figure 3: Forest plots of ARR: a) DMTs vs placebo (Samjoo 2023); b) oral DMTs vs placebo (Zhao 2026); c) DMTs vs placebo (ICER 2023)

Abbreviations: ALE, alemtuzumab 12 mg; ARR, annualised relapse rate; BID, twice a day; CI, confidence interval; CLA, cladribine 3.5 mg/kg; DMF, dimethyl fumarate 240 mg twice a day; DMT, disease-modifying therapy; FIN, fingolimod 0.5 mg; GA 20, glatiramer acetate 20 mg; GA 40, glatiramer acetate 40 mg; IFNB-1a IM, interferon beta-1a 30 µg intramuscular; IFNB-1a SC 22, interferon beta-1a 22 µg subcutaneous; IFNB-1a SC 44, interferon beta-1a 44 µg subcutaneous; IFNB-1b SC, interferon beta-1b 250 µg subcutaneous; NAT, natalizumab 300 mg; OCR, ocrelizumab 600 mg; OMB, ofatumumab 20 mg; OZA, ozanimod 1.0 mg; PBO, placebo; PON, ponesimod 20 mg; TER 7, teriflunomide 7 mg; TER 14, teriflunomide 14 mg; UTX, ublituximab 450 mg. [Doses in abbreviation list relate to Samjoo 2023]

Source: Samjoo 2023[12] Figure 3; Based on Zhao 2026[47] Supplementary Table 16; ICER 2023[46] Figure 3-1

While the comparative efficacy estimates on ARR presented above are primarily derived from RCTs, evidence from observational studies appears broadly consistent. Verweij[48] found no significant conflict between RCT and observational evidence for most treatment comparisons between DMTs and placebo, although observational studies generally reported larger treatment effects and greater heterogeneity, as would be expected in uncontrolled real-world settings. This suggests that RCT findings broadly reflect treatment effectiveness in clinical practice, while also highlighting the influence of individual patient characteristics and treatment selection on observed outcomes.

DISABILITY PROGRESSION

DMTs have similarly demonstrated significant benefits in delaying disease progression, as measured by the EDSS. Samjoo[12] assessed time to 3-month and 6-month CDP in 28 and 25 RCTs, respectively, using an EDSS definition of progression (i.e., an increase of ≥0.5 points in EDSS score from a baseline score of >5.5 or an increase of ≥1-point from a baseline score of 0 to 5.5).

Across both time points, active DMTs consistently demonstrated benefit relative to placebo. As observed for ARR, monoclonal antibody therapies ranked amongst the most efficacious treatments with hazard ratios (HR) for 3-month CDP ranging between 0.40 to 0.58 and HRs for 6-month CDP ranging between 0.43 to 0.54. First-generation DMTs tended to demonstrate smaller treatment effects (HR: 0.71 to 0.85 for 3-month CDP and 0.72 to 0.88 for 6-month CDP; Figure 4a and Figure 4b). Notably, the HR for 6-month CDP with ozanimod versus placebo was 1.01; however, this estimate was associated with a very wide confidence interval, indicating considerable uncertainty around the treatment effect. Consequently, no meaningful conclusions can be drawn from this comparison, and the overall evidence continued to favour active treatment over placebo.

Of note, there was no single treatment that was consistently the most efficacious across the 3-month CDP and 6-month CDP outcomes. Furthermore, although some therapies consistently ranked among the most efficacious across outcomes, the therapies demonstrating the greatest effects on disability progression were not always the same as those showing the greatest reductions in relapse activity. This suggests that treatment benefits may differ across clinical outcomes and reinforces the importance of considering multiple dimensions of disease control when selecting treatments.

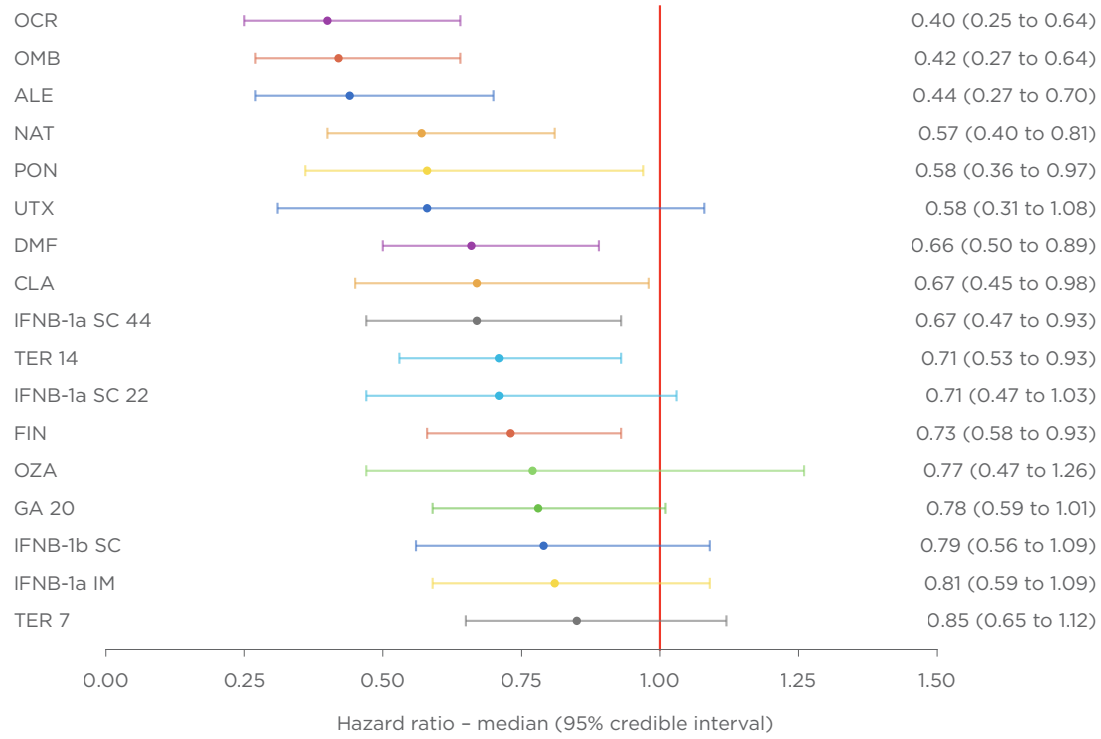
"No single therapy consistently demonstrated the greatest benefit across all outcome measures, suggesting that different treatments may offer advantages across different aspects of disease activity and progression. Therefore, treatment selection extends beyond efficacy alone."

Consistent findings were reported in the ICER[46] NMA, in which the monoclonal antibody therapies demonstrated a greater magnitude of benefit versus placebo than the oral DMTs for both 3-month and 6-month CDP. Notably, ublituximab, which was among the most efficacious therapies for relapse reduction, did not demonstrate a significant difference versus placebo for either 3-month CDP (HR: 0.57 [95% CI: 0.3, 1.13]) or 6-month CDP (HR: 0.52 [95% CI: 0.24, 1.15]; Figure 4), although the point estimates were consistent with those observed across the monoclonal antibody class. These findings indicate that the relative benefits of individual DMTs vary across clinical outcomes, and that treatment selection should be guided by the particular needs and disease characteristics of each person.

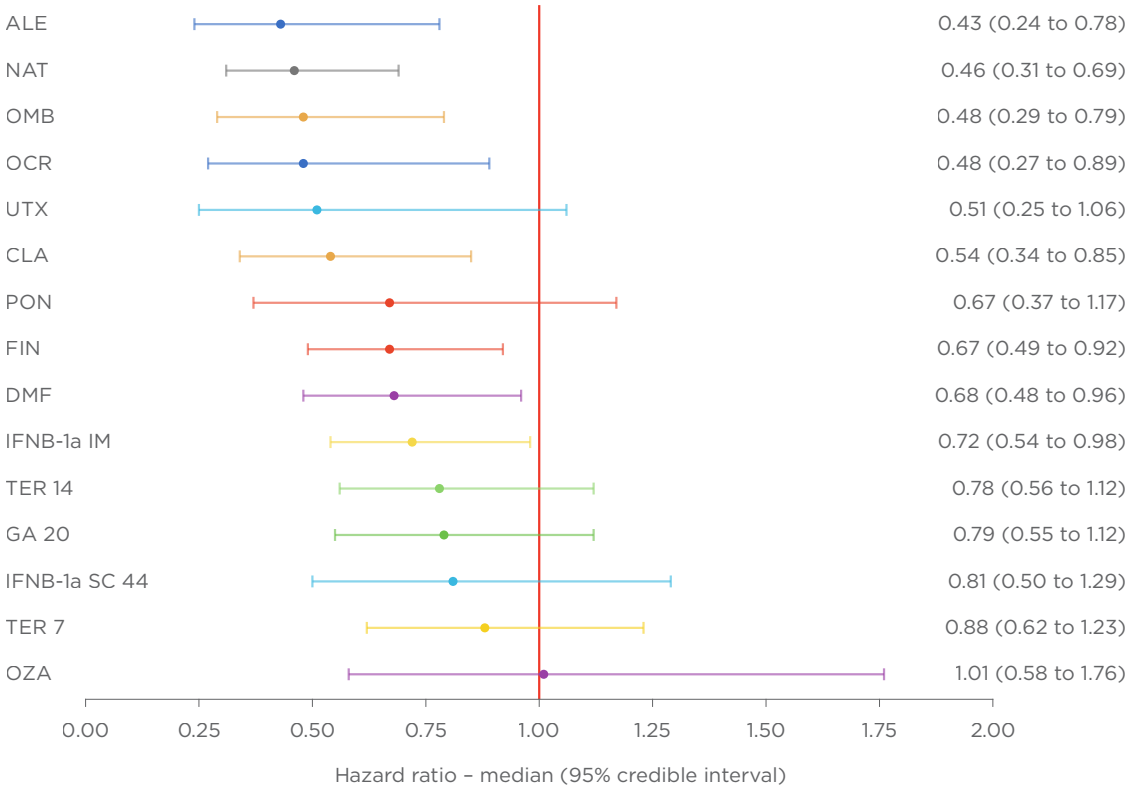
"Treatment decisions are highly personalised and are based on disease activity, response to previous therapies, side effects, medical history, lifestyle, and patient preference. What works well for one person may not be appropriate for another."

ROWENA AUCHTERLONIE
PERSON LIVING WITH MS

a


OCR 0.40 (0.25 to 0.64)
OMB 0.42 (0.27 to 0.64)
ALE 0.44 (0.27 to 0.70)
NAT 0.57 (0.40 to 0.81)
PON 0.58 (0.36 to 0.97)
UTX 0.58 (0.31 to 1.08)
DMF 0.66 (0.50 to 0.89)
CLA 0.67 (0.45 to 0.98)
IFNB-1a SC 44 0.67 (0.47 to 0.93)
TER 14 0.71 (0.53 to 0.93)
IFNB-1a SC 22 0.71 (0.47 to 1.03)
FIN 0.73 (0.58 to 0.93)
OZA 0.77 (0.47 to 1.26)
GA 20 0.78 (0.59 to 1.01)
IFNB-1b SC 0.79 (0.56 to 1.09)
IFNB-1a IM 0.81 (0.59 to 1.09)
TER 7 0.85 (0.65 to 1.12)
0.00 0.25 0.50 0.75 1.00 1.25 1.50
Hazard ratio – median (95% credible interval)

b


ALE 0.43 (0.24 to 0.78)
NAT 0.46 (0.31 to 0.69)
OMB 0.48 (0.29 to 0.79)
OCR 0.48 (0.27 to 0.89)
UTX 0.51 (0.25 to 1.06)
CLA 0.54 (0.34 to 0.85)
PON 0.67 (0.37 to 1.17)
FIN 0.67 (0.49 to 0.92)
DMF 0.68 (0.48 to 0.96)
IFNB-1a IM 0.72 (0.54 to 0.98)
TER 14 0.78 (0.56 to 1.12)
GA 20 0.79 (0.55 to 1.12)
IFNB-1a SC 44 0.81 (0.50 to 1.29)
TER 7 0.88 (0.62 to 1.23)
OZA 1.01 (0.58 to 1.76)
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Hazard ratio – median (95% credible interval)

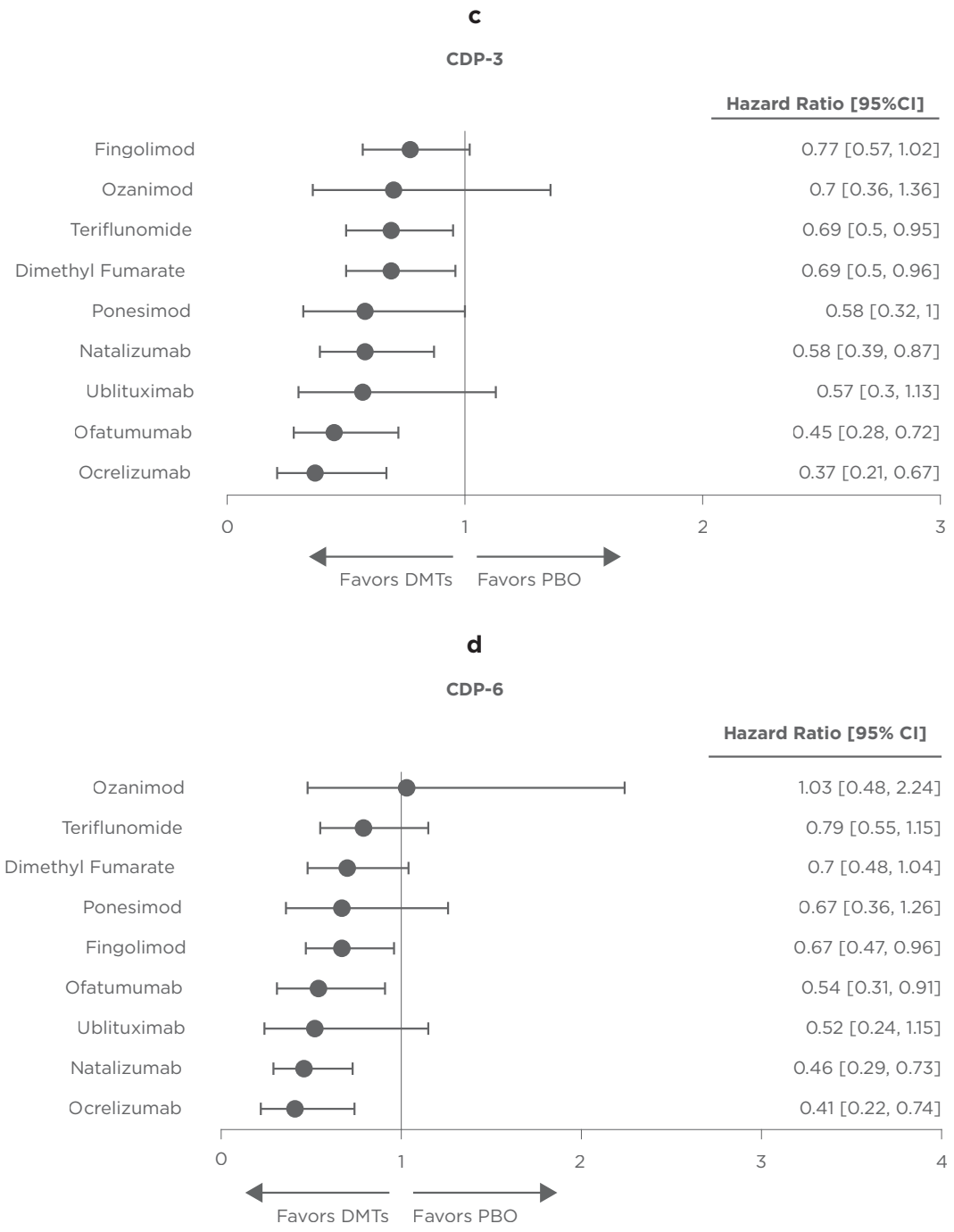


Figure 4: Forest plots of DMTs versus placebo for: a) 3-month CDP from Samjoo (2023); b) 6-month CDP from Samjoo (2023); c) 3-month CDP from ICER (2023); d) 6-month CDP from ICER (2023)

Abbreviations: ALE, alemtuzumab 12 mg; CDP, confirmed disability progression; CLA, cladribine 3.5 mg/kg; DMF, dimethyl fumarate 240 mg twice a day; DMT, disease-modifying therapy; FIN, fingolimod 0.5 mg; GA20, glatiramer acetate 20 mg; IFNB-1a IM, interferon beta-1a 30 µg intramuscular; IFNB-1a SC44, interferon beta-1a 44 µg subcutaneous; NAT, natalizumab 300 mg; OCR, ocrelizumab 600 mg; OMB, ofatumumab 20 mg; OZA, ozanimod 1.0 mg; PBO, placebo; PON, ponesimod 20 mg; TER7, teriflunomide 7 mg; TER14, teriflunomide 14 mg; UTX, ublituximab 450 mg.

Source: Samjoo 2023[12] Figure 5B and Figure 7B; ICER 2023[46] Figure 3-2 and 3-3

MRI OUTCOMES

A study by Cagol[49] assessed the effects of 16 FDA-approved DMTs on brain volume loss and MRI lesion activity, and their association with disability progression, through a NMA of 33 RCTs enrolling 26,427 adults (21,309 with relapsing MS and 4,938 with progressive MS).

The analysis found that eight DMTs were significantly superior to placebo in reducing brain volume loss, while most of the remaining DMTs showed numerical benefit. The exceptions were interferon beta-1a and peginterferon beta-1a, which demonstrated numerically worse outcomes than placebo, although these differences were not statistically significant (Figure 5a). MRI lesion activity, a key marker of focal inflammatory activity, was measured by the count of active T2-lesions in 27 RCTs and by the count of combined unique active lesions in two studies. All DMTs demonstrated significant superiority over placebo in preventing MRI lesion activity, with reductions ranging from 45% for glatiramer acetate to almost complete suppression (97%) observed with ublituximab (Figure 5b).

More recently approved DMTs generally demonstrated greater effects on brain volume loss and MRI lesion activity than earlier therapies. Notably, the treatments associated with the greatest benefits on brain volume loss were not necessarily the same as those demonstrating the largest effects on MRI lesion activity. This mirrors the pattern observed between relapse activity and disability progression in Samjoo[12], where efficacy rankings varied depending on the outcome assessed. Collectively, these findings suggest that treatment benefits may differ across distinct aspects of the disease.

In terms of disease progression, six DMTs demonstrated significant superiority over placebo, with ofatumumab exhibiting the largest treatment effect and reducing the risk of disability accumulation by more than 50% (Figure 5c). Importantly, reductions in brain volume loss were associated with lower rates of disability accumulation, and this relationship persisted after accounting for the effects of treatment on MRI lesion activity. These findings suggest that the relationship between DMT treatment, brain volume loss and disability accumulation may extend beyond the suppression of focal inflammatory lesions alone.

This observation is particularly relevant given the increasing recognition that disability accumulation in MS can occur independently of relapses and overt MRI inflammatory activity, including during RRMS, referred to as progression independent of relapse activity (PIRA). Although PIRA may signal an increased risk of subsequent transition to SPMS, it is not synonymous with SPMS and may occur early in the disease course. People experiencing PIRA have been shown to exhibit accelerated brain volume loss despite apparent control of focal inflammatory disease. The observation that DMTs may delay disability milestone attainment in people with PIRA suggests that their benefits may extend beyond controlling relapse-associated disease activity alone.

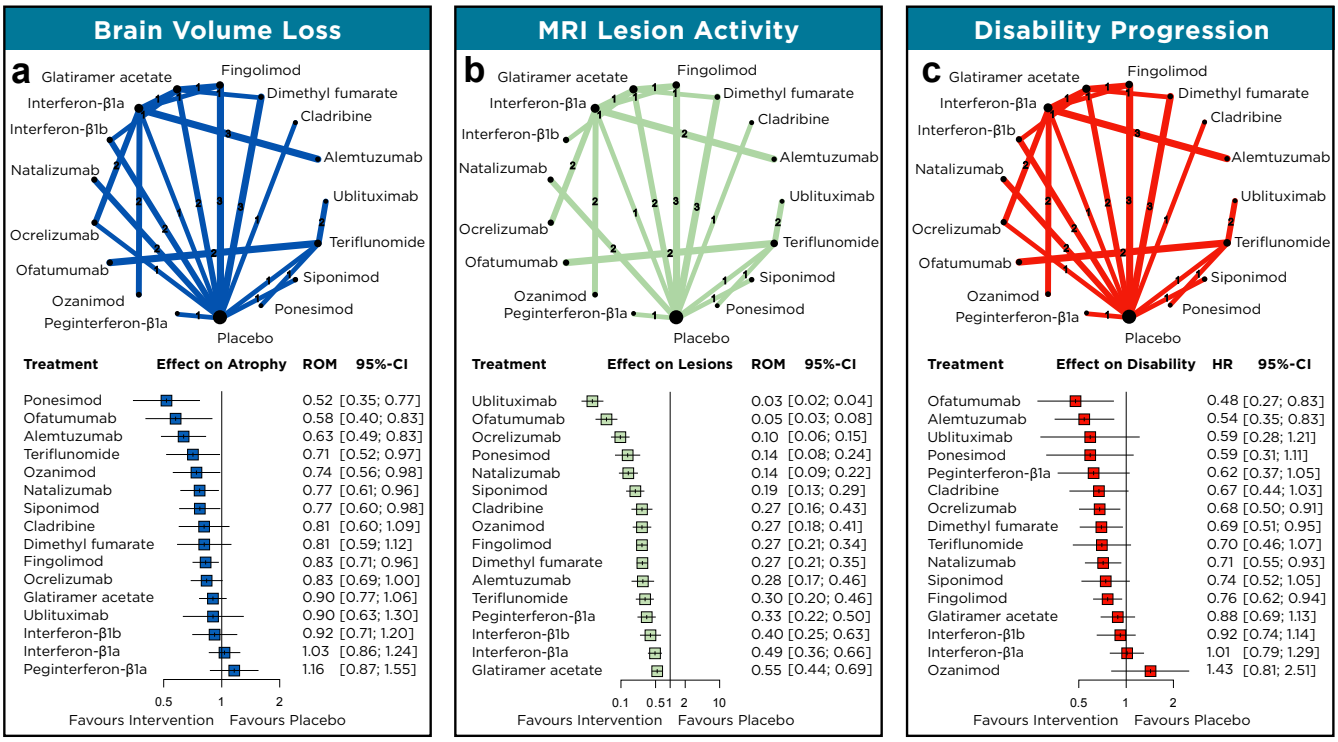


Figure 5: Forest plots of DMTs versus placebo in MRI outcomes

Abbreviations: CI, confidence intervals; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; ROM, ratio of means

Source: Cagol 2025[49] Figure 2

NEDA

Although NEDA has become increasingly recognised as a clinically relevant measure of overall disease control, relatively few studies have assessed comparative DMT efficacy using this outcome. Nevertheless, published NMAs by Siddiqui[50] and Bartosik-Psujek[51] provide comparative evidence on the ability of DMTs to achieve NEDA, where data is available.

Siddiqui[50] conducted a NMA using five studies in people with active RRMS, defining NEDA as a combined endpoint representing freedom from relapse, progression and lesion load. The study found that both natalizumab and cladribine were associated with substantially higher rates of NEDA compared with placebo at 24 months. Cladribine also demonstrated significantly greater odds of achieving NEDA than several earlier DMTs, including teriflunomide, dimethyl fumarate and glatiramer acetate (Figure 6). Importantly, the number needed to treat to achieve one additional person with NEDA, compared with placebo, was two for natalizumab and three for cladribine, compared with between 6 and 19 for the remaining DMTs. This highlights substantial differences between therapies in their ability to achieve comprehensive control across multiple manifestations of MS disease activity. These findings were broadly consistent with the pattern observed for ARR and EDSS outcomes, with therapies generally considered to be of higher efficacy tending to demonstrate greater NEDA benefit.

Similar findings were reported by Bartosik-Psujek[51], who assessed the ability of cladribine compared with other oral DMTs to achieve NEDA, defined as no clinical relapse, absence of 3-month CDP and MRI disease activity, in a NMA of six RCTs. Cladribine was associated with over four-fold greater odds of achieving NEDA than placebo (odds ratio [OR]: 4.25), as well as significantly greater odds than teriflunomide (OR: 2.78) and dimethyl fumarate (OR: 1.76). However, no significant differences were observed between cladribine and fingolimod. Although the available evidence remains limited, these findings suggest that DMTs can achieve meaningful improvements in overall disease control, with some therapies appearing more effective than others at simultaneously controlling relapse activity, disability progression and MRI disease activity.

Importantly, evidence is emerging that achievement of NEDA may be associated with improved long-term outcomes. Rotstein[52] reported that people with RRMS who achieved NEDA-3 were less likely to experience long-term disability progression, regardless of whether they were receiving low- or high-efficacy DMTs. However, the magnitude of benefit was greater among people receiving high-efficacy therapies (OR: 3.19 versus 2.32, respectively). These findings suggest that NEDA represents a clinically meaningful measure of disease control, with achievement of comprehensive disease control associated with a lower likelihood of subsequent disease progression. This reinforces the importance of therapies capable of simultaneously suppressing multiple manifestations of MS disease activity.

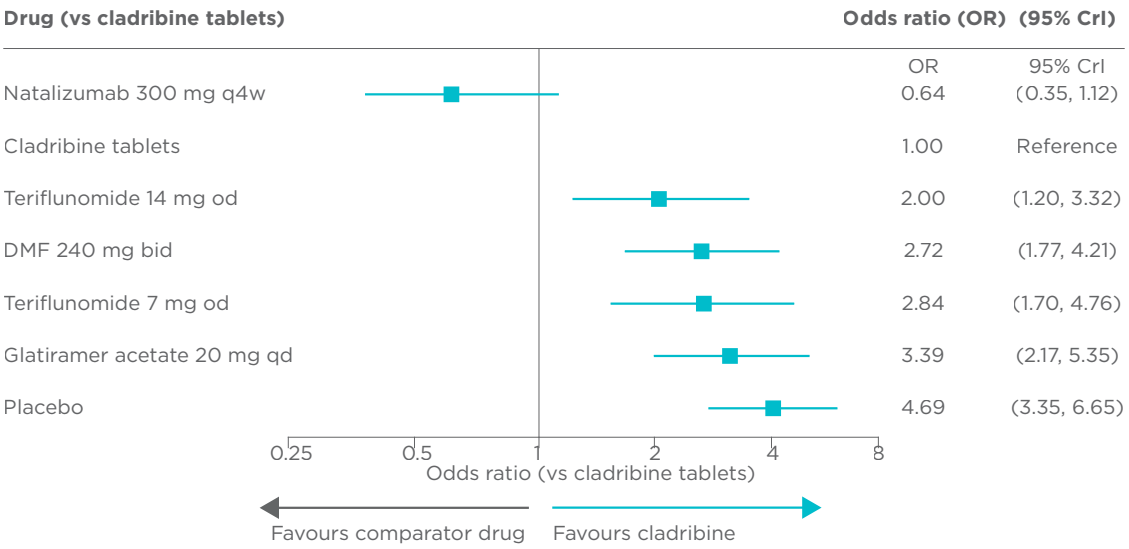


Figure 6: Forest plot of cladribine versus comparators for NEDA

Abbreviations: bid, twice a day; CrI, credible interval; od, once a day; OR, odds ratio; q4w, once every 4 weeks; qd, per day

Source: Based on Siddiqui 2018[50] Table 5

2.3.3. Tolerability of DMTs

While DMTs provide clear clinical benefits, treatment selection must also consider safety and tolerability. Zhao[47] meta-analysed adverse events (AEs), including overall AEs, AEs leading to discontinuation (DAEs), and serious AEs (SAEs) across multiple oral DMTs. Overall, tolerability profiles varied substantially between treatments, with no single therapy consistently ranked as the most favourable across all safety outcomes.

For overall AEs, statistically significant differences from placebo were observed for laquinimod 0.6 mg (mean difference [MD]: 0.78), cladribine 3.5 mg/kg (MD: 0.66), dimethyl fumarate 240 mg twice daily (MD: 0.60) and siponimod 2 mg (MD: 0.09). In terms of SAEs, siponimod 0.5 mg was the only standard treatment regimen to demonstrate a statistically significant difference from placebo (OR: 0.03), indicating a potential safety concern associated with the treatment. For DAEs, most DMTs showed similar treatment effects to placebo, with significant differences observed for laquinimod 0.6 mg, siponimod 10 mg, and fingolimod 1.25 mg. Overall, these findings suggest that the safety and tolerability profiles of DMTs differ according to both treatment and outcome assessed, reinforcing that treatment selection requires consideration of both efficacy and safety rather than efficacy alone.

The importance of balancing efficacy and tolerability is further illustrated in Zhao[47] comparing ARR and DAE outcomes (Figure 7). Therapies associated with greater efficacy were not necessarily those with the most favourable tolerability profiles. For example, siponimod 2 mg and fingolimod 1.25 mg were among the most efficacious therapies but ranked comparatively poorly for tolerability, whereas interferon beta-1a and lower-dose laquinimod regimens demonstrated favourable safety profiles but more modest efficacy. Fingolimod 0.5 mg and dimethyl fumarate occupied an intermediate position, combining relatively high efficacy with acceptable tolerability. It is important to note that these analyses were restricted to oral therapies and therefore do not capture the broader safety and tolerability profile of all available DMTs.

Together, these findings highlight an important consideration in MS management, which is achieving the balance between the required efficacy to treat the disease against treatment-related adverse effects and the likelihood of treatment discontinuation. Therapies associated with the greatest efficacy may not always represent the most appropriate treatment choice for every person, particularly where differences in safety, tolerability or treatment discontinuation are clinically relevant. Consequently, DMT selection requires consideration of disease characteristics, treatment goals, expected efficacy, safety and tolerability, alongside patient preferences.

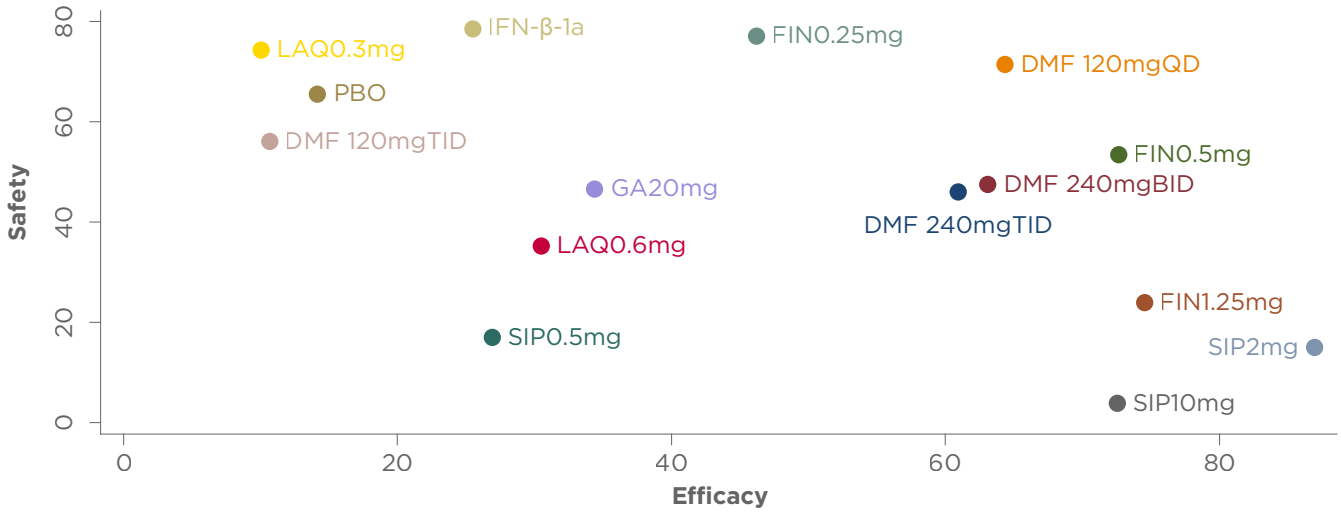


Figure 7: Two-dimensional ranking plot of efficacy and safety of oral DMTs

Abbreviations: BID, twice a day; DMF, dimethyl fumarate; DMT, disease-modifying therapy; FIN, fingolimod; GA, glatiramer acetate; IFN-β-1a, interferon beta-1a; LAQ, laquinimod; PBO, placebo; QD, per day; SIP, siponimod; TID, three times a day

Source: Zhao 2026[47] Supplementary Figure 2

2.3.4. DMT use in progressive MS

Compared with relapsing MS, the evidence supporting DMT use in progressive MS remains limited. To address this evidence gap, Wu[53] conducted a NMA of 18 RCTs evaluating the efficacy and safety of DMTs in people with primary or secondary progressive MS. The analysis assessed multiple outcomes including CDP, EDSS, T25FW, 9HPT, MRI lesion outcomes, and safety endpoints.

Several DMTs demonstrated significant benefits compared with placebo across the outcomes (Figure 8). Ocrelizumab, siponimod and interferon beta-1b were superior to placebo in delaying CDP, while interferon beta-1b and mitoxantrone demonstrated significant benefits on EDSS outcomes. Ocrelizumab and natalizumab were also superior to placebo on the 9HPT, suggesting benefits for upper-limb function. However, no significant differences were observed between active treatment and placebo for T25FW outcomes. Similar patterns were observed for MRI outcomes where interferon beta-1b demonstrated superiority to placebo in reducing new or enlarging T2 lesions, while no significant differences were observed between the remaining therapies and placebo for changes in total T2 lesion volume. Overall, the analysis demonstrated benefits for DMTs across several efficacy outcomes, although the magnitude of benefit differed between therapies and outcome measures.

More recently, the Phase 3b ORATORIO-HAND trial provided further evidence of the effect of ocrelizumab on disability progression in people with PPMS. Compared with placebo, ocrelizumab reduced the risk of 12-week CDP in 9HPT by 41% (17% progression rate with ocrelizumab versus 25% with placebo; p=0.0002) and on the EDSS by 33% (23% progression rate with ocrelizumab versus 31% with placebo; p=0.0013)[54].

DMT vs. placebo	EDSS	CDP	T25FW	9HPT	New T2	T2-weighted images	AEs	SAEs
Ocrelizumab	N/A	**1.27 (1.08, 1.48)**	1.12 (0.99, 1.27)	**1.39 (1.10, 1.77)**	N/A	**-60.10 (-62.71, -57.49)**	**0.93 (0.89, 0.98)**	1.07 (0.80, 1.44)
Natalizumab	N/A	1.08 (0.93, 1.24)	1.01 (0.85, 1.21)	**1.59 (1.20, 2.11)**	N/A	N/A	1.00 (0.96, 1.04)	1.09 (0.85, 1.40)
Rituximab	0.12 (-0.05, 0.30)	0.94 (0.63, 1.41)	N/A	N/A	N/A	10.00 (-81.31, 101.31)	**1.01 (1.00, 1.02)**	0.83 (0.51, 1.34)
Laquinimod	N/A	1.32 (0.82, 2.12)	N/A	N/A	N/A	N/A	1.02 (0.91, 1.15)	0.77 (0.30, 1.98)
Siponimod	N/A	**1.29 (1.07, 1.56)**	1.05 (0.93, 1.19)	N/A	N/A	**-613.10 (-618.38, -607.82)**	**0.92 (0.88, 0.97)**	0.85 (0.67, 1.08)
Fingolimod	N/A	1.08 (0.93, 1.25)	1.04 (0.91, 1.17)	1.09 (0.86, 1.38)	1.00 (0.95, 1.05)	N/A	0.99 (0.96, 1.02)	0.96 (0.75, 1.23)
IFN-beta-1a	N/A	1.03 (0.82, 1.30)	N/A	N/A	N/A	N/A	N/A	N/A
IFN-beta-1b	**0.17 (0.03, 0.31)**	**1.20 (1.03, 1.40)**	N/A	N/A	**1.30 (1.19, 1.43)**	N/A	N/A	N/A
Glatiramer Acetate	0.01 (-0.13, 0.15)	1.00 (0.93, 1.08)	N/A	N/A	N/A	N/A	N/A	N/A
Mitoxantrone	**0.54 (0.26, 0.82)**	1.94 (0.99, 3.81)	N/A	N/A	N/A	N/A	N/A	N/A
Dimethyl Fumarate	-0.20 (-0.85, 0.45)	N/A	N/A	N/A	1.33 (0.33, 5.40)	N/A	**0.67 (0.47, 0.94)**	1.00 (0.22, 4.52)

HIGH | MODERATE | LOW | VERY LOW

Figure 8: NMA results (risk ratios) of DMTs versus placebo for the treatment of progressive MS

Abbreviations: 9HPT, nine-hole peg test; AEs, adverse events; CDP, confirmed disability progression; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MRI, magnetic resonance imaging; MS, multiple sclerosis; N/A, not applicable; NMA, network meta-analysis; OR, odds ratio; PPMS, primary progressive multiple sclerosis; SAE, serious adverse event; SPMS, secondary progressive multiple sclerosis; T25FW, timed 25-foot walk test

Source: Wu 2024[53] Figure 3

Ocrelizumab demonstrated the most consistent benefits across the evaluated outcomes, showing superiority to placebo for multiple efficacy measures while maintaining a favourable safety profile. Siponimod also performed well in delaying disease progression and reducing MRI lesion burden, supporting its role as an important treatment option in progressive forms of MS; however, it is associated with significantly higher rates of AEs and SAEs than placebo.

Unlike relapsing MS, the evidence base for progressive disease remains comparatively limited, with relatively few therapies demonstrating consistent benefit across multiple outcome measures. While these findings support the ability of selected DMTs to modify disease progression in progressive MS, they also emphasise the ongoing need for therapeutic innovation and the development of additional treatment options for this population.

2.3.5. Conclusion

Collectively, the evidence demonstrates that DMTs provide clinically meaningful benefits across multiple dimensions of MS disease activity. Compared with placebo, DMTs consistently reduced relapse activity, delayed disability progression, suppressed MRI lesion activity, reduced brain volume loss and improved the likelihood of achieving comprehensive disease control as measured by NEDA. These findings provide a strong clinical rationale for the widespread adoption of DMTs as standard of care in RRMS management.

Importantly, the evidence also demonstrates that the magnitude of benefit differs between therapies. While first-generation DMTs established disease modification as an effective treatment strategy, many subsequently developed therapies demonstrated incrementally larger treatment effects across relapse, disability and MRI outcomes. However, no single therapy consistently demonstrated the greatest benefit across all outcome measures, suggesting that different treatments may offer advantages across different aspects of disease activity and progression. Therefore, treatment selection extends beyond efficacy alone. Safety, tolerability, route and frequency of administration, treatment adherence, quality of life and individual preferences all contribute to treatment decision-making. Consequently, the evidence supports an increasingly personalised approach to treatment selection, where therapies are chosen according to both patient characteristics and treatment goals. The growing emphasis on NEDA as a treatment target further reflects this shift towards achieving comprehensive disease control rather than focusing on individual manifestations of disease activity in isolation.

It is noted that interpretation of the available evidence should be undertaken with caution. Much of the comparative evidence presented in this section is derived from indirect comparisons and NMAs, which are inherently subject to assumptions regarding comparability of included studies. Differences in disease severity, baseline disease activity, event rates, outcome definitions and patient populations may contribute to heterogeneity between studies and influence estimates of comparative efficacy. Nevertheless, the overall consistency of findings across outcomes and evidence syntheses provides confidence that DMTs have substantially improved outcomes for people with MS over the past three decades. While important gaps remain, particularly in progressive MS and PIRA, the evidence suggests that newer therapies are increasingly capable of addressing multiple dimensions of disease activity and progression that were previously difficult to modify, supporting continued therapeutic innovation in MS.

Despite the limitations of the comparative evidence, the clinical benefits of DMTs have important consequences beyond the outcomes measured in trials. Delaying disability progression can help preserve mobility, employment, independence and participation in community life, while reducing relapses may lessen disruptions to work, study, family responsibilities and social engagement. These gains may also reduce the support required from families and carers, ease pressure on health and social care services, and help people with MS maintain greater control over their lives for longer. In this way, the value of DMTs extends beyond improvements in clinical outcomes to broader benefits for individuals, families and society.

Delaying disability progression can help preserve mobility, employment, independence and participation in community life.

3. Policy and reimbursement context shaping access to DMTs



KEY POINTS

- Since 1996, the PBS has subsidised 18 DMTs for MS, substantially expanding access to therapies with different mechanisms, efficacy profiles and modes of administration.
- PBS restrictions for DMTs for the treatment of MS do not mandate first- or later-line use or a specific treatment sequence, enabling clinicians and patients to individualise treatment selection without reimbursement barriers based on efficacy or price.
- PBAC decisions on DMTs for MS have established two pricing tiers: an initial lower-priced tier of first-generation DMTs and a higher-priced tier created when natalizumab and fingolimod demonstrated superior efficacy and acceptable cost-effectiveness relative to the lower tier.
- Since the availability of PSDs in 2005, 14 DMTs for RRMS or SPMS have been listed, 12 of which were reimbursed at price parity against existing therapies in one of the two pricing tiers rather than a demonstrated price premium. Although this approach has facilitated timely access to new treatments, repeated reference pricing does not fully recognise incremental improvements in efficacy, tolerability, administration or other patient-relevant benefits.
- Statutory price reductions, particularly following generic fingolimod entry, have lowered the reference price for the higher tier, creating challenges for future therapies and contributing to the PBAC's 2026 rapid review of PBS medicines for MS.

3.1. Role of the Pharmaceutical Benefits Advisory Committee

In Australia, health technology assessments (HTAs) of pharmaceuticals are undertaken by the PBAC, an independent statutory body appointed by the Australian Government. The PBAC is legislatively mandated to provide recommendations to the Minister for Health on which medicines should be subsidised under the PBS, with the objective of ensuring that publicly funded medicines represent value for money. A positive recommendation by the PBAC is a requirement for PBS reimbursement.

In making its recommendations, the PBAC considers the comparative clinical effectiveness, safety, and cost-effectiveness of a medicine relative to the most appropriate comparator(s), together with patient affordability and the predicted use and financial implications to the PBS and Australian Government according to established guidelines[55]. The PBAC cannot make a positive recommendation for a medicine that is substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement in efficacy and/or reduction of toxicity, according to Section 101(3B) of the *National Health Act 1953*. In relation to reference pricing, often the lowest priced drug sets a benchmark price for new entrants within the same subgroup of therapeutically related drugs.

The PBAC does not use a definitive threshold when assessing the cost-effectiveness of medicines. This enables the Committee the flexibility to consider broader or less-readily quantifiable factors including availability of existing therapies for the indication, clinical need, severity and/or rarity of disease, patient demographic factors, equity of access, quality of the evidence, and other relevant factors that may affect the suitability of the medicine for listing on the PBS[55, 56].

The rationale underpinning PBAC's reimbursement decisions are published in Public Summary Documents (PSDs)[a], which have been made publicly available since July 2005, enhancing the transparency and consistency of PBAC's decision-making process.

3.2. Timeline and indications of PBS listings of DMTs for MS

Prior to the availability of PSDs in July 2005, four DMTs were available on the PBS: interferon beta-1b (Betaferon), interferon beta-1a (Avonex and Rebif), and glatiramer acetate (Copaxone). Since then, the PBS reimbursement landscape has evolved substantially, with the listing of numerous new therapies and the subsequent delisting of several others, including interferon beta-1a (Avonex and Rebif) and daclizumab (Zinbryta). Figure 9 represents the timeline of the 18 DMTs reimbursed in Australia between November 1996 and January 2026 for the treatment of MS.

With the exception of siponimod (Mayzent), access to treatment with currently available DMTs is restricted to people with a confirmed diagnosis of MS, who have had at least two documented attacks of neurological dysfunction believed to be due to MS in the preceding two years and who remain ambulatory without assistance or support. To maintain continuing treatment access, people with MS must not have progression of disability and must remain compliant and tolerant to therapy. Several DMTs have the additional requirement that people must be treated by a neurologist. Siponimod is the only DMT currently available on the PBS for the treatment of SPMS, with reimbursed access restricted to people with SPMS following a prior diagnosis of RRMS, mild to moderate disability, and who remain ambulatory with or without support.

The PBS restrictions for DMTs for RRMS do not distinguish between first- and later-line use, nor do they mandate a specific treatment sequence and as such, there are currently no PBS-enabled barriers based on cost or efficacy considerations. Accordingly, pricing and reimbursement considerations are not enforced in sequencing decisions, rather treatment pathways can be individualised according to clinical judgement and patient preference.

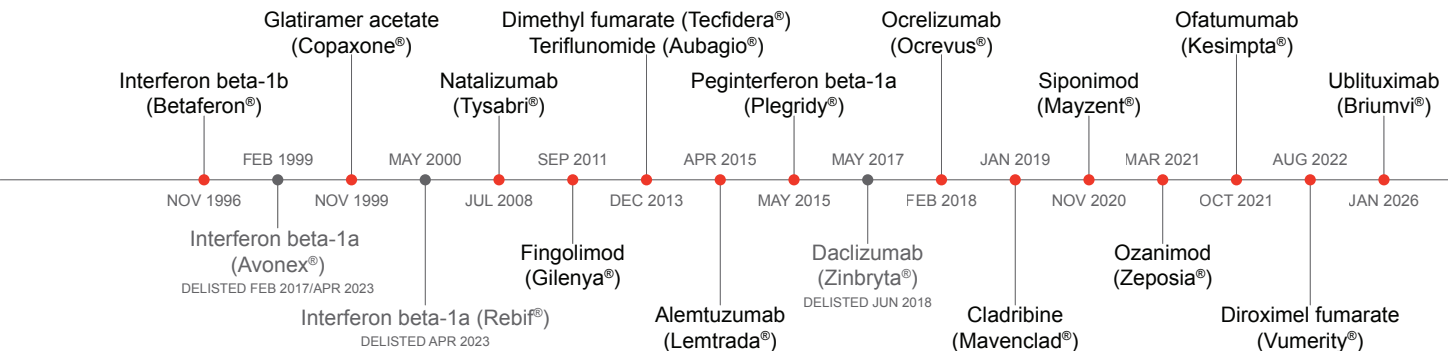


Figure 9: Timeline of listing of DMTs for MS on the Pharmaceutical Benefits Scheme

3.3. Basis of PBAC recommendations

3.3.1. Overview of PBAC considerations

Interferon beta-1b (Betaferon) was the first DMT to be reimbursed through the PBS in November 1996. Although no publicly available information describes the basis for this PBAC recommendation, it is expected that the listing was supported by an assessment that interferon beta-1b offered sufficient clinical benefit to justify its price relative to standard medical management for MS at the time. Supportive care measures comprised corticosteroids for the management of acute relapses, as well as supportive therapies such as antispasmodics and antidepressants for symptom management[18].

a PBAC PSDs available at: https://pbs.gov.au/industry/pbac/psd

Subsequently, interferon beta-1a (Avonex), glatiramer acetate (Copaxone) and interferon beta-1a (Rebif) were subsidised on the PBS in February 1999, November 1999 and May 2000, respectively. They were recommended by the PBAC on a cost-minimisation basis, indicating that their value was assessed in terms of offering comparable efficacy and safety relative to existing DMTs for MS, and that listing should occur at an equivalent price per patient[b].

Natalizumab (Tysabri), listed on the PBS in July 2008, was the first DMT to achieve a price premium over existing MS therapies based on a positive PBAC recommendation following its demonstrated cost-effectiveness compared with interferon beta-1b. Similarly, fingolimod (Gilenya) was recommended by the PBAC on the basis of acceptable cost-effectiveness relative to interferon beta-1a, representing the first orally administered DMT for MS. Both therapies underwent two PBAC considerations each; in the case of natalizumab this followed an initial rejection, whereas fingolimod received an out-of-session positive recommendation following a further price reduction offered by the Sponsor.

Since the listing of fingolimod in September 2011, 12 DMTs have been reimbursed on the PBS for the treatment of MS, all of which received positive PBAC recommendations on the basis of acceptable cost-minimisation analyses against existing DMTs. In these cases, the PBAC accepted that these new therapies were clinically equivalent compared with the nominated comparator and any incremental clinical benefits were not deemed sufficient to justify a price premium. Consequently, subsequent DMT listings have been anchored to price parity with currently listed alternatives rather than to a demonstrated cost-effective improvement over existing DMTs (Table 2).

Table 2: Overview of PBAC considerations and outcomes for DMTs for MS

DMT (originator brand)	PBAC consideration		PBAC outcome	Sponsor's request for listing	PBAC decision / basis of listing	No. of submissions required for listing
	Year	Meeting				
Interferon beta-1b (Betaferon)	N/A	N/A	N/A	N/A	CEA vs SoC	N/A
Interferon beta-1a (Avonex)	N/A	N/A	N/A	N/A	CMA vs T1	N/A
Glatiramer acetate (Copaxone)	N/A	N/A	N/A	N/A	CMA vs T1	N/A
Interferon beta-1a (Rebif)	N/A	N/A	N/A	N/A	CMA vs T1	N/A
Natalizumab (Tysabri)	2006	Nov	Rejected	CEA vs T1	-	2
	2007	Nov	Recommended	CEA vs T1	CEA vs T1	
Fingolimod (Gilenya)	2011	Mar	Deferred	CEA vs T1	-	2
	2011	OOS*	Recommended	CEA vs T1	CEA vs T1	
Dimethyl Fumarate (Tecfidera)	2013	July	Recommended	CEA vs T1 & CMA vs T2	CMA vs T1	1
Teriflunomide (Aubagio)	2012	Nov	Rejected	CMA vs T1	-	2
	2013	July	Recommended	CMA vs T1	CMA vs T1	
Alemtuzumab (Lemtrada)	2014	July	Recommended	CMA vs T2	CMA vs T2	1
Peginterferon beta-1a (Plegridy)	2014	Nov	Recommended	CMA vs T1	CMA vs T1	1

b PBS Therapeutic Relativity sheets, available at: https://www.pbs.gov.au/industry/pricing/pbs-items/therapeutic-relativity-sheets

DMT (originator brand)	PBAC consideration		PBAC outcome	Sponsor's request for listing	PBAC decision / basis of listing	No. of submissions required for listing
	Year	Meeting				
Daclizumab (Zinbryta)	2016	July	Deferred	CMA vs T2	-	2
	2016	Nov	Recommended	CMA vs T2	CMA vs T2	
Ocrelizumab (Ocrevus)	2017	July	Recommended	CMA vs T2	CMA vs T2	1
Cladribine (Mavenclad)	2011	Mar	Rejected	CEA vs T1 / T2	-	4
	2017	Nov	Rejected	CMA vs T2	-	
	2018	Mar	Rejected	CMA vs T2	-	
	2018	July	Recommended	CMA vs T2	CMA vs T2	
Siponimod (Mayzent)	2019	Nov	Rejected	CUA vs SoC/ DMTs	-	2
	2020	July	Recommended	CMA vs T2	CMA vs T2	
Ozanimod (Zeposia)	2020	Mar	Deferred	CMA vs T2	-	2
	2020	Sep OOS*	Recommended	CMA vs T2	CMA vs T2	
Ofatumumab (Kesimpta)	2021	Mar	Recommended	CMA vs T2	CMA vs T2	1
Diroximel fumarate (Vumerity)	2022	Mar	Recommended	CMA vs T1	CMA vs T1	1
Ublituximab (Briumvi)	2025	May	Recommended	Cost-comparison vs T2 (superior vs FIN; non-inferior vs OMB/OCR)	CMA vs lowest cost T2	1

Abbreviations: CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; DMT, disease-modifying therapy; FIN, fingolimod; MS, multiple sclerosis; N/A, not applicable/available; OCR, ocrelizumab; OMB, ofatumumab; OOS, out-of-session; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; SoC, standard of care; T, tier.

Source: PBS website: https://www.pbs.gov.au/industry/pbac/psd

Note: Only PSDs for submissions since July 2005 are publicly available; hence MS DMTs listed prior to this date were not included in the review. The review was also limited to the decision for first listing of a DMT molecule, therefore PSDs for listings that related to additional strengths / formulations of previously listed MS DMTs were not reviewed.

*The PBAC recommended listing fingolimod at an out-of-session meeting, following a price reduction offered by the Sponsor post-meeting (No PSD available). The PBAC recommended listing ozanimod at an out-of-session meeting in September 2020, following TGA registration of ozanimod (PSD for this meeting available).

3.3.2. Treatment tiers

The basis of these recommendations by the PBAC has effectively led to categorisation of DMTs for the treatment of MS within two PBS-established pricing categories or 'tiers', as illustrated in Figure 10. Accordingly, many of the more recently PBS-listed drugs have been recommended based on cost-minimisation analyses with fingolimod despite demonstrating incremental improvements in efficacy. Whilst it is likely this has enabled timely access to treatments by avoiding repeated resubmissions, it has also had consequences for how newer DMTs are valued. In particular, successive cost-minimisation recommendations have created a relative pricing profile that may not completely reflect the incremental improvements in outcomes delivered by newer treatments.

Furthermore, this dual-tier pricing categorisation of DMTs diverges against classifications within several treatment guidelines (see Section 2.1.3; Table 1), including the Australian and New Zealand consensus recommendations which categorise DMTs according to low-, intermediate- and high-efficacy groups. A submission for ofatumumab in March 2024 to sub-divide the high-efficacy tier, with natalizumab, alemtuzumab, ocrelizumab and ofatumumab remaining high-efficacy and fingolimod, cladribine and ozanimod being re-classified as mid-efficacy, was rejected by the PBAC. Ultimately, the PBAC did not support the formation of three efficacy tiers as superior comparative effectiveness for ofatumumab versus fingolimod was not demonstrated[57].

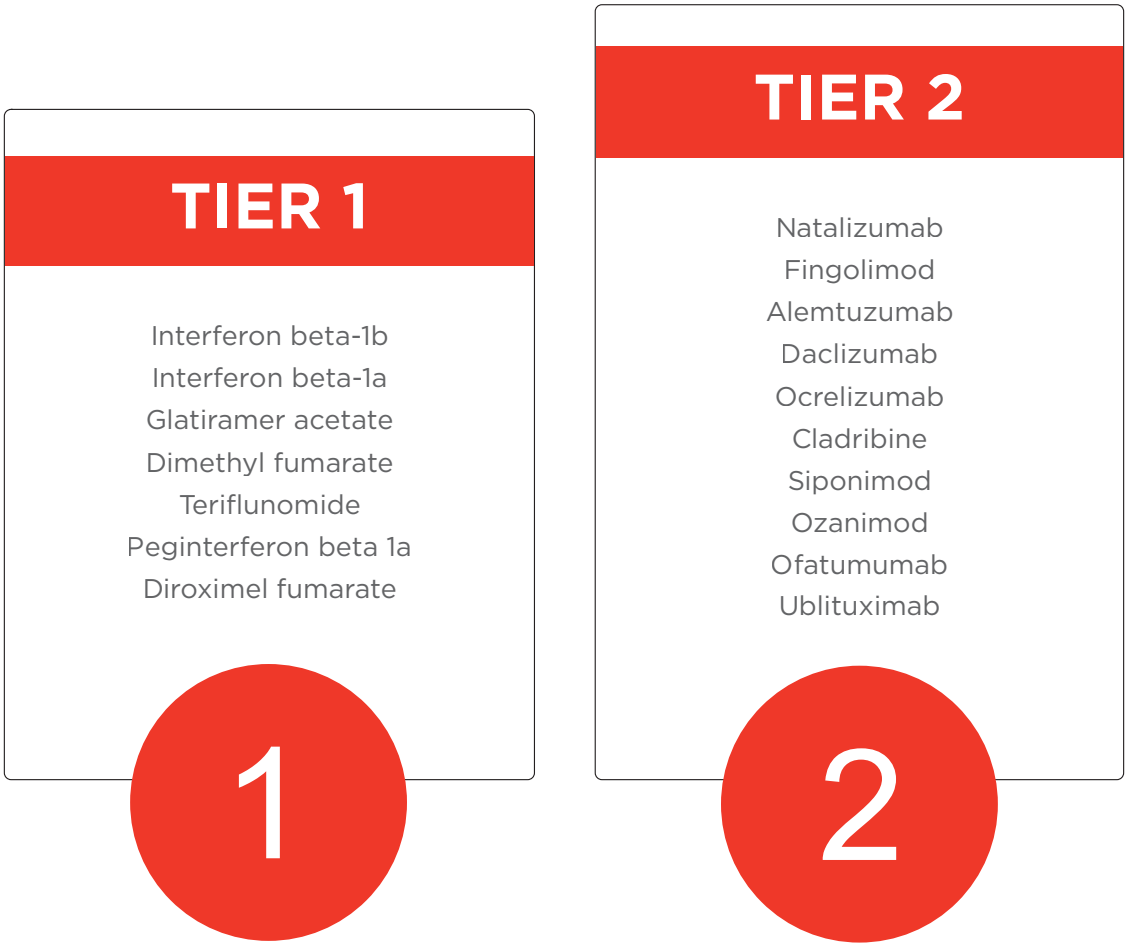


Figure 10: DMTs for MS categorised according to PBS-established pricing tiers (tier 1=lower pricing/moderate efficacy; tier 2=higher pricing/high efficacy)

Note: Interferon beta-1a (tier 1) and daclizumab (tier 2) have been delisted.

3.3.3. Statutory price reductions

Despite being reference priced to existing DMTs at the time of PBS listing, pricing differences have emerged within pricing tiers over time, largely as a result of generic market entry and other statutory price reductions (SPRs). Figure 11 depicts the published per-annum price of DMTs at the time of PBS listing compared with the current list price as of June 2026 (or the last published price prior to de-listing). The vast majority of DMTs have undergone various price reductions; in the case of fingolimod, the PBS price decreased by 25% following the listing of a first new brand (i.e., generic brand) in December 2022, with a further 12.75% price disclosure reduction applied in October 2024. As a result, fingolimod now has a lower pricing profile than several other high-efficacy DMTs for RRMS, including therapies that were originally recommended for PBS listing on a cost-minimisation basis relative to fingolimod. Consistent with these price reductions, PBS benefits paid for fingolimod declined by 72.3%, from $129 million in 2019 to $35.7 million in 2024[58].

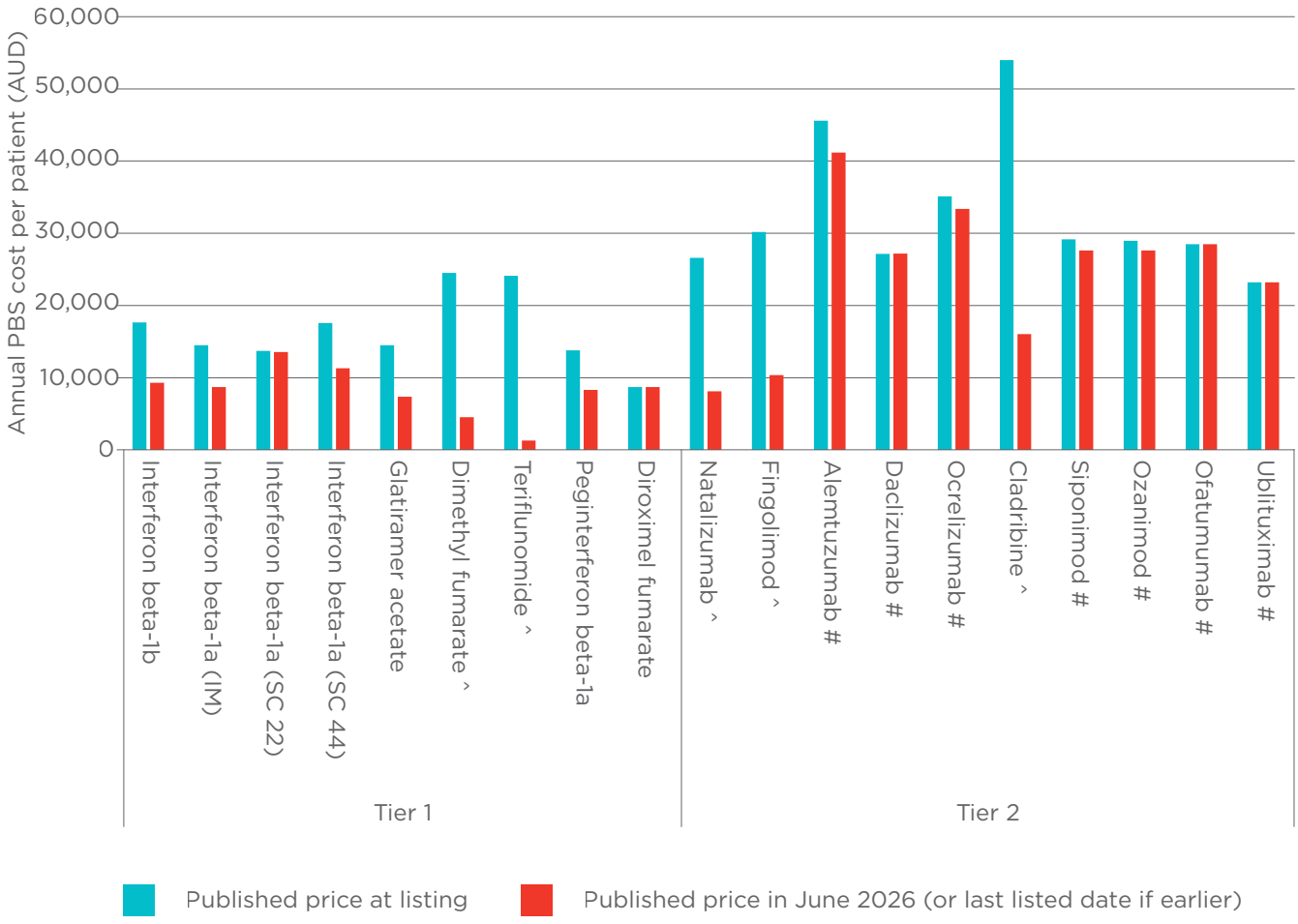


Figure 11: Annual price of DMTs at time of listing vs current (June 2026 or last listing), by efficacy tier [published prices]

Abbreviations: DMT, disease-modifying therapy; IM, intramuscular; SC, subcutaneous; SPA, Special Pricing Arrangement

The prices at listing and at the current reference date (June 2026, or the last listing date) reflect a confidential SPA.

^ The price at listing reflects a confidential SPA; the current price does not.

Notes: Where loading or titration packs are listed, annual costs are calculated using continuing-treatment pack prices (e.g., ublituximab, ofatumumab and ozanimod). For DMTs listed under Section 100 (e.g., ublituximab, ocrelizumab, alemtuzumab and natalizumab), the average pack price across private and public hospital settings was used. The price of siponimod was based on the most commonly dispensed 2 mg pack. The annual price of alemtuzumab was calculated as the average of Year 1 and Year 2 costs. The price of cladribine was based on an average body weight of 76.6 kg and seven tablets per prescription.

These pricing differentials are creating significant barriers for future therapies seeking to enter the RRMS market under the current dual-tier PBS pricing structure. In the most recent PBS listing case in RRMS, the Sponsor requested price parity for ublituximab against ofatumumab and ocrelizumab, and a price premium relative to fingolimod[59]. However, the PBAC did not accept that the clinical evidence was sufficient to justify a premium over fingolimod. Instead, consistent with Section 101(3B) of the *National Health Act 1953*, the PBAC recommended listing ublituximab on a cost-minimisation basis against the least costly alternative DMT within the existing higher-tier RRMS treatment group at the time of consideration. As a result, ublituximab was reference priced against fingolimod, which at the time had been subject to a series of SPRs (Figure 12). This prompted a requirement for the Department of Health to subsequently extend the substantial price reductions to the other listed Tier 2 DMTs, including ocrelizumab and ofatumumab. These price cuts were rejected by Sponsors and due to concerns raised that high-efficacy DMTs could be delisted from the PBS, a rapid review of DMTs for MS[c] initiated by the PBAC is currently underway.

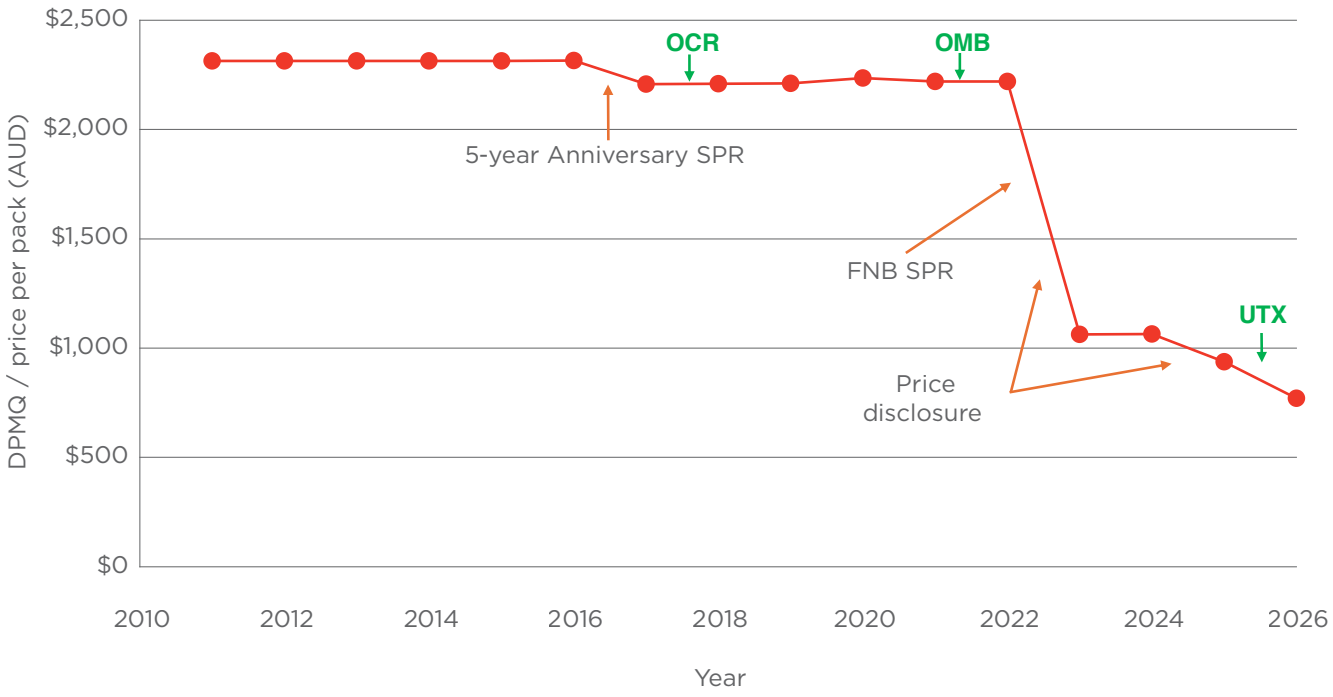


Figure 12: PBS price (DPMQ) per pack of fingolimod with major pricing milestones and listing dates of selected Tier 2 DMTs

Abbreviations: DPMQ, dispensed price maximum quantity; FNB, first new brand; OCR, ocrelizumab; OMB, ofatumumab; SPR, statutory price reduction; UTX, ublituximab.

Note: Price of fingolimod as of July per year is shown.

3.4 Further Contextualisation of PBAC Decision-Making

The PBAC's assessment of DMTs over the past two decades provides a useful resource to examine how public investment in MS treatment has been justified through reimbursement decisions. A report by Phan[60] reviewed the factors influencing reimbursement decisions by the PBAC for a range of treatments for MS based on PBAC considerations between January 2006 to January 2018.

The present assessment focuses on DMTs for MS and extends the review period from July 2005 (earliest availability of PSDs) to June 2026, providing an updated qualitative evaluation of how the factors influencing reimbursement have evolved as the MS treatment class has expanded.

c PBAC Rapid Review of RRMS medicines: https://www.pbs.gov.au/reviews/rapid-review-of-pbs-medicines-for-relapsing-remitting-multiple-sclerosis-rrms

A total of 23 considerations (including out-of-session discussions) relating to the initial PBS listing of 14 DMTs for RRMS (n=13) and SPMS (n=1) were reviewed, as outlined in Table 2 above. This captured the reimbursement pathway for each molecule, including recommendations, deferrals and rejections preceding first listing. Subsequent submissions for additional formulations or other requests (e.g., restriction changes) of already-listed DMTs were excluded, as these were less informative for understanding the basis on which new therapeutic entrants were valued.

A total of seven DMTs (50%) achieved a first-time recommendation, while four (28.6%) were initially rejected and three (21.4%) were deferred. Cladribine had the highest number of submissions (n=4) prior to achieving a recommendation following three rejected applications, and the mean number of submissions per DMT was 1.6. The three most recent PBAC considerations, for ofatumumab in March 2021, diroximel fumarate in March 2022 and ublituximab in May 2025, each resulted in a positive recommendation following the first submission.

Note: The PBAC considered submissions to extend the PBS listing of ocrelizumab to include the treatment of PPMS in November 2017 and July 2020. Both submissions, which were supported by cost-utility analyses versus best supportive care, were rejected by the PBAC. As the current assessment was limited to submissions for the initial PBS listing of each DMT molecule, these indication-extension submissions were excluded.

3.4.1. Submissions to the PBAC based on a price premium

Since the availability of published PSDs, two DMTs have been recommended with a price premium relative to existing therapies through a cost-effectiveness approach: natalizumab in November 2007 and fingolimod in an out-of-session meeting post-March 2011. In both cases, the PBAC accepted evidence of superior efficacy against the relevant interferon comparator, establishing a higher pricing tier than the earlier-listed DMTs. The accepted incremental cost-effectiveness ratios (ICERs) associated with these recommendations were within the range of $45,000–$75,000 per quality-adjusted life year (QALY), and each recommendation followed a price reduction, with a risk-sharing arrangement (RSA) also applied for natalizumab.

Three submissions, for dimethyl fumarate in July 2013, cladribine in March 2011 and siponimod in November 2019, sought to justify a higher price through a cost-effectiveness approach but did not establish an accepted basis for a premium. For dimethyl fumarate and cladribine, the PBAC did not accept the superiority claims related to the clinical evidence, with comparator selection also a key issue for cladribine. For siponimod, the PBAC accepted evidence of benefit versus placebo in SPMS, but rejected the submission because the comparative framework, model assumptions and corrected ICER did not support cost-effectiveness at the proposed price. These DMTs were subsequently recommended and listed on the basis of non-inferiority and hence, cost-minimisation to existing DMTs.

Across these submissions, three issues repeatedly determined whether premium pricing could be justified: the acceptability of the nominated comparator, the validity of the comparative evidence used to establish relative efficacy, and whether that evidence sustained an accepted claim of superiority. Where superiority was accepted, price reduction and risk-sharing served as mechanisms for managing residual clinical and economic uncertainty.

NATALIZUMAB

In the original November 2006 submission, the PBAC accepted that natalizumab demonstrated superior efficacy but identified the validity of the indirect treatment comparison (ITC) as the principal source of uncertainty. The comparability of the trial populations was highlighted as a key concern for the PBAC, noting that the populations were not exchangeable at baseline and requiring the assumption that treatment effect is independent of baseline relapse risk. The trials were also conducted more than a decade apart, introducing potential differences in clinical management.

While the ITC was accepted as suggesting superior efficacy in relapse reduction, the PBAC considered that the economic model structure did not adequately reflect the natural history of MS or relevant treatment pathways, including disease progression and treatment discontinuation. The estimated ICER of $75,000–$85,000 per QALY was regarded as a best-case estimate. The

submission was rejected on the grounds that the claimed clinical advantage was accompanied by substantial uncertainty in the indirect evidence, and that the economic model was likely to understate the true cost per QALY gained.

In the November 2007 resubmission, uncertainty in the indirect comparison persisted, but revisions to the economic evaluation reduced the ICER to a range the PBAC considered high but acceptable (i.e., $45,000–$75,000 per QALY). This was weighed against the demonstrated improvement in ARR, the high unmet clinical need in RRMS, and the inclusion of an RSA to mitigate financial uncertainty. The superiority claim was accepted as supporting a clinically meaningful improvement over existing PBS-funded therapies, notwithstanding the unresolved questions regarding exchangeability, and the therapy was recommended for listing. That said, the PBAC highlighted the serious adverse effect profile of natalizumab and noted that the proposed PBS restriction criteria would likely result in second-line use following failure or intolerance to interferon therapy.

FINGOLIMOD

The March 2011 fingolimod submission was supported by a head-to-head randomised trial (TRANSFORMS) against interferon beta-1a, and the PBAC accepted the claim of superior comparative effectiveness with a comparable safety profile. The availability of direct evidence distinguished this submission from those reliant on indirect comparison, although an unadjusted indirect comparison against natalizumab suggested natalizumab may have a lower ARR. The Sponsor's attempt to account for differences between those trial populations was not accepted, and the natalizumab comparison was interpreted with caution.

The principal concerns arose in the economic model, where several assumptions were considered likely to bias results in favour of fingolimod and to underestimate the ICER. The MSBase registry population was not representative of those receiving DMTs through the PBS, particularly with respect to baseline EDSS scores. Disease progression was modelled in an oversimplified manner, and treatment discontinuation assumptions were unrealistic, with people with MS assumed not to switch therapies. The model was also highly sensitive to the assumed disutility associated with frequent injections for existing DMTs. When this disutility was removed, the ICER increased from $45,000–$75,000 to $75,000–$105,000 per QALY. The base-case ICER was consequently regarded as both underestimated and unacceptably high.

The PBAC indicated that an ICER in the range of $15,000–$45,000 per QALY would be required to support listing and deferred its decision pending price negotiation. Following a price reduction, fingolimod was recommended out-of-session. This sequence indicates that, where the PBAC accepts superiority but remains concerned that the base-case ICER is underestimated, it may require a substantially lower and more certain ICER before recommending reimbursement.

CLADRIBINE

The March 2011 cladribine submission failed on the first two factors before the economic case was reached. Natalizumab was rejected as the nominated comparator, with interferon beta-1a considered the more appropriate first-line comparator. The supporting ITC was undermined by the same exchangeability problem observed for natalizumab, with the placebo-arm ARRs differing markedly across the trials (0.33 in CLARITY versus 1.28 in PRISMS), indicating non-comparable populations. The indirect comparison against natalizumab was not statistically significant, and the point estimate suggested cladribine may be less effective. This was not accepted as evidence of equivalence, further weakening the claim of superiority over interferon beta-1a. The PBAC also noted a lack of justification for the method used to calculate the minimum clinically important difference underpinning the non-inferiority assessment.

As the superiority claim was not accepted, the accompanying cost-effectiveness analysis was considered inappropriate. The estimated ICER of approximately $200,000 per QALY was, in any case, unacceptable. The submission was rejected on the grounds of an inappropriate comparator, uncertain clinical benefit, and unacceptable cost-effectiveness. In the July 2017 resubmission, cladribine was again rejected, owing to persistent uncertainty in the clinical evidence, including an unconvincing non-inferiority claim versus fingolimod, and unrealistic assumptions regarding treatment switching, which together undermined the validity of the cost-minimisation approach.

Cladribine was eventually recommended in 2018 following a shift away from the original superiority-based claim and towards a cost-minimisation framework. The revised submissions positioned cladribine as non-inferior to fingolimod and aligned pricing accordingly. Although uncertainty remained regarding aspects of the evidence base, the revised reimbursement approach no longer depended on demonstrating a superior clinical benefit sufficient to justify premium pricing.

DIMETHYL FUMARATE

The July 2013 dimethyl fumarate submission occupied an intermediate position between the premium and parity pathways. The submission claimed superior efficacy compared with injectable ABCR therapies (i.e., Avonex, Betaferon, Copaxone, and Rebif) and non-inferiority relative to fingolimod. However, the PBAC was not persuaded that the available indirect evidence supported the superiority claim to the extent required to justify a higher price. While dimethyl fumarate demonstrated clinically relevant efficacy, uncertainty in the comparative evidence limited the PBAC's willingness to accept a premium pricing framework. Ultimately, the therapy was listed within the existing reimbursement structure rather than establishing a new premium tier. This outcome illustrates that superior efficacy claims alone were insufficient. Comparative evidence was needed to support a reliable estimate of incremental benefit before a higher reimbursed price could be accepted.

SIPONIMOD

Siponimod differed from the preceding premium submissions because it was the first therapy seeking reimbursement for SPMS, a setting in which there was a recognised unmet clinical need. The November 2019 submission relied primarily on placebo-controlled evidence and sought reimbursement on a cost-effectiveness basis. While the PBAC accepted that siponimod demonstrated clinical benefit in SPMS, substantial uncertainty remained regarding the economic model, comparative effectiveness against alternative therapies, and the resulting cost-effectiveness estimates. The submission was therefore rejected despite the absence of alternative PBS-listed DMTs for this population. Following resubmission, siponimod was ultimately recommended on a cost-minimisation basis against fingolimod. This case suggests that even where unmet clinical need is substantial, the PBAC has generally required an accepted comparative framework and a pricing approach consistent with established DMT tier structure, rather than creating a new reimbursement tier solely based on unmet need.

DECISION-MAKING PATTERNS ACROSS PRICE PREMIUM SUBMISSIONS

Across these submissions, the central recurring issue was the credibility of the comparative evidence, particularly where indirect comparisons relied on trial populations that were not exchangeable. The outcomes diverged according to whether an accepted superiority claim survived that uncertainty. For natalizumab and fingolimod, superiority was accepted, and subsequent price concessions made the residual uncertainty acceptable. However, whereas natalizumab was ultimately listed with a risk-sharing agreement, fingolimod was recommended following a further price reduction that reduced the ICER to a range the PBAC considered acceptable. For cladribine, the comparator was rejected, and superiority was not established, leaving no accepted incremental benefit to justify a premium. That the PBAC has accepted indirect comparisons where populations were more comparable, as for peginterferon beta-1a, indicates that the objection was not indirect evidence itself, but to indirect evidence that could not support a reliable estimate of relative effect. Premium pricing was therefore contingent on both an accepted superiority claim and price concession sufficient to offset residual uncertainty.

Two implications follow for the assessment of DMT value. First, the premium pathway demonstrates that the PBAC has been willing to reimburse above the least-cost alternative where a therapy offered an accepted clinical advance over existing options, even where evidentiary uncertainty remained. Public investment through this pathway has therefore been directed toward therapies considered to provide meaningful additional clinical value. Second, the ICERs accepted in these cases were derived from a deliberately narrow cost base. Broader societal costs are not typically incorporated into the base-case ICER, yet in MS these may include lost productivity, presenteeism and absenteeism, reduced earnings from changes in occupation or reduced hours, premature withdrawal from the workforce including forgone superannuation, and the value of informal care

provided by family members. Benefits associated with more convenient administration, including oral treatment, may also not be completely captured. To the extent that these costs and benefits are material, the accepted ICERs may understate the value delivered by these therapies and, correspondingly, the return on public investment.

The premium cases therefore establish the circumstances in which incremental clinical benefit translated into a higher reimbursed price. However, as the treatment class expanded, most subsequent DMT submissions were not assessed as offering superiority over existing options. The reimbursement question increasingly shifted from whether a new therapy justified a premium, to whether it could be accepted as clinically no worse than existing alternatives and therefore listed at price parity.

3.4.2. Submissions to the PBAC based on price parity

The PBAC's approach to establishing non-inferiority has not relied on formal, pre-specified statistical margins. Between 2012 and 2013, a shift is evident from structured statistical thresholds toward qualitative clinical judgement, in which the Committee weighs the magnitude of difference in ARR, the associated confidence intervals, and the consistency of the evidence base, before reaching a conclusion informed by clinical plausibility.

The two teriflunomide submissions illustrate this shift. In November 2012, a claim of non-inferior efficacy and superior safety relative to interferon beta-1a and beta-1b was rejected on grounds of insufficient evidence; without an accepted non-inferiority claim, the accompanying cost-minimisation analysis could not be supported. The July 2013 resubmission incorporated an additional head-to-head trial, updated indirect comparisons, post hoc analyses, and adopted ARR as the primary outcome. On this basis, the PBAC accepted the non-inferiority claim, citing the improved consistency and clinical plausibility of the evidence considered as a whole.

Direct head-to-head evidence is uncommon in this therapeutic class, and indirect comparisons vary considerably in strength. Pharmacological plausibility and the consistency of the broader evidence network have, in several instances, supported an inference of non-inferiority even where confidence intervals exceeded historically applied margins. In the March 2021 submission of ofatumumab, indirect comparisons with fingolimod were individually assessed as low quality and at high risk of bias; the PBAC nonetheless accepted the non-inferiority claim on the basis of the totality of evidence and its consistency across the network.

PRICING FRAMEWORK

Where non-inferiority is accepted, the PBAC's pricing approach has been one of price parity rather than value-based pricing, where a therapy assessed as no better than its comparator is priced to match that comparator, without recognition of differences that are unquantified or have not been demonstrated as superior. Of the 14 DMTs reviewed, 12 (86%) were listed on this basis. In the March 2022 submission of diroximel fumarate, non-inferiority to dimethyl fumarate was accepted and the therapy cost-minimised to price parity, notwithstanding a claimed improvement in tolerability.

From approximately 2020, the reference point for cost-minimisation broadened from a single nominated comparator to the therapeutic class as a whole. In the March 2021 submission of ofatumumab, the PBAC required cost-minimisation against the least-cost alternative within the higher-tier class, rather than the Sponsor's nominated comparator alone. In May 2025, the Committee rejected both a weighted-average pricing approach and a proposed price premium over fingolimod for ublituximab, consistent with this class-wide reference point.

This class-wide floor has consistently constrained attempts at price inheritance, in which a Sponsor nominates a higher-cost comparator in order to inherit its pricing relativity. In the July 2016 submission of daclizumab, the PBAC declined to accept inheritance from a comparator that was not itself the least expensive alternative and accordingly, deferred the submission.

CLINICAL NEED

Clinical need appears to have exerted limited influence on pricing outcomes once a therapy has been assessed against an equivalent comparator, including in cases where that need was substantial. An earlier exception is natalizumab, which secured a premium despite considerable uncertainty, reflecting high unmet need in RRMS prior to the emergence of the class-wide anchoring approach described above. Submissions occurring after this shift do not exhibit comparable outcomes, suggesting that the influence of unmet need on pricing may be time-dependent, tied to the evolution of the Committee's broader assessment framework rather than a stable feature of its decision-making.

Siponimod provides a further illustration. As the first PBS-listed therapy for SPMS, it addressed a population with no prior treatment option; nonetheless, it was not reimbursed on the basis of a superiority-based cost-effectiveness claim. The existence of a genuine treatment gap did not alter the applicable pricing logic once the therapy was assessed against an equivalent comparator.

Where multiple effective therapies were already listed, unmet need appears to have carried still less weight. The submissions for ozanimod (March 2020), ofatumumab (March 2021), and diroximel fumarate (March 2022) each entered an increasingly crowded therapeutic class, substituting for already-listed therapies rather than addressing an unmet need, and each was cost-minimised to an existing comparator. Arguments emphasising greater treatment choice were acknowledged in these submissions but do not appear to have influenced the pricing outcome.

SUMMARY

Across the cases reviewed, the PBAC's decision-making follows a consistent sequence: an assessment of whether inferiority can be excluded, followed by an assessment of whether additional benefit has been demonstrated. Where no additional benefit is established, price is set at the lowest cost equivalent within the class. This pattern holds irrespective of clinical need, with the possible exception of the earlier, pre-2020 natalizumab decision. Attributes such as convenience, route of administration, and product design are generally not reflected in price in the absence of demonstrated superiority.

4. Utilisation of DMT and economic impact

KEY POINTS

- PBS-subsidised DMT use in MS expanded substantially between 1996 and 2025: annual services increased from 14,662 in 1997 to 201,724 in 2025, with an estimated 24,000 people receiving treatment in 2025.
- Treatment has progressively shifted from first-generation injectable therapies towards newer, higher-efficacy DMTs; the proportion of treated people receiving therapies within the higher PBS pricing tier reached 83% in 2025.
- By 2025, ocrelizumab was the most commonly used DMT, accounting for an estimated 33% of treated people, followed by ofatumumab, natalizumab, fingolimod and cladribine.
- Patterns of administration have also changed with oral therapies overtaking injectables after 2013, while infusion therapies became the predominant route among treated people from 2023 to 2025.
- Government expenditure based on published prices increased from $18.5 million in 1997 to more than $558 million in 2025, with cumulative PBS benefits paid for DMTs for MS totalling approximately $6.7 billion over 1996–2025.
- Published-price expenditure overstates the net cost to Government. DUSC data indicate that effective-price expenditure declined by 14.4% between 2019 and 2024 despite a 13.3% increase at published prices, suggesting that confidential rebates have materially offset the budget impact of rising uptake of newer DMTs.

This section examines trends in the use and economic impact of DMTs for MS over the past three decades, through a review of publicly available PBS services and expenditure data. The review comprised an evaluation of published PBS utilisation resources, including Drug Utilisation Sub-Committee (DUSC) reports and peer-reviewed literature, and direct extraction of data from Services Australia PBS Item Reports across the 30-year history of PBS listing of DMTs for MS from 1996 to 2025.

4.1. Published PBS utilisation data

4.1.1. DUSC reviews

To contextualise patterns of PBS utilisation and expenditure for MS DMTs, publicly available DUSC Public Release Documents[d] relevant to MS treatments were reviewed. DUSC is a subcommittee of the PBAC that assesses projected medicine use and financial costs, analyses actual PBS utilisation, and provides advice to the PBAC on how real-world use compares with the assumptions underpinning reimbursement decisions.

Five published DUSC reports reviewing utilisation of RRMS treatments were identified: two broader reviews of DMTs for MS, published in June 2025 and October 2015, respectively, and three DMT-specific reviews of alemtuzumab, ocrelizumab and cladribine, published in February 2020, October 2020 and February 2022, respectively. An earlier June 2013 DUSC review of DMTs for MS was available only as a limited outcome statement and was therefore not included in this assessment.

d DUSC Public Release Documents available at: https://www.pbs.gov.au/industry/listing/participants/drug-utilisation-subcommittee

OVERVIEW OF FINDINGS FROM PAST DUSC/DEPARTMENT REVIEWS

In preparation for the PMR, DUSC undertook a review of **DMTs in June 2025**[58] to examine the utilisation of PBS-subsidised DMTs for RRMS using prescription processing data between January 2019 and December 2024. The review found that the number of people receiving DMTs, prescription volume and PBS expenditure (based on published prices) increased over the analysis period, alongside a shift away from early injectable therapies towards newer-generation DMTs such as ocrelizumab, ofatumumab and natalizumab. Treatment initiation was most common among people aged 40–44 years and was predominantly in women, reflecting the epidemiology of RRMS. The review also highlighted increasing treatment switching and sequencing possibilities as well as time-on-treatment.

The DUSC review of **cladribine in February 2022**[6] assessed predicted versus actual utilisation of cladribine following PBS listing in January 2019. It was reported that in 2021, prescriptions for RRMS were supplied to 22,120 people overall. DUSC observed continued shifts in the RRMS market away from older injectable therapies and towards oral and higher-efficacy treatments. Cladribine utilisation had not yet stabilised, with DUSC noting that treated patient numbers and prescriptions differed from estimates and may have been influenced by the COVID-19 pandemic. The review also found high persistence with the second cladribine treatment course, low rates of probable co-supply with other RRMS therapies, and substantial use of cladribine among people previously treated with oral therapies.

The DUSC review of **ocrelizumab in October 2020**[61] assessed predicted versus actual utilisation of ocrelizumab following PBS listing in February 2018. Treated patient numbers were slightly below predicted in the first year and broadly aligned with predictions in the second, however prescription volumes remained lower than forecast because people received fewer prescriptions on average than assumed. DUSC concluded that ocrelizumab had not substantially increased growth in the RRMS market but had rapidly substituted for older medicines. The review also highlighted differences in treatment patterns by route of administration (oral, injectable, infusion) and geographic remoteness, suggesting that dosing frequency and access to infusion services may have influenced treatment choice.

The DUSC review of **alemtuzumab in February 2020**[62] compared predicted and actual utilisation of alemtuzumab following its PBS listing in April 2015. At the time of listing, alemtuzumab was considered to address a potential clinical need in people with high disease activity, including those with poor prognostic features and those requiring escalation therapy. DUSC found that alemtuzumab had minimal impact on the overall RRMS market and was used substantially less than other DMTs, particularly natalizumab and ocrelizumab. It was reported that in 2018, 18,715 people were supplied a PBS-listed medicine for RRMS and, of these, 459 (2.5%) were supplied alemtuzumab. Most of its use (84%) was as a second or subsequent-line treatment for RRMS. Utilisation was higher than predicted in the first year but declined in subsequent years, with DUSC noting that emerging safety concerns and the availability of newer RRMS treatments (e.g., ocrelizumab) may have contributed to the declining use of alemtuzumab. The review also identified quality use of medicines issues, including the use of other RRMS medicines within the expected period of alemtuzumab clinical benefit, contravening the PBS restriction, and the need for ongoing safety monitoring.

The DUSC review of **DMTs in October 2015**[63] reviewed the utilisation of all PBS-listed medicines for RRMS at the time (n=9), with a focus on assessing the predicted versus actual use of the oral DMTs; dimethyl fumarate, teriflunomide and fingolimod. The review found that the introduction of oral therapies was associated with growth in the treated RRMS population and a shift away from injectable therapies, resulting in growth in overall expenditure. Overall, 13,648 people were treated with a PBS medicine for RRMS in 2014, with dimethyl fumarate the most frequently used DMT for people with MS new to therapy. Fingolimod was the most widely used drug, while dimethyl fumarate uptake in its first year was higher than predicted and teriflunomide use was substantially lower than expected. DUSC considered that the RRMS market had grown at a steady rate, largely driven by the uptake of dimethyl fumarate, fingolimod and to a lesser extent, teriflunomide. While increased treatment uptake may partly reflect changes to diagnostic criteria that enabled earlier or more frequent MS diagnosis, it also suggests greater willingness of people with MS to commence therapy and the unmet need for more convenient treatment options.

4.1.2. Other published sources

A series of published PBS prescription data analyses for DMTs for MS were identified in the literature, including estimation of MS prevalence by geographic area using prescription data from 2024[5]; 2021[64] and 2018–2022[65] to elicit spatio-temporal trends in MS distribution; and evaluations of PBS utilisation and cost trends for RRMS DMTs from 1996–2019[66], 2010–2021[67] and 2013–2022[68].

OVERVIEW OF FINDINGS FROM PUBLISHED PBS UTILISATION DATA SOURCES

The latest prevalence estimates from the Menzies Institute for Medical Research, derived from PBS prescription data for MS therapies, indicate sustained increases in both the number and crude rate of Australians living with MS[5]. The estimated prevalence rose from almost 21,300 people (95.6 per 100,000 population) in 2010 to more than 25,600 (104.1 per 100,000) in 2017, more than 33,300 (131.1 per 100,000) in 2021 and almost 37,800 (139.2 per 100,000) in 2024.

Goudarzi[66] examined PBS-subsidised DMT utilisation for RRMS over the longest study period, from the inception of PBS funding in 1996 to 2019 and reported average annual growth in total DMT prescriptions of 18%. The predominant therapy shifted from interferon beta-1b (1996–2000) to interferon beta-1a (2001–2014) and then to fingolimod (2015–2019), reflecting the progressive uptake of newer therapies, particularly oral agents. Utilisation varied geographically and was highest in Tasmania in 2019, while fingolimod and ocrelizumab together accounted for 55% of total DMT expenditure that year.

The study by **Wang[67]** examined utilisation patterns and treatment persistence of DMTs for MS using a 10% sample of PBS dispensing data supplied by Service Australia as well as healthcare resources from a payer perspective based on expenditure from PBS item reports. The sample included 2,315 people who received their first DMT treatment between 2010 and 2021, reporting the number receiving treatment increased approximately five-fold, while PBS expenditure increased 4.5-fold, from AUD $109.4 million to $492.9 million. Higher-efficacy DMTs increasingly replaced lower-efficacy therapies for both initiation and switching and were associated with longer median persistence (25.5 versus 20.8 months). Growth in expenditure was attributed principally to increasing numbers of people with MS, greater use of higher-efficacy therapies and longer treatment persistence.

PBS utilisation and cost trends for MS-related DMTs between 2013 and 2022 were examined by **Zhao[68]**. The study reported that the number of people prescribed DMTs per 10,000 population increased by 125% nationally, while costs increased by 164%. The proportion of treated people receiving higher-efficacy DMTs rose from 54% in 2013 to 75% in 2022. Fingolimod was the most commonly used DMT until 2020, after which ocrelizumab became predominant.

4.2. PBS utilisation and expenditure

To extend on the information sources described above, PBS services and Government expenditure data were directly extracted for the 18 DMTs listed on the PBS for MS between 1996 and 2025. These data were sourced from the Australian Government Services Australia website which publishes Pharmaceutical Benefits Schedule Item Reports comprising of prescription and expenditure data from PBS and Repatriation Pharmaceutical Benefits Scheme (RPBS) services.

The extracted data were analysed to characterise utilisation and expenditure trends overall, by individual DMT and by PBS-established efficacy tier and route of administration. Furthermore, the approximate number of people on treatment for each DMT was estimated using the average annual prescription frequency as per the recommended dosing schedule. As most PBS maximum quantities of DMTs provide sufficient supply for one month of therapy (28 or 30 days), annual prescription volumes were divided by either 13.04 or 12.18, respectively, to approximate the number of patient-years on treatment. For DMTs with less frequent dosing, annual prescription volumes were divided by the expected number of PBS supplies per year, e.g., two for ocrelizumab, cladribine and ublituximab, and one for alemtuzumab as well as other adjustments for initiation/titration packs.

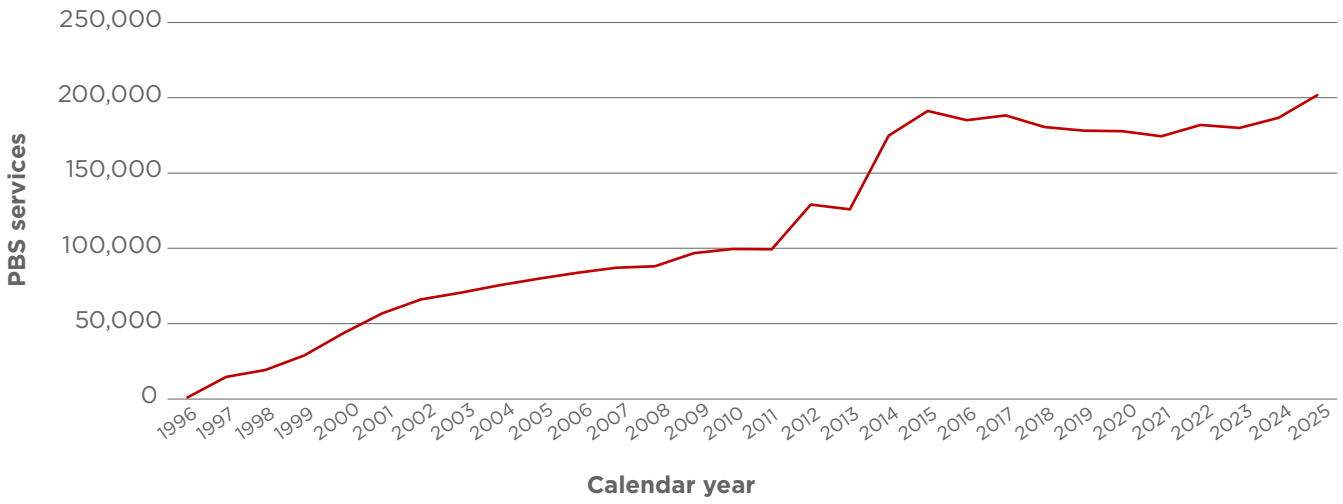
Note: No utilisation was recorded for ublituximab during the analysis period, as its PBS listing commenced in January 2026.

4.2.1. PBS services

The total number of Government-subsidised services/prescriptions for PBS-listed DMTs for MS has increased from 14,662 services in 1997 (interferon beta-1b in its first full year of listing) to 201,724 services in 2025, with an observable plateau in prescription volumes between 2015 and 2025 (Figure 13). This plateau could in part be explained by the lower frequency of supply of newer listed agents, such as ocrelizumab, cladribine and alemtuzumab.

Overall, 3,466,332 services for DMTs for MS have been supplied through the PBS between 1996 and 2025, with an average of approximately 180,000 prescriptions per year over the most recent 10-year period (2016 to 2025).

Figure 13: Number of PBS services/prescriptions for PBS-listed DMTs for MS (1996–2025)



Note: Data extracted from Services Australia Pharmaceutical Benefits Schedule Item Reports [April 2026]

The relative market share of PBS-listed DMTs as a function of the number of services/prescriptions supplied was relatively evenly distributed across the ABCR therapies prior to 2010, with interferon beta-1b accounting for the largest share. Following the listing of natalizumab and subsequently, the oral therapies (fingolimod, dimethyl fumarate and teriflunomide), utilisation shifted away from the earlier injectable therapies. After its listing in 2011, fingolimod emerged as the most common DMT for RRMS, with an average of approximately 60,000 prescriptions per year between 2014 and 2020. Fingolimod has continued to account for a substantial share of services, broadly comparable with natalizumab and ofatumumab in recent years. As noted above, the seemingly lower service volumes for ocrelizumab, cladribine and alemtuzumab should be interpreted in the context that these medicines require fewer PBS supplies per year because of their less frequent dosing schedules.

4.2.2. Estimated number of people treated with DMTs for MS

Figure 14A shows the number of people estimated to be treated with DMTs for MS, stratified by DMT. Approximately 24,000 people were estimated to be treated with DMTs for MS in 2025.

This analysis suggests that interferon beta-1b accounted for the largest share of treated people during the first 12 years of PBS-subsidised DMT availability, before its use gradually declined coinciding with the listing of natalizumab in 2008. Natalizumab uptake increased steadily before stabilising at approximately 13% market share from 2013 onwards. Fingolimod was listed in 2011 as the first oral DMT for MS and was rapidly adopted, representing the largest market share of people with MS between 2013 and 2019. Its use subsequently declined coinciding with the listing and rapid uptake of ocrelizumab in 2018. In 2025, treatment was dominated by ocrelizumab (33%), followed by ofatumumab (15%), natalizumab (13%), fingolimod (11%), cladribine (10%), and dimethyl fumarate and teriflunomide (5% each), with all remaining DMTs accounting for less than 3% market share each.

Annual growth in the number of treated people was lower in the most recent 10-year period, at 5.4% from 2016 to 2025, compared with 9.5% from 2006 to 2015. This earlier higher rate of growth may have been driven by the availability of fingolimod and dimethyl fumarate, with an approximately 30% year-on-year increase in people treated in 2012 and 2014, respectively.

Since the introduction of the higher-efficacy DMTs and the PBS dual-tier pricing system in 2008, use of MS DMTs has increasingly shifted towards the higher-efficacy, higher-priced therapies. With utilisation relatively evenly distributed across the two pricing tiers in 2015, the share of people treated with higher-priced DMTs has continually increased since, reaching 83% in 2025 (Figure 14B).

Considering DMTs by route of administration, most people were treated by injection until 2013, after which oral treatment comprised the most predominant form. Uptake of intravenous (IV) infusion therapies was initially modest following the availability of natalizumab in 2008 and alemtuzumab in 2015. The listing of ocrelizumab in 2018 coincided with a further increase in infusion use, with infusion therapies subsequently surpassing both injectables and oral therapies during the final three years of the analysis period (2023–2025). As infusion therapies gradually dominated market share, injection therapies decreased until the availability of ofatumumab in 2021 and the injectable form of natalizumab in 2024, whilst oral therapies have remained relatively stable over the past 10 years (Figure 14C).

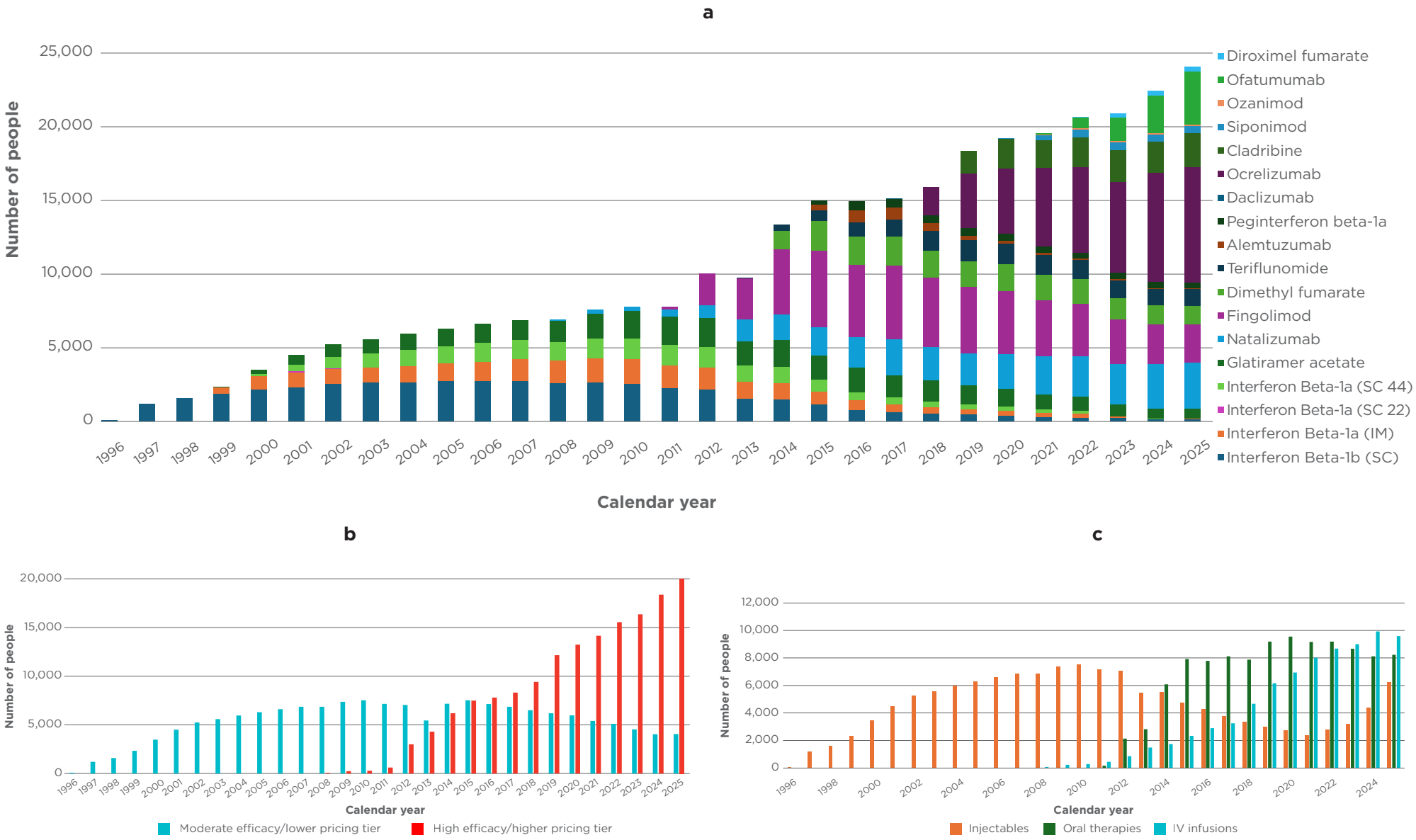


Figure 14: Estimated number of people treated with PBS-listed DMTs for MS (1996–2025) a) by drug; b) by lower and higher PBS pricing tiers; c) by route of administration

Note: Data extracted from Services Australia Pharmaceutical Benefits Schedule Item Reports [April 2026]

4.2.3. PBS benefits

The benefits paid for services describes the economic impact of DMTs on the Australian healthcare system. It should be noted these costs are based on published or list drug prices and therefore do not account for rebates paid where confidential special pricing arrangements (SPAs) exist between the Department of Health and manufacturers. As of June 2026, the following DMTs for MS have a SPA: alemtuzumab, ocrelizumab, siponimod, ozanimod, ofatumumab and ublituximab. Several DMTs had a SPA at the time of listing which are no longer in effect: natalizumab, fingolimod, dimethyl fumarate, teriflunomide and cladribine.

Figure 15 shows the total benefits paid for PBS-listed DMTs for MS based on published prices depicting the net costs of subsidising DMTs in Australia between 1996 and 2025. The net cost of DMTs rose from over $18.5 million in 1997 (first full year of DMT listing) to over $558 million in 2025. Overall, the total Government expenditure on DMTs over the past 30 years equated to $6.7 billion. However, the June 2025 DUSC analysis (described in Section 4.1.1 above) reveals that the benefits paid based on **effective** prices decreased from $326,119,635 in 2019 to $279,256,048 in 2024 (a decrease of 14.4%), compared with benefits paid based on published prices increasing from $448,814,609 in 2019 to $508,595,516 in 2024 (an increase of 13.3%). The difference between listed-price and effective-price expenditure suggests that approximately 50% of current drug costs are offset through rebates. This is likely attributable to the increasing use of DMTs in contemporary practice subject to confidential SPAs.

At the individual DMT level, expenditure was dominated by interferon beta-1b for the first 15 years following PBS listing (1996–2011). This was followed by a shift towards fingolimod, which accounted for over one-third of DMT expenditure between 2012 and 2018, before ocrelizumab became the predominant driver of benefits paid from 2020 onwards. By 2025, ocrelizumab accounted for almost half of DMT spending (46%), followed by ofatumumab (19%) and cladribine (15%); while natalizumab and fingolimod represented 7% and 6% of expenditure, respectively, and all other DMTs each accounted for less than 3%.

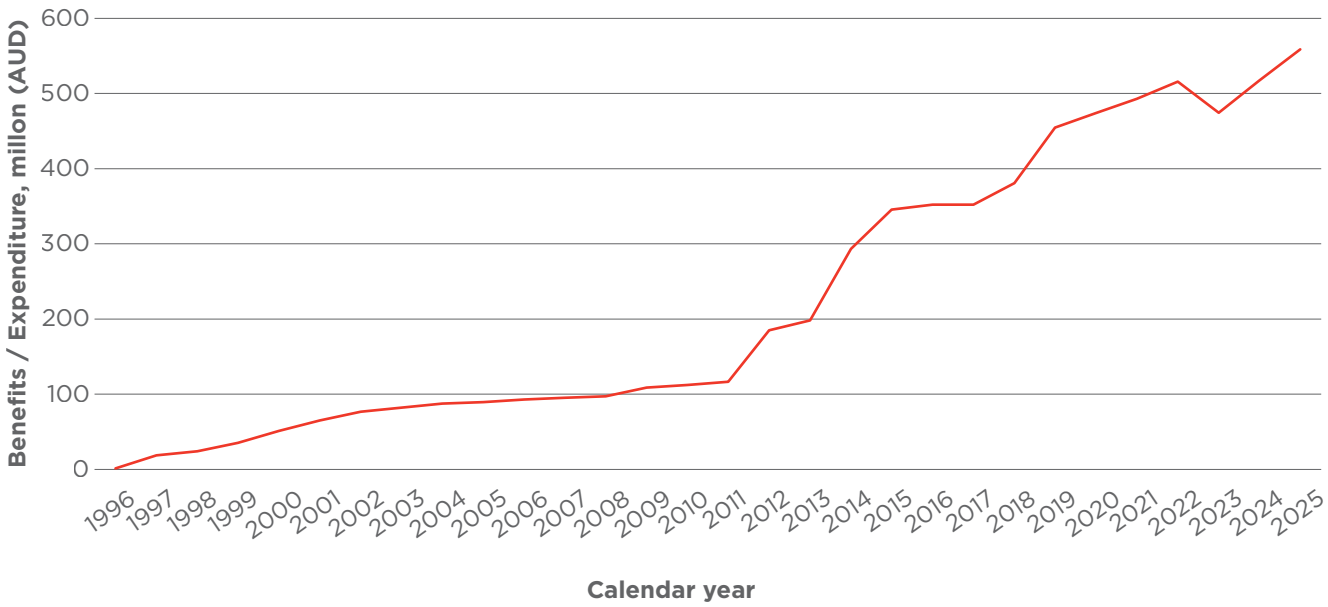


Figure 15: PBS benefits paid (expenditure) for PBS-listed DMTs for MS (1996–2025) [published prices; nominal unadjusted values]

Note: Data extracted from Services Australia Pharmaceutical Benefits Schedule Item Reports [April 2026]

DMTs within the higher PBS pricing tier surpassed those in the lower pricing tier in expenditure by 2013, within five years of the first PBS listing in this higher tier, and have since dominated MS-related PBS spending (Figure 16B). In 2025, DMTs within the higher PBS pricing tier accounted for 96% of the MS market, corresponding to $535.4 million in benefits paid, compared with 4% for DMTs in the lower pricing tier ($23.1 million). However, the June 2025 DUSC analysis (described in Section 4.1.1 above), based on effective rather than published prices, estimated 2024 benefits paid of $253.2 million for DMTs in the higher pricing tier and $23 million for those in the lower pricing tier, representing 91% and 9% of expenditure, respectively.

When considered by route of administration, injectables accounted for the greatest share of expenditure at published prices until 2012, before being overtaken by oral therapies in 2013. From 2021 onward, IV infusions became the predominant driver of expenditure. By 2025, IV infusions accounted for half of DMT spending, followed by oral therapies (26%) and injectables (24%) (Figure 16C).

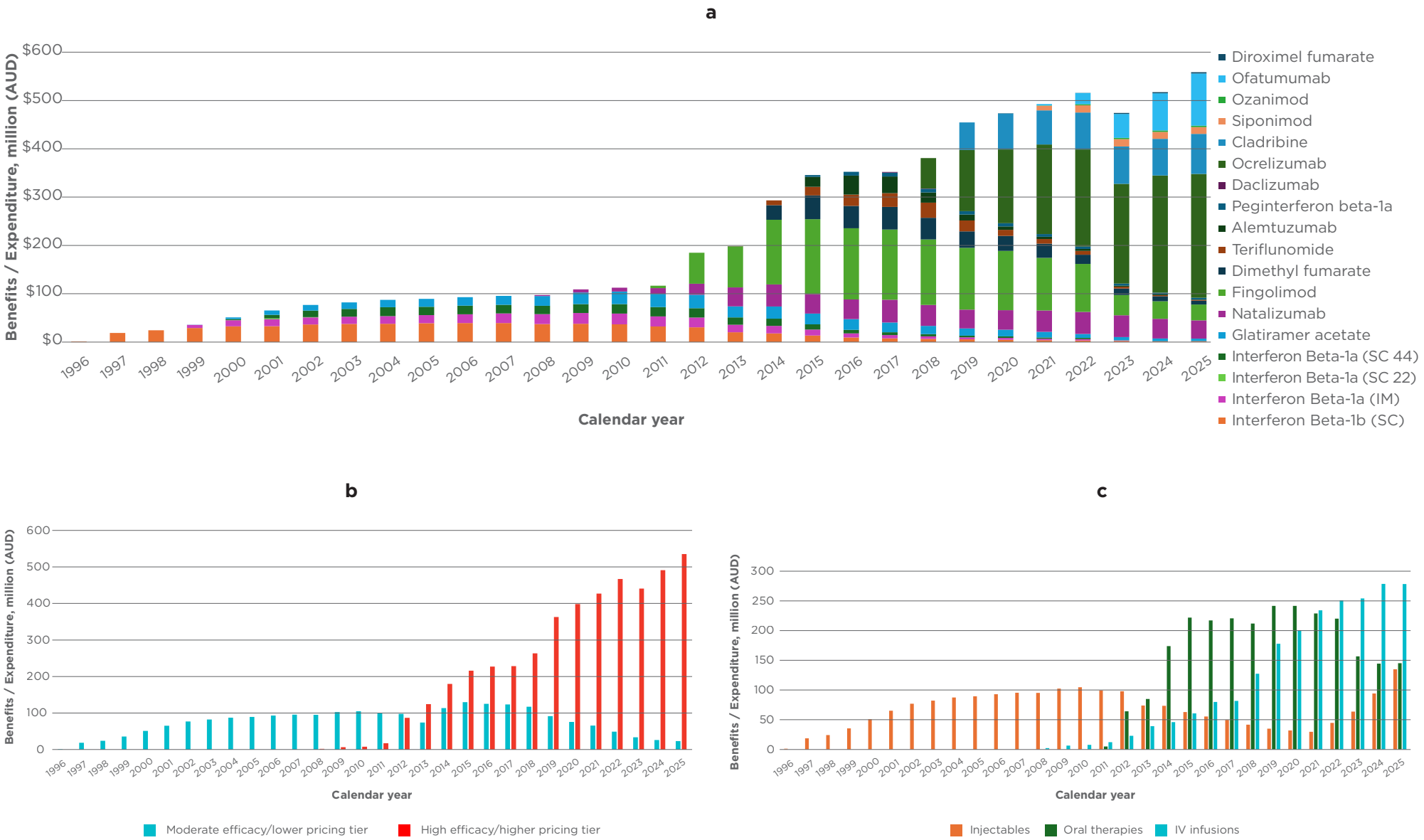


Figure 16: Benefits paid (expenditure) by the Australian Government for PBS-listed DMTs for MS based on published prices (1996–2025): a) by drug; b) by lower and higher PBS pricing tiers; c) by route of administration (nominal unadjusted values)

Note: Data extracted from Services Australia Pharmaceutical Benefits Schedule Item Reports [April 2026]. See Appendix A for details of DMTs with SPAs.

4.2.4. Summary

Overall, this bespoke analysis of PBS utilisation and expenditure highlights substantial growth and diversification in DMT use since interferon beta-1b was first listed in 1996, with the MS treatment market increasingly shifting towards a select group of newer-generation, higher-efficacy and higher-priced therapies. This is consistent with monoclonal antibodies directed against CD20-expressing B cells emerging as the first-line therapy of choice in many settings due to favourable efficacy and safety[16].

Over the analysis period, the number of individuals receiving DMTs for MS has increased substantially, contributing to growth in the total cost of subsidising these therapies for the Australian Government. Notably, DUSC estimated that the number of people receiving a PBS-listed DMT for RRMS is increasing at an annualised rate of 4.4%, exceeding what would be expected from population growth alone[58].

In recent years, treatment use has increasingly favoured infusion and other high-efficacy therapies, with ocrelizumab (IV infusion) emerging as the most commonly used DMT for RRMS, followed by ofatumumab (subcutaneous injection), natalizumab (IV infusion) and fingolimod (oral therapy). This pattern suggests that prescribing is increasingly oriented towards treatments perceived to provide greater disease control, supported by a combination of clinical efficacy, safety considerations, clinician and patient preference, and practical factors such as route and frequency of administration. While ocrelizumab and ofatumumab accounted for the largest shares of Government net cost expenditure, broadly consistent with patient utilisation, cladribine represented the next highest contributor to net costs despite lower patient use.

Importantly, although PBS expenditure based on published prices has increased over time, net costs have declined when assessed using effective prices. This suggests that confidential pricing arrangements and rebates have helped offset the budgetary impact of increasing use of newer-generation, high-cost DMTs. As a result, the PBS has supported access to higher-efficacy therapies while containing growth in Government expenditure, thereby improving the value achieved from public investment in MS treatment.

5. Cumulative value of DMTs to people with MS and society

KEY POINTS

- A disease simulation model, with model structure and inputs informed by the economic literature, was developed to estimate the long-term health outcomes associated with individual DMTs relative to natural history.
- Long-term estimates of treatment-specific outcomes were combined with historical PBS utilisation data to estimate the aggregate value generated by DMT use at the population level over time.
- Between 1996 and 2025, the uptake of DMTs can be attributed to the prevention of an estimated **446 MS-related deaths** and **80,866 relapses**.
- Over the same period, the uptake of DMTs resulted in an estimated **3,479 life years gained** and **61,836 quality-adjusted life years (QALYs) gained**.
- In total over the period 1996 to 2025, 319,786 patient years of treatment with the DMTs has accrued $8.4 billion in PBS expenditure ($2025) and returned $21.6 billion in economic value through savings in MS-related health care costs ($3.6 billion), productivity costs ($1.9 billion), informal care costs ($0.5 billion) and QALYs gained ($15.6 billion).
- After accounting for PBS expenditure, the net monetary value of the DMTs is **$13.2 billion**, equating to a benefit to cost ratio of 2.58. That is for every $1 spent on DMTs between 1996 and 2025, $2.58 has been returned in health care cost savings and improved quality and/or length of life.
- Focusing on the period between 2018 and 2025, it is estimated the cumulative monetary benefit of DMTs in Australia was almost three times their aggregate PBS expenditure.

5.1. Objectives

Section 4 above quantified the total PBS utilisation and spend on DMTs over their reimbursed lifespan in Australia. This section seeks to estimate and then place an economic value on the additional health outcomes accrued by people with MS treated with DMTs over the same period, to contextualise these benefits relative to total costs via a cost-benefit analysis.

We used an economic evaluation to firstly estimate the per-patient and per-patient year health outcomes attributable to DMT use (relative to natural history), specific to each of the individual DMTs reimbursed in Australia since their introduction. Secondly, by applying this output to population-level PBS utilisation estimates in Section 4, a year-by-year assessment of DMT-attributable health outcomes can be gained and analysed respective to total costs.

5.2 Methods

5.2.1. Review of published economic models of MS interventions

A literature review of recently published and HTA-reviewed cost-effectiveness models of DMTs for RRMS was conducted to inform the model structure and input values of the economic evaluation. A total of four economic models were selected for detailed review as potentially relevant for guiding the approach of the current economic model.

BAHARNOORI (2022)[69]

Baharnoori[69] is an industry-sponsored cost-utility analysis calculated from the perspective of the Canadian healthcare system. The economic evaluation used a Markov cohort model to calculate the incremental cost-effectiveness of ofatumumab compared to glatiramer acetate and best supportive care (BSC) in people with RRMS. A lifetime model horizon (65 years) was assumed with costs and outcomes discounted at 1.5% per annum. Health states of the Markov model were defined by EDSS (0–9), plus death. Transition probabilities (for disease progression) and relapse rates for natural history were informed by the British Columbia MS (BCMS) database (Figure 17). The treatment effect of ofatumumab was applied via HRs and RRs sourced from a published NMA. Treatment discontinuation rates were modelled as constant probabilities up until a maximum treatment duration of 10 years, reflecting clinician opinion rather than trial-observed rates. People with RRMS reaching an EDSS score of ≥7 were assumed to discontinue treatment and switch to BSC consistent with Canadian clinical practice and current recommendations from the ABN.

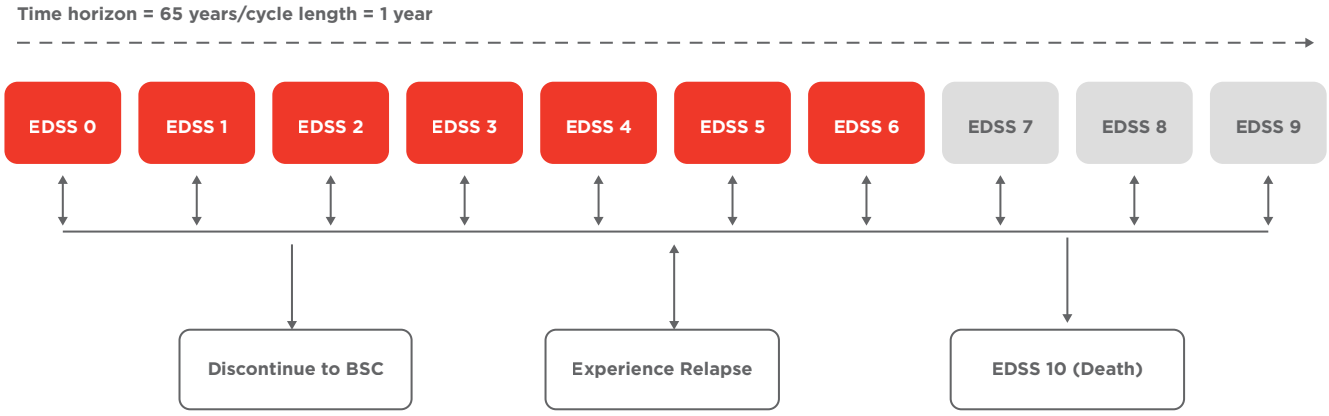


Figure 17: Baharnoori (2022)[69] model structure

NICE (2021)[70]

This is a UK HTA appraisal submission featuring an economic evaluation that is structurally similar to Baharnoori[69]. The Markov model based on EDSS, using BCMS data for RRMS transitions but London Ontario data (supplemented by EXPAND trial data) for RRMS to SPMS transitions, giving it a more granular 21-state structure (10 RRMS states, 10 SPMS states, death) than the Canadian model. NICE's Evidence Review Group challenged and revised assumptions including having disease management costs specific to SPMS rather than shared across phenotypes and declining rather than fluctuating relapse rates with increasing EDSS. All-cause discontinuation rates were accepted as a reasonable proxy for treatment waning in the absence of longer-term trial data with waning scenarios required as sensitivity analyses. A limitation of this model is that it does not capture treatment sequencing, despite this being standard clinical practice.

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW (2023)[46]

This US-based, payer-oriented report[46] developed a de novo Markov model comparing ublituximab, natalizumab, ofatumumab, and ocrelizumab. A NMA was used to determine comparative efficacy among the included DMTs. The economic model used a 20-state EDSS structure (EDSS 0–9 in RRMS, 1–9 in SPMS, plus death), a lifetime horizon, annual cycles, and a 3% discount rate (Figure 18). Health state transition probabilities for natural history were sourced from the same underlying placebo-arm/London Ontario evidence base used in earlier ICER reviews.

A strength of this model is its explicit choice to anchor all comparisons to a single reference comparator (dimethyl fumarate) rather than letting Sponsors nominate bespoke comparators. The report is transparent about the limitations of its own natural history data, explicitly stating that use of >10-year-old progression rates likely biases treatments toward appearing more cost-effective than they would with contemporary (slower-progressing) natural history data. It also addressed the EDSS ≥8/9 utility problem, where community-preference (EQ-5D) data implied utilities worse than death. Rather than accepting this at face value, ICER extrapolated a non-linear function to avoid implausible negative utilities.

The model explicitly does not permit head-to-head comparison between the monoclonal antibodies, which limits its direct usefulness for a project focused on comparing DMTs against one another. Post-discontinuation, people are all switched to a fixed "market-leading monoclonal antibody" proxy rather than a modelled realistic treatment sequence, and treatment benefit is assumed to persist unchanged after conversion to SPMS. These are both simplifying assumptions that may not reflect biological plausibility or real-world prescribing patterns. As with the other models, discontinuation after the first two years is assumed to be driven only by serious AEs, thereby disregarding treatment switching or discontinuation due to perceived lack of efficacy, breakthrough disease activity, tolerability issues, or patient preference.

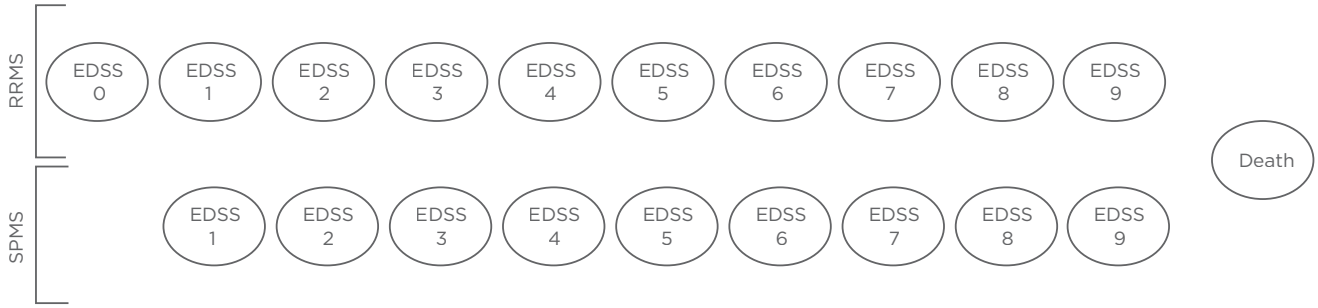


Figure 18: ICER (2023)[46] model structure

PALMER (2026)[71]

This is a natural history model rather than treatment comparator model developed from an Australian healthcare perspective. It updated the earlier Australian model[72] by adopting a more granular 5-state structure (no/mild/moderate/severe disability plus death, rather than a 4-state no/mild-combined structure) (Figure 19). It also draws on substantially larger and more contemporary data, including the MSBase Australian cohort (n = 6,369) and the MS Prevalence and Health Economic Impact in Australia 2025 Report, replacing decade-old, small-cohort (n = 330–2,146) inputs from the original model.

Separating "no disability" from "mild disability" addressed a genuine face-validity concern in the earlier model, since these groups differ meaningfully in cost and quality of life. Critically for the purposes of this analysis, the model does not distinguish between individual DMTs but uses a pooled real-world mix of DMT transition probabilities. As such, it cannot itself be used to compare the cost-effectiveness of specific therapies, only to describe the natural history burden of MS in Australia under current practice. The authors flag this explicitly as future work. The model also does not account for comorbidities, end-of-life costs, time-varying transition probabilities and carer or broader societal impacts. Mortality risk ratios were instead drawn from a 1997 UK study[73], due to known underestimation of mortality within MSBase itself.

Of the reviewed economic models, Palmer[71] is the most directly relevant to the local context, being Australian-specific (in terms of transitional probabilities, costs and utilities) and the most recently published.

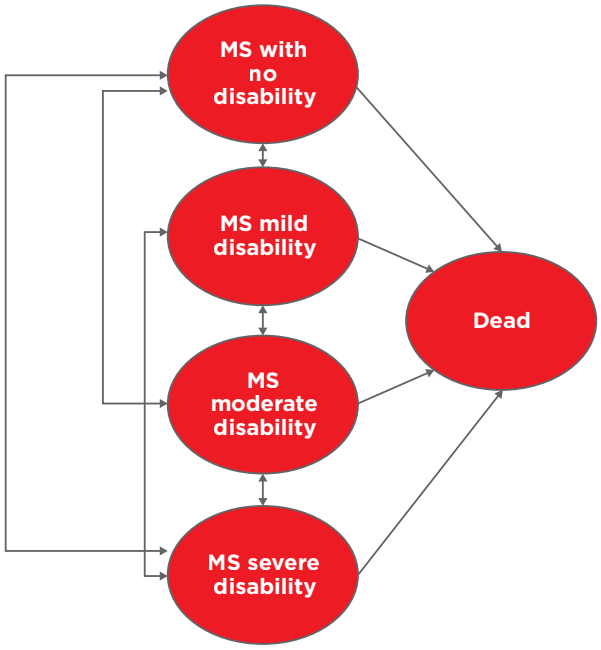


Figure 19: Palmer (2026)[71] model structure

Health states defined on the basis of disability level: MS with no disability (EDSS: 0.0); MS with mild disability (EDSS 1.0–3.5); EDSS with moderate disability (EDSS 4.0–6.0); and severe disability (EDSS 6.5–9.5). Note any health state was allowed to transition to itself, or to other health states, including death. Death was an absorbing state, with no possibility of any further transitions. Transient relapse events (not shown) can occur from each health state, the probability of which is state dependent.

APPROACHES TO THE CURRENT MODEL

Across the reviewed models, several consistent modelling conventions were identified. The use of cohort Markov structures based on EDSS-defined disability states were common. Identified models incorporated relapses as transient events, applied treatment effects to relapse and disability progression and projected outcomes over long-term or lifetime horizons. These features were considered appropriate for the present analysis because they allow the cumulative clinical consequences of DMT exposure to be estimated over time. However, the review also highlighted important limitations, including reliance on older natural history datasets, simplified treatment discontinuation and sequencing assumptions, limited representation of broader societal outcomes, and variable use of jurisdiction-specific costs and utilities. These findings informed the present model, which adopted an EDSS-based Markov structure consistent with prior evaluations, while adapting the framework to estimate the cumulative historical value associated with DMT availability and uptake in Australia.

5.2.2. Overview of model framework

Conventional economic evaluations (including those of MS therapies) are designed to estimate the incremental cost-effectiveness of a single intervention relative to a comparator at a specific point in time. However, in contrast, the objective of the present analysis was to estimate the overall cumulative clinical, economic and societal value generated by the availability and uptake of DMTs in Australia between 1996 and 2025, rather than assessing the value of an individual DMT at a single point in time.

To achieve this, a two-stage analytical framework was developed. First, a disease simulation model was used to estimate the long-term health outcomes associated with individual DMTs relative to natural history. Second, these treatment-specific outcomes were combined with historical PBS utilisation data to estimate the aggregate value generated by DMT use at the population level over time.

The disease simulation stage generated long-term estimates for outcomes including life years, QALYs, relapses and healthcare utilisation. These outcomes were then converted into representative annual treatment benefits (i.e. per-patient year of treatment), enabling patient-level model outputs to be linked with annual population-level treatment utilisation data. Historical PBS utilisation and expenditure data were subsequently used to allow an estimate of the cumulative value generated by DMT use in Australia. This approach allowed treatment benefits accrued over three decades of DMT availability to be quantified within a common analytical framework. A natural history scenario was included to estimate outcomes in the absence of DMT treatment. In addition, a hypothetical cure scenario was explored to provide an estimate of the maximum achievable reduction in disease burden and to contextualise the proportion of disease burden addressed by currently available therapies.

5.2.3. Model structure

The disease simulation component was implemented as a cohort-based Markov model comprising 30 living health states and one absorbing death state. Health states were defined according to disease phenotype, treatment status and disability severity as measured by the EDSS. Specifically, the model included:

- treated RRMS (EDSS 0–9)
- untreated RRMS (EDSS 0–9)
- SPMS (EDSS 0–9)

The RRMS states were stratified by treatment status to reflect treatment exposure. People entered the model with RRMS at an EDSS of 0. During each annual model cycle, people could remain in their current health state, improve, progress to a higher disability level, transition from RRMS to SPMS, or die. Relapses were modelled as transient events rather than separate health states with risks applied according to disease phenotype and EDSS status.

General population all-cause mortality was adjusted using EDSS-specific excess mortality risks. The model accumulated life years, QALYs, relapses and healthcare resource utilisation over the selected time horizon.

This approach is echoed across the literature and in a recent systematic review[74] on the evolution of economic evaluation models of relapsing MS, where Markov cohort models based on the EDSS were predominantly applied for MS economic evaluations.

5.2.4. Analysis perspective and valuation

The analysis adopted a broad Australian societal perspective. Health outcomes were assessed using life years and QALYs, while economic outcomes incorporated direct healthcare costs, indirect productivity costs and informal care costs where data were available. The disease simulation component was conducted without discounting and without the application of costs. This stage was intended solely to estimate the clinical outcomes associated with DMT exposure over time.

Costs and monetary valuations were subsequently incorporated during the historical aggregation stage. This enabled health outcomes generated under historical patterns of DMT utilisation to be valued using contemporaneous expenditure data and expressed in 2025 Australian dollars. PBS expenditure was analysed separately to quantify public investment in DMT access over time and to compare this investment with the clinical and societal benefits generated.

5.3. Model Inputs

Model input selection prioritised Australian-specific evidence where available, and sufficiently granular for model structure. However, no single source provided all required parameters at the level of detail required. Consequently, international sources were used where Australian evidence was unavailable or where phenotype-specific or EDSS-specific estimates were required.

5.3.1. Model population

The model simulated a hypothetical cohort of Australian females aged 35 years at treatment start, entering the model with no disability (EDSS 0), consistent with the population used in Palmer[71], and reflecting the typical age of onset of MS in Australia (30–40 years) and the predominance of females among people with MS.

5.3.2. Excess mortality risk by EDSS health state

Age- and sex-specific all-cause mortality was adjusted to reflect excess mortality associated with MS using EDSS-dependent relative risk multipliers of 1.60 for EDSS 1-3, 1.84 for EDSS 4-6, and 4.44 for EDSS 7-9, sourced from Palmer[71, Table 3] (Figure 20). Palmer[71] was selected in preference to earlier model sources, including the Palmer[72] and Baharnoori[69] models, which relied on mortality estimates from Pokorski[73]. Although the relative risk estimates reported in Palmer[71] ultimately derive from Pokorski[73] due to the absence of more contemporary mortality evidence, it was considered the most recent and contextually relevant Australian source for model parameters.

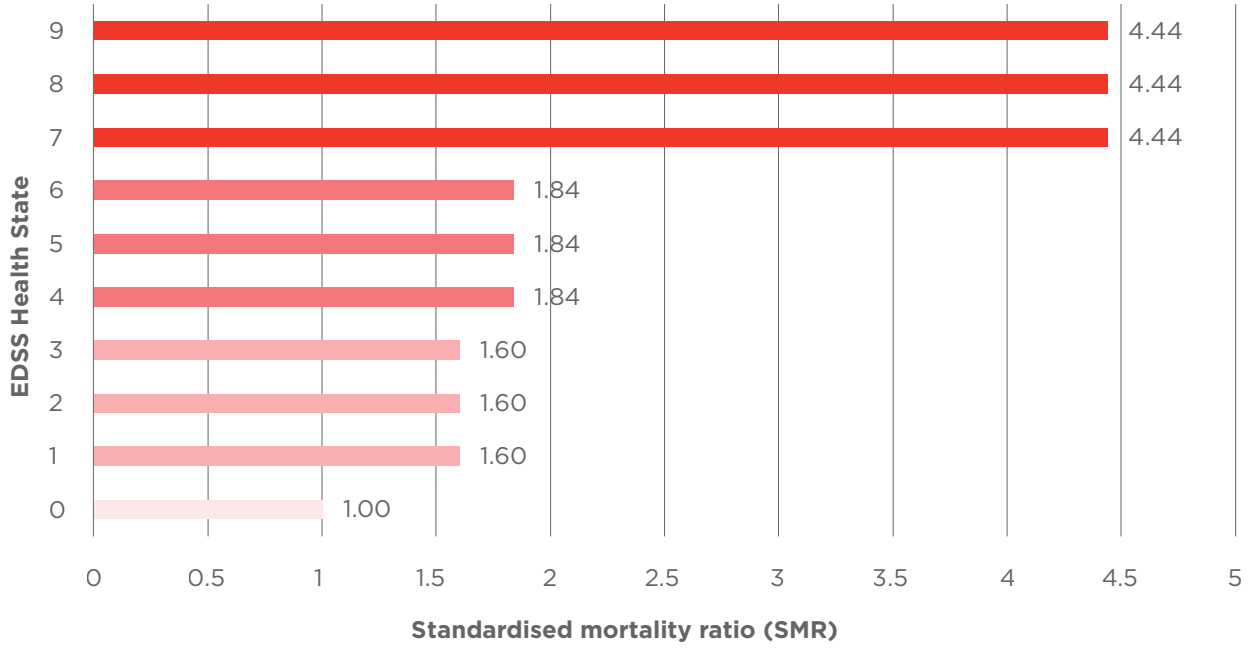


Figure 20: Excess mortality by EDSS

Abbreviations: EDSS, Expanded Disability Status Scale

Source: Palmer 2026[71]

5.3.3. Relapse rates by disease phenotype and EDSS health state

EDSS-specific annual relapse rates for the RRMS and SPMS health states were derived from Patzold and Pocklington[75], as reported in supplementary Table A.4 of Mauskopf[76]. These estimates were based on a small German cohort (n=102) followed between 1976 and 1980, comprising a mix of people with RRMS and progressive MS and categorised according to disease duration rather than EDSS score. Mauskopf[76] subsequently mapped these data to EDSS health states (Table 3). Given the age of the dataset, its small sample size, and the mixed patient population, the resulting relapse rates should be considered approximate rather than robust contemporary RRMS-specific estimates. In this data, SPMS relapse rates for EDSS 0 and 1 were reported as 0.00, reflecting the rarity of SPMS diagnoses at such low disability levels.

Table 3: Annualised relapse rates, by EDSS health state

EDSS	Annualised relapse rates	
	RRMS	SPMS
0	0.71	0.00
1	0.73	0.00
2	0.68	0.47
3	0.72	0.88
4	0.71	0.55
5	0.59	0.52
6	0.49	0.45
7	0.51	0.34
8	0.51	0.34
9	0.51	0.34

Abbreviations: EDSS, Expanded Disability Status Scale

Source: Mauskopf (2016)76 Supplementary Table A.4

5.3.4. Health state utilities and relapse disutilities

RRMS health state utilities by EDSS were derived from Orme[77]. Values were calculated as the reference case (EDSS 0, no relapse) value plus the relevant EDSS coefficient from the study's regression analysis. SPMS utilities were derived by additionally applying the study's SPMS coefficient (–0.045) as a flat offset across all EDSS states, an assumption of the underlying regression model rather than an empirically observed SPMS-specific utility profile (Table 4).

State-dependent relapse probabilities and health state utilities from Palmer[71] were also considered as a more Australian-specific option. However, these estimates were pooled across RRMS and progressive MS phenotypes, whereas Mauskopf[76] and Orme[77] provided relapse rates specific to each modelled health state. Accordingly, these estimates were considered more appropriate for informing state-specific relapse risks and health state utility in the analysis.

Relapse disutility was applied by disability severity band (no/mild/moderate/severe), corresponding to EDSS 0/1–3/4–6/7–9, sourced from Palmer[71, Table 3]. The values were applied equally to RRMS and SPMS health states and combined with an assumed relapse duration of 0.25 years (3 months). Palmer[71] was selected as the most contemporary source reporting on this parameter and reflects an Australian-context AQoL-based estimate[78].

Table 4: Health state utility values and disutility of relapse, by EDSS health state

EDSS	Health state utility value		Disutility of relapse
	RRMS	SPMS	RRMS/SPMS
0	0.870	0.825	−0.115
1	0.799	0.754	−0.060
2	0.705	0.660	
3	0.574	0.529	
4	0.610	0.565	−0.108
5	0.518	0.473	
6	0.460	0.415	
7	0.297	0.252	−0.176
8	−0.049	−0.094	
9	−0.195	−0.240	

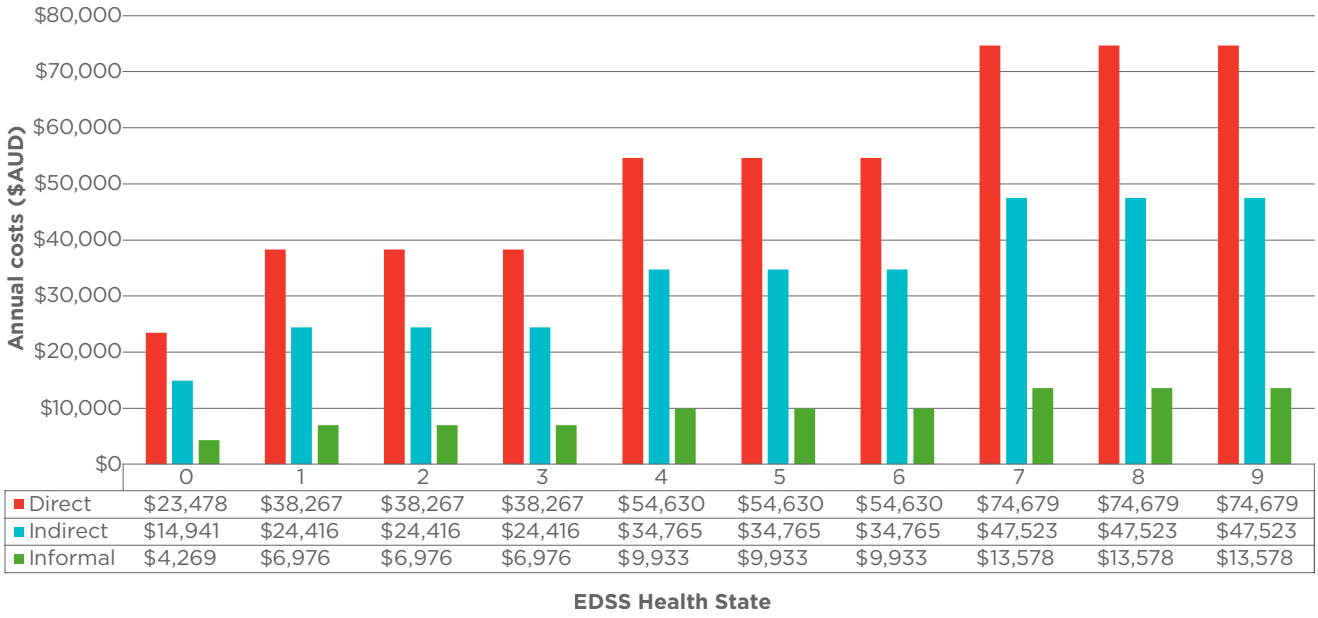
Abbreviations: EDSS, Expanded Disability Status Scale

Source: Orme (2007)[77], Table 4; Palmer (2026)[71], Table 3

5.3.5. Direct, indirect and informal resource utilisation costs by EDSS

Annual direct, indirect, and informal costs by disability severity were sourced from the MS Prevalence and Health Economic Impact of MS in Australia report[5, Tables 5.2 and 5.3] (Figure 21). The report presents costs according to disability severity only and does not provide estimates stratified by MS phenotype. Although distributions of disability severity and MS type are reported separately, these data are not cross-tabulated. Consequently, disability-specific costs were applied equally across the corresponding RRMS and SPMS health states. This approach is consistent with previous economic evaluations in MS, including Mauskopf[76], Palmer[72], and Palmer[71]. To estimate individual cost categories, the cohort-wide distribution of total costs was applied uniformly across all disability levels, with direct, indirect, and informal costs assumed to account for 55%, 35%, and 10% of total costs, respectively.

The direct healthcare cost per relapse was estimated using the average charge per separation for AR-DRG B68A ("Multiple Sclerosis and Cerebellar Ataxia, Major Complexity"), sourced from the AR-DRG Hospital Casemix Protocol Annual Report (2022–23; Table 10). Australian AR-DRG costing data were preferred to international relapse-cost estimates as they reflect local patterns of hospital resource use and reimbursement, reducing the need for currency adjustments and assumptions regarding cross-jurisdictional transferability. While the AR-DRG code captures all MS-related hospitalisations and does not isolate hospitalisations specifically attributable to relapse, it was considered the most suitable Australian source available for informing relapse-related hospital costs.



	0	1	2	3	4	5	6	7	8	9
Direct	$23,478	$38,267	$38,267	$38,267	$54,630	$54,630	$54,630	$74,679	$74,679	$74,679
Indirect	$14,941	$24,416	$24,416	$24,416	$34,765	$34,765	$34,765	$47,523	$47,523	$47,523
Informal	$4,269	$6,976	$6,976	$6,976	$9,933	$9,933	$9,933	$13,578	$13,578	$13,578

Figure 21: Annual costs by cost category, by EDSS health state

Abbreviations: EDSS, Expanded Disability Status Scale

Source: MS Prevalence and Health Economic Impact of MS in Australia (Campbell 2025)[5], Mauskopf (2016)[76], Palmer (2020)[72], Palmer (2026)[71]

5.3.6. Effectiveness of the DMTs applied to the economic model

Comparative effectiveness of each of the treatments included in the analysis, covering all DMTs used in Australia between 1996 and 2025, is modelled via a RR for relapse and a RR for disease progression. A systematic literature review and NMA[12] was utilised for this purpose, estimating RRs for ARR, as well as EDSS disability progression for each individual treatment relative to placebo as listed in Table 5.

Table 5: Relative treatment effect by DMT compared to placebo in the economic model

Treatment	RR of disability progression	RR of annualised relapse rate
Natural history	1.00 (reference)	1.00 (reference)
Interferon beta-1b (SC)	0.79	0.72
Interferon beta-1a (IM)	0.81	0.77
Interferon beta-1a (SC 22)	0.70	0.69
Interferon beta-1a (SC 44)	0.66	0.64
Glatiramer acetate	0.70	0.65
Natalizumab	0.57	0.32
Fingolimod	0.74	0.42
Dimethyl fumarate	0.66	0.50
Teriflunomide	0.70	0.67
Alemtuzumab	0.43	0.28
Peginterferon beta [a]	0.43	0.65
Daclizumab [b]	0.74	0.42

Treatment	RR of disability progression	RR of annualised relapse rate
Ocrelizumab	0.39	0.34
Cladribine	0.67	0.42
Siponimod [c]	0.74	0.45
Ozanimod	0.77	0.43
Ofatumumab	0.46	0.30
Diroximel fumarate [d]	0.66	0.50
Ublituximab	0.59	0.31

Abbreviations: DMT, disease-modifying therapy; IM, intramuscular; RR, rate ratio; SC, subcutaneous

Source: Samjoo (2023)[12]

a. Tolley 2015[79] (disability progression value reflects a HR for 6-month disability progression, treated as equivalent to RR for consistency)

b. Non-inferior to fingolimod (proxied to fingolimod based on PBAC's accepted non-inferiority determination, November 2016 daclizumab resubmission)

c. Kappos 2018[80] (siponimod not evaluable within Samjoo 2023's RMS-restricted network due to SPMS-predominant pivotal trial population. Estimate sourced from pivotal EXPAND trial)

d. Non-inferior to dimethyl fumarate (proxied to dimethyl fumarate based on PBAC's accepted determination, March 2022 Diroximel fumarate submission)

5.4. Model Results

The Markov cohort analysis was separately run for each of the DMTs, reporting estimated outcomes for a 30-year time horizon accounting for treatment-specific RRs for progression and relapse relative to placebo. By expressing modelled outcomes relative to estimated treatment durations, benefits per year of DMT exposure can be calculated, capturing the expected MS-related deaths avoided, life years gained, QALYs gained, relapses avoided by treating people with RRMS with DMTs instead of placebo.

5.4.1. Results of the economic model for each DMT

The results of the economic evaluation are presented in Table 6. These results express the estimated incremental outcomes per patient year of treatment of each of the included DMTs relative to placebo. Lower rates of disability progression and relapse for each of the DMTs are translated into fewer MS-related deaths and relapses, which in turn converts to gains in life years and QALYs. Slower disability progression and fewer relapses translated to direct healthcare cost savings, productivity cost savings and informal costs savings. All costs are expressed as A$2025 values. These results are later combined with the total number of patient years of treatment made accessible through the PBS to estimate the cumulative benefit of the PBS listing of DMTs since 1996.

Table 6: Net impact per patient year of DMT exposure, by treatment

Treatment	MS-related deaths prevented	Life-years gained	QALYs gained	Relapses avoided	Direct health care costs saved	Productivity costs saved	Informal costs saved
BET	0.0009	0.0073	0.1257	0.1406	6,963	3,687	1,053
AVO	0.0008	0.0067	0.1141	0.1104	6,182	3,349	957
R22	0.0013	0.0100	0.1734	0.1410	9,305	5,174	1,478
R44	0.0014	0.0111	0.1940	0.1675	10,535	5,816	1,662
COP	0.0013	0.0100	0.1740	0.1690	9,537	5,174	1,478
NAT	0.0017	0.0134	0.2412	0.3749	14,460	7,223	2,064
FIN	0.0011	0.0088	0.1566	0.3390	9,912	4,520	1,291
DMF	0.0014	0.0111	0.1961	0.2658	11,346	5,816	1,662
TER	0.0013	0.0100	0.1737	0.1550	9,421	5,174	1,478
ALE	0.0022	0.0165	0.3015	0.3801	17,810	9,328	2,665
PEG	0.0008	0.0067	0.1141	0.1104	6,182	3,349	957
DAC	0.0011	0.0088	0.1566	0.3390	9,912	4,520	1,291
OCR	0.0023	0.0173	0.3162	0.3318	18,340	9,919	2,834
CLA	0.0014	0.0108	0.1923	0.3240	11,576	5,656	1,616
SIP	0.0022	0.0165	0.3015	0.3801	17,810	9,328	2,665
OZA	0.0010	0.0079	0.1406	0.3387	9,127	4,023	1,149
OMB	0.0021	0.0159	0.2891	0.3705	17,031	8,882	2,538
DIR	0.0014	0.0111	0.1961	0.2658	11,346	5,816	1,662
UTX	0.0017	0.0129	0.2322	0.3857	14,064	6,914	1,976

Abbreviations: ALE, alemtuzumab; AVO, Avonex; BET, Betaferon; CLA, cladribine; COP, Copaxone; DAC, daclizumab; DIR, diroximel fumarate; DMF, dimethyl fumarate; DMT, disease-modifying therapy; FIN, fingolimod; MS, multiple sclerosis; NAT, natalizumab; OCR, ocrelizumab; OMB, ofatumumab; OZA, ozanimod; PBO, placebo; PEG, peginterferon beta-1a; QALYs, quality-adjusted life years; R22, Rebif 22; R44, Rebif 44; SIP, siponimod; TER, teriflunomide; UTX, ublituximab

5.4.2. Aggregate value of DMTs, 1996 to 2025

An estimate of the aggregate value of DMTs in the Australian setting is obtained through the application of per-patient year benefits to overall utilisation estimates, by individual DMT. The total patient years of each DMT supplied through the PBS from 1996 to 2025 was summarised in Section 4 (see Figure 14A). This utilisation of treatment is combined with the expected benefits and cost savings from each year of treatment in Table 6 above.

Table 7 presents the aggregated clinical impact of the DMTs on the PBS over the period 1996 to 2025. From 1996 to 2025 there were 319,786 patient years of DMT supplied through the PBS. Collectively, DMT treatment was estimated to prevent 80,866 relapses and 446 MS-related deaths. In turn, this resulted in 3,479 life years and 61,836 QALYs gained.

Table 7: Aggregated outcomes: Clinical impact

Outcome	Value
Patient years of DMT treatment	319,786
Relapses avoided	80,866
MS-related deaths prevented	446
Life years gained	3,479
QALYs gained	61,836

Abbreviations: DMTs, disease-modifying therapies; MS, multiple sclerosis; QALYs, quality-adjusted life years

Table 8 presents the aggregated cost impact of DMT's, quantifying the overall health care costs saved, productivity costs saved, and informal cost saved. To enable a cost-benefit analysis, an economic value can be placed on the clinical outcomes achieved, with QALYs used as the primary measure because they capture the combined effects of mortality and morbidity.

What do these outcomes mean for Australians living with MS?

Behind these figures are thousands of Australians who have been able to remain in the workforce longer, maintain independence, continue caring for families, participate in their communities and delay or avoid significant disability. While not every person experiences the same benefit, the cumulative impact of DMT access has been to help many people live fuller and more productive lives with MS.

The Office of Impact Analysis (within the Department of the Prime Minister and Cabinet) calculates the value of statistical life year to be $253,000 in 2025 dollars[e]. This figure can be applied to the QALYs gained with DMTs to calculation the total monetary benefit of DMTs over their lifespan in Australia (1996 to 2025). That is to say, the 61,836 QALYS gained (Table 7) translates to $15.6 billion in value (61,836 x $253,000).

In addition, the 319,786 patient years of treatment combined to save MS-related health care, productivity and informal care costs by $3.6 billion, $1.9 billion, and $0.5 billion, respectively.

In total, the economic benefit of DMTs over the period 1996 to 2025 is estimated to be $21.6 billion.

Table 8: Aggregated outcomes: Economic impact

Outcome	Value
Patient years of DMT treatment	319,786
Direct health care costs saved	$3,587,201,922
Productivity costs saved	$1,855,577,741
Informal costs saved	$530,162,230
Economic value of QALYs gained	**$15,644,493,585**
Total monetary benefit of DMTs	**$21,617,435,477**

Abbreviations: DMTs, disease-modifying therapies; QALYs, quality-adjusted life years

"Timely and affordable access to my current DMT means that I can receive regular treatment which keeps my MS as under control as possible. That allows me to lead the kind of life I want – working, travelling, exercising and engaging with friends, family and the community."

KATE CASEY
PERSON LIVING WITH MS

Over the same period that the estimated $21.6 billion in value is accrued the PBS has accumulated $8.4 billion in expenditure (in 2025 value). This means the net monetary benefit of DMTs over the period is **$13.2 billion** (Table 9). A benefit to cost ratio can also be calculated, quantifying the value of monetary benefits relative to the cost expenditure. For our analysis, the introduction of DMTs in Australia has generated a monetary benefit in excess of 2.5 times the cost outlay of these treatments on the PBS for the period 1996 to 2025.

e OIA Guidance Note, Value of statistical life, January 2026, https://oia.pmc.gov.au/sites/default/files/2026-02/value-statistical-life-guidance-note.pdf

Table 9: Net monetary benefit and benefit to cost ratio (1996–2025)

Outcome	Value
Total DMT expenditure	$8,366,480,250
Total monetary benefit of DMTs	$21,617,435,477
Net monetary benefit of DMTs	**$13,250,955,277**
Benefit to cost ratio	**2.58**

Abbreviations: DMTs, disease-modifying therapies; MS, multiple sclerosis; QALYs, quality-adjusted life years

For every $1 invested in PBS-subsidised DMTs between 1996 and 2025, an estimated $2.58 was returned in health and societal value.

5.4.3. Changing value of DMTs over time

The above estimates of net monetary benefit and benefit to cost ratio (Table 9) are aggregated values for the 1996–2025 interval as a whole and are therefore not descriptive of any trends over time in the results. By presenting DMT expenditure and DMT monetary benefit cumulatively over the study period a distinctive pattern emerges (Figure 22), with the monetary benefits of DMT's outgrowing DMT expenditure over time. That is DMT benefits continue to accrue faster than the expenditure on DMTs has accrued.

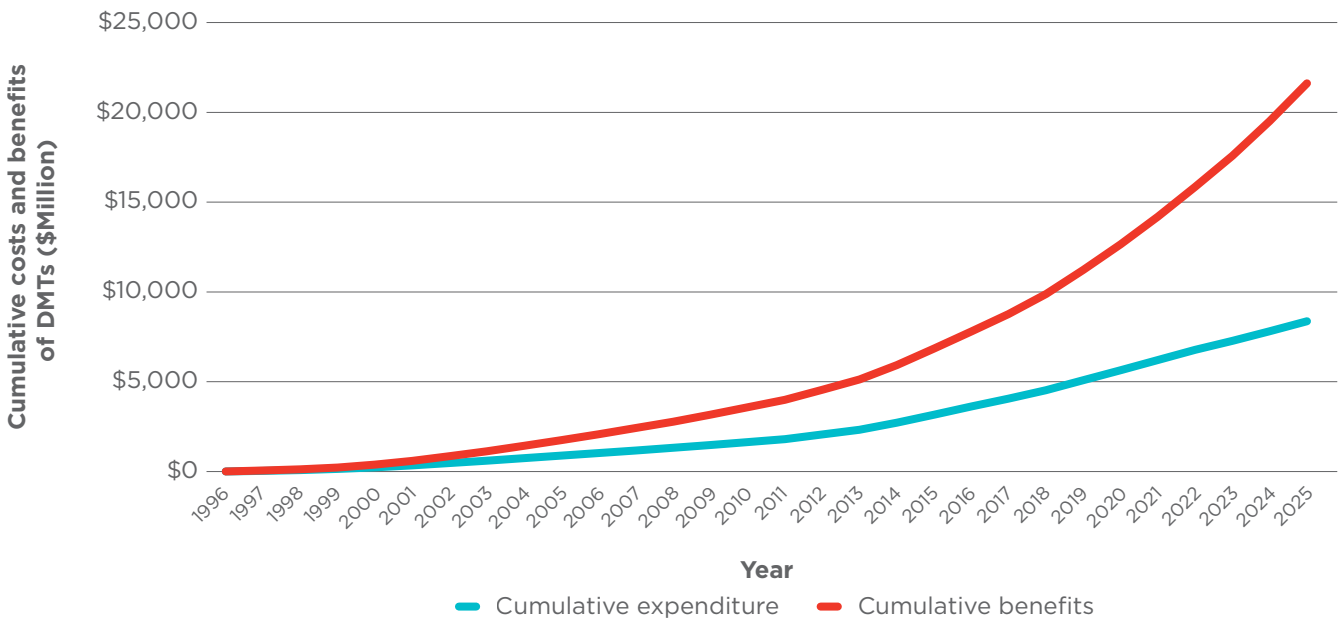


Figure 22: Cumulative DMT expenditure vs cumulative DMT monetary benefit (1996–2025)

In some respects, the accumulation of benefits and expenditure over time in Figure 22 is predictable in that it could be considered an inevitable consequence of effective treatments being available over time. Therefore, the relationship between DMT expenditure and DMT monetary benefit is examined on an annual basis in Figure 23. Specifically, Figure 23 compares the total benefits accrued by DMTs with the total expenditure on DMTs in each calendar year. Three distinct 'eras' can be observed from the results:

- **1996–2011:** Separation between DMT monetary benefit and DMT expenditure is achieved and remains relatively constant.

- **2012–2017:** Divergence between DMT monetary benefit and DMT expenditure is increased, with DMT monetary benefits outstripping DMT expenditure at an ever-increasing rate. This is likely driven by the arrival of the first oral treatment (fingolimod) to the PBS.
- **2018–2025:** Further escalation of DMT monetary benefits as DMT expenditure stagnates. This could be driven by the arrival of the higher efficacy treatments (e.g. ocrelizumab, ofatumumab) to the PBS.

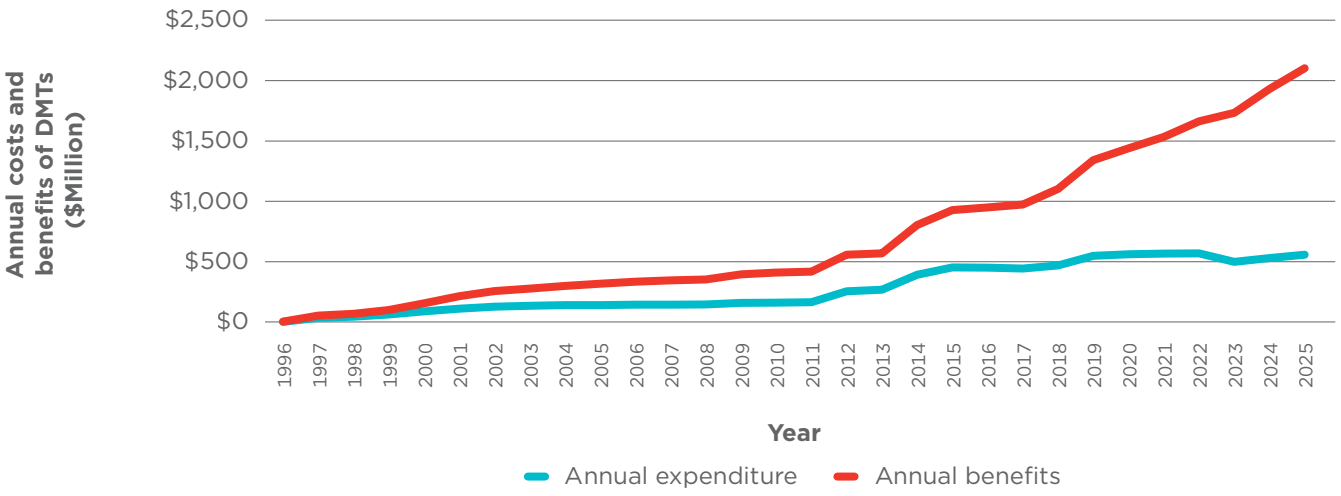


Figure 23: Year-on-year DMT expenditure vs DMT monetary benefit (1996–2025)

Table 10 presents aggregated results of the analysis, stratified by the three distinct 'eras' defined above. The results show that the quantified total monetary benefit of DMTs is increasingly outgrowing DMT expenditure. A cost-benefit analysis of the 2018 to 2025 period estimates a monetary benefit for DMTs of almost three times their estimated cost to the Commonwealth.

Table 10: Net benefit of DMTs disaggregated by each treatment "era"

Outcome	All	1996–2011	2012–2017	2018–2025
Patient years	319,786	79,835	78,598	161,353
Total expenditure ($2025)	$8,366,480,250	$1,803,135,579	$2,259,226,763	$4,304,117,908
MS-related deaths prevented	446	84	98	264
Life years gained	3,479	668	775	2,037
QALYs gained	61,836	11,551	13,672	36,613
Relapses avoided	80,866	11,777	20,059	49,030
Direct health care costs saved ($2025)	$3,587,201,922	$634,736,221	$801,136,692	$2,151,329,009
Productivity costs saved ($2025)	$1,855,577,741	$341,557,493	$403,870,809	$1,110,149,439
Informal costs saved ($2025)	$530,162,230	$97,587,404	$115,391,102	$317,183,723
Value of QALYs gained ($2025)	$15,644,493,585	$2,922,432,562	$3,458,999,178	$9,263,061,846
Total monetary benefit of DMTs ($2025)	$21,617,435,477	$3,996,313,680	$4,779,397,781	$12,841,724,017
Net monetary benefit of DMTs ($2025)	$13,250,955,227	$2,193,178,101	$2,520,171,018	$8,537,606,108
Benefit to cost ratio	2.58	2.22	2.12	2.98

Abbreviations: DMTs, disease-modifying therapies; MS, multiple sclerosis; QALYs, quality-adjusted life years

6. Future treatment pathways, unmet need, and policy priorities

KEY POINTS

- Current DMTs are highly effective at suppressing relapse activity but have limited impact on PIRA, progressive MS, neurodegeneration and established disability, leaving substantial unmet clinical need.
- The emerging pipeline suggests that MS therapies are increasingly shifting towards targeting compartmentalised neuroinflammation, slowing disability progression, repairing existing neurological damage, neuroprotection and intervening earlier in the disease pathway.
- Frexalimab and Bruton's tyrosine kinase (BTK) inhibitors are among the most advanced novel pharmacological approaches currently in Phase 3 development.
- Among the BTK inhibitors, tolebrutinib has demonstrated a significant reduction in disability progression in non-relapsing SPMS and has recently been approved by the TGA (May 2026), while fenebrutinib and remibrutinib have reported positive Phase 3 results, including fenebrutinib in PPMS.
- Cell-based and immune-reconstitution approaches, including chimeric antigen receptor (CAR) T-cell and tolerogenic dendritic cell therapies, are experimental therapies that may provide durable immune control or treatment-free remission, but remain limited by early-stage evidence, safety concerns and implementation complexity.
- Remyelinating and neuroprotective therapies aim to reverse or slow neurological damage and disability progression. Candidate remyelinating treatments such as clemastine have so far shown only modest biological effects without sustained clinically meaningful improvements. Candidate neuroprotective therapies show promise, although further work is required.
- Epstein-Barr virus (EBV)-targeted vaccines, antiviral strategies and earlier preventative interventions may ultimately reduce MS risk or delay disease onset.

6.1 Unmet need

The evolution of DMTs has transformed the management of MS by enabling early and sustained suppression of inflammatory disease activity. High-efficacy DMTs, particularly anti-CD20 monoclonal antibody therapies, have been shown to be highly effective at preventing relapses and MRI lesion formation and have markedly improved outcomes in relapsing MS for the vast majority of people[81, 82]. However, these therapies have limited effects on the mechanisms driving progressive disease activity, where inflammation is less prominent than neurodegeneration, as well as on the reversal of existing disability and disease prevention.

Horizon scanning was performed to identify and evaluate emerging treatments and approaches in clinical development for the management of MS. The review comprised of searches of clinical trial registries, including ClinicalTrials.gov and ANZCTR, MS treatment guidelines, and targeted published literature to characterise the types of emerging therapies, the strength of the existing evidence base and anticipated development timelines.

6.1.1. Progression Independent of Relapse Activity (PIRA) / progressive disease

PIRA is broadly classified as confirmed disability worsening that occurs outside a pre-specified period surrounding a clinical relapse, although definitions vary across studies in the required duration of confirmation, relapse-free interval and disability measure used[83, 84]. PIRA has been found to be a major contributor to long-term disability accumulation in MS across the full spectrum of MS phenotypes, highlighting the importance of relapse-independent mechanisms in driving disease progression[84-86].

High-efficacy DMTs are associated with a lower risk of PIRA, suggesting that ongoing inflammatory activity contributes to at least some PIRA events and that relapse-independent progression is not solely attributable to non-inflammatory neurodegenerative mechanisms[86]. However, approximately 30–40% of treated people will transition to SPMS within 10–12 years of RRMS diagnosis[87], with approximately 2–3% of people with RRMS transitioning to SPMS each year[88, 89]. The substantial residual burden of PIRA highlights an ongoing unmet need for treatments that more effectively prevent or slow relapse-independent disability progression. Despite the substantial disease burden, siponimod is the only DMT currently available through the PBS specifically for SPMS, highlighting the limited treatment options for this population.

Furthermore, a primary progressive disease course affects approximately 10–15% of people with MS[90]. Across both PPMS and SPMS, disability may worsen steadily and independently of relapse activity, reflecting disease mechanisms that are less responsive to therapies primarily targeting acute inflammation. Ocrelizumab is the only DMT currently licenced for PPMS in Australia, however two attempts at achieving PBS reimbursement for this indication were unsuccessful, at the November 2017 and July 2020 PBAC meetings. Nevertheless, the PBAC explicitly acknowledged at the time that *"there is a high clinical need for effective therapies for PPMS"* [91, pg. 27].

The unmet need is further underscored by the greater disease burden and poorer quality of life experienced by people with progressive MS compared with those with RRMS[92, 93]. Current treatment options remain insufficient to prevent or meaningfully slow the sustained, relapse-independent accumulation of disability, particularly for people with PPMS who lack access to a PBS-subsidised DMT.

> "Having just been diagnosed with primary progressive MS, I wasn't sure what was worse, the diagnosis itself or being told that there is no medication that I can take to manage the disease."
>
> **LOUIS ZIRAS**
> **PERSON LIVING WITH MS**

Bruton's tyrosine kinase (BTK) inhibitors are a novel drug class of small molecules that have attracted particular attention because they are capable of crossing the blood brain barrier, thereby targeting both peripheral adaptive immunity (B cells) and CNS-compartmentalised innate immunity (microglia and macrophages). This contrasts with anti-CD20 therapies, which primarily target peripheral B cells[94]. This feature is particularly significant for progressive forms of MS, where CNS inflammation and microglial activation are major contributors to disease progression[94, 95]. Several BTK inhibitors are in various stages of clinical development for both relapsing and progressive MS as discussed further in Section 6.2.1.

6.1.2. Disability reversal/repair

Current therapeutic strategies for MS primarily suppress immune-mediated inflammation without addressing demyelination or established axonal injury. In individuals with MS, an autoimmune attack on myelin leads to the formation of lesions characterised by the presence of demyelinated axons and sustained injury to myelin-producing oligodendrocytes, which hampers the natural repair mechanisms of remyelination. Chronic demyelination can leave axons vulnerable to further degeneration leading to progressive and permanent disability in MS[96].

A promising area of experimental therapeutics in MS is focused on enhancing myelin repair and growth within these lesions by stimulating oligodendrocyte precursor cells (OPCs) to remyelinate denuded but still viable axons[16]. Restoring myelin has the potential to re-establish nerve conduction, protect underlying axons from irreversible degeneration, and improve functional outcomes[97, 98]. This shift in therapeutic approach addresses a key limitation of existing DMTs and represents a critical and transformative area of interest for advancing MS treatment in terms of achieving functional restoration[96].

Advances in remyelination biology have identified promising therapeutic targets, including antagonism of muscarinic M1 receptors (e.g., clemastine, PIPE-307), inverse agonism of H3 receptors (e.g., GSK239512), agonism of retinoic acid X receptors (e.g., bexarotene), and selective estrogen receptor modulation (e.g., bazedoxifene). However, demonstrating the additional neuroprotective benefit of remyelination remains challenging because of highly sensitive outcome measures required (such as visual evoked potential [VEP] latency), long-term follow-up required to establish clinically meaningful effects and background use of DMTs attenuating observable differences[97].

6.1.3. Disease prevention

Despite advances in understanding the genetic, environmental and biological determinants of MS, the disease cannot yet be prevented. Recent efforts to develop a global prevention agenda for MS recommended primary prevention strategies should focus on addressing established modifiable risk factors, such as obesity or vitamin D deficiency, whilst secondary prevention efforts intend to identify disease at its earliest presentation, so that interventions can prevent or delay further disease evolution[99]. These developments are beginning to translate into coordinated international research programs aimed at preventing MS before clinical symptoms emerge. For example, the Global MS Prevention Initiative, led by MS Canada and MS Australia, is bringing together researchers, clinicians and people living with MS to improve understanding of preclinical disease, identify opportunities for earlier intervention, and ultimately prevent MS altogether.

Epidemiological studies provide strong evidence that Epstein-Barr virus (EBV) infection is a major causal contributor to MS, with the risk of MS increasing approximately 32-fold following EBV infection[100]. These findings have stimulated interest in both prophylactic EBV vaccination and antiviral treatment strategies directed at EBV-infected cells at preventing or ameliorating MS[101].

6.2. Emerging MS treatments

6.2.1. BTK inhibitors

A recent systematic review and meta-analysis compared the relatively non-selective BTK inhibitors, **tolebrutinib and evobrutinib**, against an established oral DMT, teriflunomide[102]. The synthesis combined evidence from four randomised trials involving 4,163 people predominantly with RRMS (GEMINI 1 and 2; evolution RMS 1 and 2). In a pooled analysis, no significant difference was found in ARR between the BTK inhibitors and teriflunomide (risk ratio: 1.03 [95% CI: 0.90, 1.19]). MRI outcomes also showed no advantage for new or enlarging T2 lesions, while new gadolinium-enhancing T1 lesions slightly favoured teriflunomide. Serious AEs were comparable, with a risk ratio of 1.13 (95% CI: 0.92, 1.40)[102]. There was, however, an early disability signal; in the pooled analysis, tolebrutinib and evobrutinib reduced the risk of three-month confirmed disability worsening by 19% relative to teriflunomide, with a HR of 0.81 (95% CI: 0.67, 0.97). This effect was not statistically significant for six-month confirmed disability worsening, for which the HR was 0.88 (95% CI: 0.63, 1.24). The difference between the three- and six-month results means that the durability and clinical importance of this pooled disability signal remain uncertain[102].

The clearest evidence of potential differentiation has emerged in non-relapsing SPMS. In the Phase 3 HERCULES trial involving 1,131 participants, **tolebrutinib** significantly reduced the risk of 6-month CDP by 31% relative to placebo and was associated with a modestly increased probability of confirmed disability improvement[103]. This result is notable since it was achieved in the context of participants having non-relapsing disease, and the treatment effect was observed without a major relapse-related mechanism. It supports the proposition that a brain-penetrant BTK inhibitor

may affect progression-associated biology within the CNS. It is also the first Phase 3 evidence of a therapy reducing CDP in a specifically non-relapsing SPMS population[81, 103, 104]. Tolebrutinib was associated with elevations in liver enzymes, making regular liver-function monitoring and risk-management measures potentially necessary. More broadly, the failure of evobrutinib to demonstrate superiority to teriflunomide shows that benefit cannot be assumed to be a class effect. Differences in brain penetration, target selectivity, dosing and off-target activity may determine whether an individual BTK inhibitor provides clinically meaningful benefit[81, 103].

In a recently published NMA of therapeutic strategies for SPMS, tolebrutinib and siponimod were among the most effective agents in delaying disability progression compared with other studied treatments[105]. Tolebrutinib (Cenrifki) was registered on the Australian Register of Therapeutic Goods (ARTG) in May 2026 for the treatment of adults with non-relapsing SPMS and to slow disability accumulation in the absence of relapse activity in adults with SPMS. As of September 2026, there was no publicly available indication that an application for PBS reimbursement had been lodged with the PBAC.

Positive top-line results for additional BTK inhibitors have also recently been reported; with the Phase 3 FENhance-2 trial of **fenebrutinib** in people with RRMS demonstrating a significant reduction in ARR compared to teriflunomide, while the pivotal PPMS study (FENtrepid) showed that fenebrutinib slowed disability progression at least as effectively as ocrelizumab[f], the first positive Phase 3 signal for a BTK inhibitor in primary progressive disease. Furthermore, **remibrutinib**, a highly selective oral BTK inhibitor, demonstrated superiority versus teriflunomide in reducing ARR and inflammatory brain lesions in people with RRMS in the pivotal Phase 3 REMODEL-1 and -2 trials[106]. Further clinical trials for remibrutinib are currently underway investigating efficacy and safety following switching from ocrelizumab compared with continuous ocrelizumab treatment among people with RRMS (NCT06846281) and efficacy and safety in people with SPMS (REMASTER / NCT07225504) (Table 11). As of September 2026, no publicly available information indicated that regulatory applications for fenebrutinib or remibrutinib had been lodged with the TGA.

Horizon scanning of clinical trial registries for BTK inhibitor therapies identified several additional BTK inhibitors in late-stage clinical development, including **VT7208**, which is being evaluated in Australia (NCT07085507); **rocbrutinib**, which is being investigated in people with paramagnetic rim lesion (PRL)-positive RRMS (NCT07776743); and **orelabrutinib**, which is currently undergoing Phase 3 investigation in people with SPMS or PPMS (NCT07299019 and NCT07067463, respectively) (Table 11).

POTENTIAL IMPLICATIONS FOR THE SOCIETAL VALUE OF DMTS

Early evidence does not indicate that BTK inhibitors will materially improve relapse prevention in a treatment environment where high-efficacy therapies already achieve strong control of relapses and focal inflammatory disease activity. Sabatino[81] reports that highly effective monoclonal antibody DMTs can provide near-complete suppression of focal inflammatory activity in many people with relapsing MS. In the available head-to-head trials, the estimated effect of BTK inhibitors on ARR relative to teriflunomide was effectively neutral. A meta-analysis of four randomised trials reported an ARR ratio of 1.03, with no significant difference between treatments[102]. The potential value of BTK inhibitors may therefore depend primarily on whether the emerging disability-progression signal can be independently replicated, sustained over longer follow-up, and translated into meaningful preservation of functioning, independence and participation.

A durable reduction in progression could nevertheless provide value beyond direct healthcare savings. Disability severity is a major driver of MS-related costs through reduced employment and productivity, premature workforce exit, informal care requirements, home and transport modifications, rehabilitation, and increased use of health and community services[5, 107]. Because MS frequently affects people during their most productive working years, even a modest delay in progression could generate cumulative benefits over time. An intervention that prevents or delays approximately ten progression events per 100 treated people over a trial-length period, as suggested by the HERCULES trial, may therefore have greater societal significance than its limited effect on relapses would imply[103].

f Roche 10 Nov 2025: https://www.roche.com/investors/updates/inv-update-2025-11-10

6.2.2. Next-generation B-cell and co-stimulation therapies

Vidofludimus calcium (IMU-838) is an oral, small molecule that combines selective inhibition of dihydroorotate dehydrogenase (DHODH), the same enzyme targeted by teriflunomide, with activation of the neuroprotective transcription factor nuclear receptor-related 1 (Nurr1). By targeting both inflammatory and neurodegenerative pathways, it aims to address aspects of disease progression not fully captured by existing anti-inflammatory therapies. Following positive results from the Phase 2 investigation in RRMS (EMPhASIS / NCT03846219)[108,109], two identical Phase 3 placebo-controlled studies in people with RRMS are currently underway (ENSURE program / NCT05134441 & NCT05201638), with the completion of the primary study expected in November 2026 (Table 11). In a Phase 2 trial (CALLIPER / NCT05054140) in people with progressive MS, vidofludimus reduced the risk of 24-week CDP by 20% in the overall population and by 30% in the PPMS subgroup. Following these encouraging results, a Phase 3 trial in progressive MS is expected to commence later in 2026[g].

Frexalimab (SAR441344) is an innovative monoclonal antibody that targets the upstream biology of MS by blocking the CD40/CD40L co-stimulatory pathway. This pathway plays an important role in interactions between activated T cells, B cells and antigen-presenting cells that drive both adaptive and innate immune responses, while potentially avoiding the lymphocyte depletion associated with several existing therapies. In a Phase 2 trial, the higher intravenous dose of frexalimab reduced the number of new gadolinium-enhancing T1 brain lesions by approximately 89% relative to placebo at 12 weeks[110]. Open-label extension results suggest that suppression of MRI activity was maintained for up to two years and was accompanied by reductions in serum neurofilament light, a biomarker associated with neuroaxonal injury[111]. Although these findings are encouraging, the Phase 2 study was not designed to evaluate long-term effects on disability progression. Phase 3 trials are currently underway in people with RRMS vs teriflunomide (FREXALT / NCT06141473) and in people with non-relapsing SPMS vs placebo, where effects on disability progression will be of particular interest (FREVIVA / NCT06141486). A Phase 3 pharmacokinetic study comparing the subcutaneous and intravenous formulations of frexalimab is also currently underway (FREXCITE / NCT07325292) (Table 11).

Foralumab is a novel, intranasal, anti-CD3 monoclonal antibody in clinical development for non-active SPMS. It is designed to stimulate regulatory T cells and modulate neuroinflammation, representing a novel therapeutic approach for neuroinflammatory and neurodegenerative diseases. Early data from an Expanded Access Program (NCT06802328) showed either an improvement or stability of disease within 6 months in all people with non-active SPMS. Results from the Phase 2a, placebo-controlled INFORM-MS trial (NCT06292923), evaluating PET imaging for microglial activation as a primary endpoint, are expected in Q4 2026[h].

Other advanced therapeutic strategies in earlier stage clinical development identified through horizon scanning included the combination therapies of **ofatumumab plus NK042** cell injection (NCT07546110) and **ocrelizumab plus RO7268489** (NCT07282574). These dual therapy approaches aim to combine the immunomodulatory effects of anti-CD20 monoclonal antibodies with the neuroprotective effects of NK042, an experimental cell-based injection, or RO7268489, an experimental, oral small-molecule drug. RO7268489 is specifically being evaluated in people with progressive MS, with study sites in Australia (Table 11).

6.2.3. Cell-based and immune-reconstitution therapies

A distinct group of investigational treatments aim to achieve prolonged disease control through a single immune-reconstitution intervention rather than continuous treatment.

Chimeric antigen receptor (CAR) T-cell therapies have shown significant therapeutic potential, particularly in targeting malignant B cells in haematologic cancers, and are in early Phase 1 and Phase 2 development for MS. CAR T-cell approaches aim to selectively target and deplete pathogenic immune cells, with the goal of achieving sustained reconstitution and reducing disease

g Immunic Therapeutics 2026: https://imux.com/pipeline/imu-838/
h Tiziana 21 May 2026: https://ir.tizianalifesciences.com/news-releases/news-release-details/tiziana-fully-enrolls-its-phase-2-placebo-controlled-multiple/

activity[95, 112]. Initial reports indicate that CAR T-cells can be detected in the CNS and can produce marked depletion of targeted B-cell populations, including in people with treatment-refractory progressive disease[113]. The potential for deep, long-lasting B-cell depletion and possibly drug-free remission is promising, although the evidence is currently limited to small case series and early safety studies. Horizon scanning of clinical trial registries for emerging CAR T-cell therapies in MS identified a growing number of early phase clinical trials underway for relapsing and progressive forms of MS (Table 11).

Horizon scanning revealed emerging antigen-specific tolerance inducing strategies in the pipeline, including **tolerogenic dendritic cells (tolDCs)** loaded with myelin-derived peptides and **mesenchymal stem cells (MSCs)**. These approaches aim to achieve long-term remission of MS similar to immune-reconstitution therapies (such as alemtuzumab, cladribine and aHSCT), with the advantage of precise targeting of myelin-reactive clones. Sustained complete remission could support a shift away from lifelong continuous treatment towards a model in which highly effective therapies are used until durable remission is achieved, followed by structured off-treatment monitoring[114].

6.2.4. Remyelinating and neuroprotective therapies

A preliminary clinical trial with **clemastine**, an M1 muscarinic receptor antagonist, showed improved VEP latencies in people with RRMS, suggesting remyelination of the visual pathways. However, the effect size was small, and the trial did not demonstrate a corresponding improvement in disability or day-to-day function[115]. Subsequent work has examined combinations such as **metformin and clemastine**, intended to improve the capacity of OPCs to generate new myelin[116]. In addition, the anti-LINGO-1 monoclonal antibody **opicinumab** (BIIB033) has also been investigated in several clinical trials in RRMS[117]. Early biomarker findings have provided evidence of biological activity, but no remyelinating therapy has yet demonstrated a sustained reduction in MS-related disability[81].

Horizon scanning of clinical trial registries for therapies targeting remyelination identified currently active early phase trials of **clemastine** in RRMS (NCT05359653 [ReVIVE]; NCT06065670 [ReINFORCE]), as well as a Phase 2 study due to begin enrolment in Australia examining the VEP latency potential of **PRO-1562** in addition to DMT in people with RRMS and chronic optic nerve damage (NCT07826689). PRO-1562 is an oral, CNS-penetrating small molecule specifically designed to induce remyelination (Table 11).

Emerging therapeutic strategies for MS also encompass neuroprotection, preserving neurons/axons or reducing neurodegeneration, rather than stimulating remyelination. This may be particularly relevant to slowing disease progression. Although the earlier MS-STAT study of simvastatin produced encouraging findings in slowing brain atrophy, the large Phase 3 MS-STAT2 study was negative[118].

The OCTOPUS trial (ISRCTN14048364) and its Australian extension, PLATYPUS, together form the world's first adaptive multi-arm, multi-stage (MAMS) clinical trial designed to rapidly evaluate multiple potential treatments for progressive MS. The trial is testing therapies with the potential to protect neurons and slow disability progression, enabling promising candidates to be prioritised and ineffective therapies to be discontinued more efficiently than in conventional clinical trial programs. Interim Stage 1 results reported in September 2026 showed early promise for **alpha-lipoic acid** in slowing MS progression, using a composite measure of brain atrophy and clinical measures, while **metformin** did not meet the criteria to advance to Stage 2[i].

Alpha-lipoic acid has potent antioxidant and anti-inflammatory properties and is required for proper mitochondrial function. Oxidative stress is a key contributor to the pathophysiology of MS, as it can damage neurons, myelin, and other critical structures in the CNS. The brain is particularly vulnerable to oxidative stress due to high oxygen consumption[119].

i OCTOPUS/PLATYPUS trials: https://ms-octopus.mrcctu.ucl.ac.uk/participants/about-the-trial/

6.2.5. EBV-targeted and preventative approaches

An EBV-targeted messenger RNA (mRNA)-based vaccine in people with CIS, RIS and RRMS was identified as currently in Phase 2 clinical development (Horizon trial / NCT06735248). mRNA-1195 is designed as a therapeutic vaccine encoding latent antigens to target established EBV infections in people with early-stage, relapsing MS. An additional mRNA vaccine (mRNA-1189) is also being investigated in individuals without MS (NCT05164094 / NCT07478952) for the primary prevention of MS.

Landmark Phase 3 trials are also underway in Australia and Europe evaluating antiviral therapies (including spironolactone or famciclovir/tenofovir) for the prevention of progression in MS (STOP-MS / ACTRN12623000849695), for reducing fatigue in relapsing MS (FIRMS-EBV / ACTRN12624000423516) and for preventing neuronal damage and disease activity in MS (TARGET-EBV in MS / EUCT2025-522140-40-00).

6.2.6. Other emerging evidence

Horizon scanning also revealed multiple trials of ocrelizumab biosimilars (e.g., NCT07606521, NCT07597668, NCT07321093), as well as studies evaluating a new subcutaneous ocrelizumab formulation (NCT07667322) and outcomes following switching from other anti-CD20 therapies to the current subcutaneous ocrelizumab formulation (NCT07609719). A subcutaneous formulation and alternative delivery devices for ublituximab are also being evaluated (NCT07503873). Although these developments are unlikely to provide incremental clinical benefits over the reference therapies, biosimilar competition and more convenient administration may reduce treatment and service-delivery costs.

Table 11: Select therapeutic strategies in MS currently in active clinical development

Category	Drug / product name	Trial identifier	Phase	Location	MS phenotype	Route of administration	Primary completion date	Primary endpoint
BTK inhibitor	VT7208	NCT07085507	Phase 3	Australia	MS	Oral	Oct-2026	Safety and tolerability
	Rocbrutinib (LP-168)	NCT07776743	Phase 2a	China	PRL-positive RRMS	Oral	Jun-2028	Number and new occurrence of PRL by 7T MRI
	Remibrutinib	NCT06846281	Phase 3b	Global (including Australia)	RMS	Oral	Jul-2029	Annualised rate of new or enlarging T2 lesions
	Remibrutinib	NCT07225504 (REMASTER)	Phase 3	Global (including Australia)	SPMS	Oral	Dec-2030	Time to 6-month CDP
	Orelabrutinib	NCT07299019 / NCT07067463	Phase 3	USA, Europe	SPMS or PPMS	Oral	Jun-2030	Time to onset of CDP
Next-generation immune modulation	Foralumab	NCT06292923	Phase 2a	USA	Non-active SPMS	Intranasal	Sep-2026	Microglial activation and safety
	Vidofludimus (IMU-838)	NCT05134441 & NCT05201638 (ENSURE-1 and 2)	Phase 3	Global	RRMS or active SPMS	Oral	Nov-2026	Time to first relapse
	Frexalimab	NCT06141473 (FREXALT)	Phase 3	Global	RMS	IV infusion	May-2027	ARR
	Frexalimab	NCT07325292 (FREXCITE)	Phase 3	USA, Europe, Asia	RMS	Subcutaneous	Jul-2027	PK (area under the curve and trough concentration)
	Frexalimab	NCT06141486 (FREVIVA)	Phase 3	Global (including Australia)	Non-relapsing SPMS	IV infusion	Mar-2028	Time to 6-month cCDP
	Ofatumumab plus NK042 cell injection	NCT07546110	Early Phase 1	China	RRMS, SPMS or PPMS	Subcutaneous	Dec-2027	Safety and tolerability
	RO7268489 add-on to ocrelizumab	NCT07282574 (Mintaka)	Phase 2	Australia, NZ, Europe, UK	PMS	Oral	May-2028	Time to first occurrence of cCDP

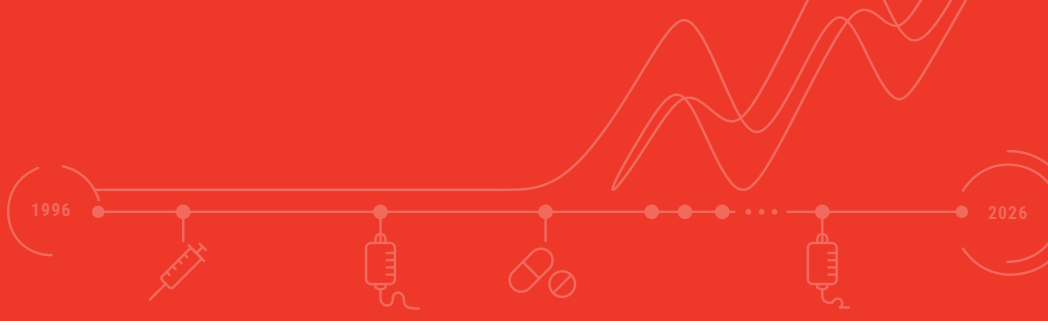
Category	Drug / product name	Trial identifier	Phase	Location	MS phenotype	Route of administration	Primary completion date	Primary endpoint
Cell-based: CAR T-cell therapy	GC012F	NCT07303790	Early Phase 1	China	RRMS, SPMS or PPMS	IV infusion	Jan-2027	Dose-limiting toxicity and adverse event incidence
	Universal STAR-T-cell injection	NCT07523100	Phase 1	China	RRMS, SPMS or PPMS	IV infusion	Apr-2027	Dose-limiting toxicity and adverse event incidence
	KYV-101	NCT06138132	Phase 1	USA	Progressive MS	IV infusion	Jun-2027	Dose-limiting toxicities
	S103 (BCMA-CAR-T)	NCT07587125 (RESET-MS)	Phase 1	China	RRMS, SPMS or PPMS	IV infusion	Nov-2027	Dose-limiting toxicities and safety
	TRX319	NCT07477639 (IMPACT-MS)	Phase 1/2a	USA	PPMS or SPMS	IV infusion	Aug-2028	Safety and tolerability
	AZD0120	NCT07224373 (ZENITH)	Phase 1b	Australia, USA, Canada, Germany, UK	Refractory RMS or PMS	IV infusion	Dec-2028	Safety and tolerability
	SYS6020 injection	NCT07756268	Phase 1b/2	China	RRMS, SPMS or PPMS	IV infusion	Feb-2029	Safety and tolerability
	KITE-363	ACTRN12625001346460p	Phase 1	Australia	MS	IV infusion	Jun-2029	Safety and tolerability; MS efficacy including Gd-enhancing lesions, T2 lesions and CDP-12
	Obecabtagene autoleucel (obe-cel)	NCT07139743 (BOBCAT)	Phase 1	USA, UK, Spain	PMS	IV infusion	Aug-2029	Dose-limiting toxicities and safety
	C-CAR168	NCT07825389	Phase 1b/2	Global	SPMS or PPMS	IV infusion	Feb-2030	Safety, incidence of cCDP
	Rapcabtagene autoleucel (YTB323)	NCT06675864	Phase 1/2	Australia, Canada, Europe	Non-active SPMS or PPMS	IV infusion	Jun-2030	Dose-limiting toxicities and safety
	MB-CART2019.1	NCT07178431	Phase 1/2	Germany	RRMS, SPMS or PPMS	IV infusion	Aug-2030	Safety and tolerability, NEDA
	P-CD19CD20-ALLO1 with cyclophosphamide/ fludarabine	NCT07008378	Phase 1	USA	PMS or RMS	IV infusion	Aug-2032	Dose-limiting toxicity and adverse event incidence

Category	Drug / product name	Trial identifier	Phase	Location	MS phenotype	Route of administration	Primary completion date	Primary endpoint
Cell-based: Regenerative / tolerogenic cell therapy	NG01 (mesenchymal stem cell therapy)	NCT06961383	Phase 2	USA, Israel	SPMS	Intrathecal injection	Mar-2028	Walking ability and safety
	Vitamin D3-treated tolerogenic dendritic cells (tolDC)	NCT07020715 (MS-tolDC_2a)	Phase 2a	Belgium, Spain	PMS	Vaccination	Sep-2029	Change in EDSS score, safety and tolerability
Remyelinating / regenerative / neuroprotective	Clemastine	NCT05359653 (ReVIVE)	Phase 1/2	USA	RRMS	Oral	Jun-2027	Corpus Callosum Myelin Water Fraction
	Clemastine	NCT06065670 (ReINFORCE)	Phase 1/2	USA	RRMS	Oral	Oct-2028	Corpus Callosum Myelin Water Fraction
	PRO-1562 (plus DMT)	NCT07826689	Phase 2a	Australia	RRMS	Oral	Dec-2028	Safety and VEP latency
	Alpha-lipoic acid (stage 2); metformin (stage 1)	OCTOPUS (ISRCTN14048364), PLATYPUS	Phase 3	UK, Australia	Progressive MS	Oral	Dec-2028	Time to initial disability progression
EBV-targeted therapies	mRNA-1189	NCT05164094 (Eclipse)	Phase 1/2	USA	Healthy people	Vaccination (IM injection)	Oct-2026	Safety and tolerability
	mRNA-1189	NCT07478952	Phase 1	Australia	Healthy people	Vaccination (IM injection)	May-2027	Safety and tolerability
	mRNA-1195	NCT06735248 (Horizon)	Phase 2	Australia, USA, UK,	CIS, RIS, RRMS	Vaccination (IM injection)	Jan-2029	Safety and tolerability
	Tenofovir alafenamide	EUCT2025-522140-40-00 (TARGET-EBV in MS)	Phase 2b	Norway, Finland	MS (any subtype)	Oral	Jan-2028	Change in the mean CSF NfL level
	Spironolactone / tenofovir alafenamide	ACTRN12624000423516 (FIRMS-EBV)	Phase 3	Australia	RRMS with clinical fatigue	Oral	May-2028	Fatigue
	Spironolactone / famciclovir	ACTRN12623000849695 (STOP-MS)	Phase 3	Australia	PPMS or SPMS	Oral	Jun-2029	Salivary EBV DNA and time to CDP

Abbreviations: ACTRN, Australian Clinical Trials Registration Number; aGVHD, acute graft-versus-host disease; Allo-HCT, allogeneic haematopoietic cell transplantation; ARR, annualised relapse rate; Auto-HSCT, autologous haematopoietic stem cell transplantation; BCMA, B-cell maturation antigen; BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; cCDP, composite confirmed disability progression; CDP, confirmed disability progression; CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; DNA, deoxyribonucleic acid; EBV, Epstein–Barr virus; EDSS, Expanded Disability Status Scale; Gd, gadolinium; HCT, haematopoietic cell transplantation; HSCT, haematopoietic stem cell transplantation; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; mRNA, messenger RNA; MS, multiple sclerosis; NCT, National Clinical Trial number; NEDA, no evidence of disease activity; NfL, neurofilament light chain; NZ, New Zealand; PK, pharmacokinetics; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; PRL, paramagnetic rim lesion; RIS, radiologically isolated syndrome; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T, tesla; tolDC, tolerogenic dendritic cell; UK, United Kingdom; USA, United States of America; VEP, visual evoked potential.

Source: ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry; as of September 2026

7. Conclusions



Over the past 30 years, PBS-funded access to DMTs has transformed outcomes for people living with MS in Australia, particularly those with relapsing forms of the disease. MS has shifted from a disease characterised by expected disability accumulation to one where many Australians can live productive, independent lives for substantially longer. PBS-subsidised access has enabled treatment to evolve from a limited set of injectable therapies to a broad and increasingly personalised range of options, including high-efficacy treatments that substantially reduce relapses, delay disability progression and support improvements in long-term quality of life for people with MS. Beyond the clinical outcomes measured in trials, the benefits of DMTs are reflected in the ability of many people living with MS to remain employed, maintain independence, participate in family and community life, and pursue long-term goals that may once have been compromised by progressive disability.

The scale of this benefit is evident in both treatment uptake and modelled outcomes. By 2025, approximately 24,000 Australians were receiving DMTs, with 83% receiving therapies within the higher PBS pricing tier. Between 1996 and 2025, DMT use was estimated to prevent approximately 80,866 relapses, and 446 MS-related deaths, while generating 3,479 life years and 61,836 QALYs. These gains translated into benefits valued at more than twice the cost of treatment, with an estimated benefit-to-cost ratio of 2.58 and a net monetary benefit of $13.2 billion, demonstrating that sustained public investment in DMTs has delivered substantial value to people with MS, the health system and Australian society. Notably, the incremental improvements achieved over the past decade, compared with early DMT use, reflect the cumulative benefits of greater uptake of higher-efficacy therapies.

Despite the significant progress made over the past 30 years, important unmet clinical needs remain. Treatment options remain limited for progressive forms of MS and PIRA, while effective therapies to repair existing neurological damage are still lacking. There are also evident gaps between Australian and international access for some groups of people with MS. Emerging therapies such as BTK inhibitors, next-generation B-cell and remyelinating treatment approaches offer the potential to address these gaps, but their value will depend on reimbursement and pricing frameworks that recognise meaningful clinical innovation while maintaining affordability and timely access. Historically conservative cost-minimisation approaches, recommendations based on price parity, generic entry and ongoing price reductions risk undervaluing future innovation and undermining the viability of both recently reimbursed and emerging therapies.

These findings are consistent with broader discussions regarding how reimbursement frameworks can support timely access to innovative medicines while maintaining sustainability of the health system, including Medicines Australia's Access Unlocked report[120]. Continued investment in evidence generation, innovative treatments and equitable access will be essential not only to sustain the gains achieved over the past three decades, but also to ensure that all people living with MS can benefit from the next generation of advances in prevention, treatment and repair.

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Appendix A: PBS information on DMTs for MS

DMT	Brand	Strength/pack	Mode of administration & frequency	PBS item number	Listing date	Listing status (date of delisting)	DPMQ at listing	DPMQ June 2026 (or latest available)	SPA at time of listing	SPA June 2026 (or latest available)
Interferon beta 1b	Betaferon	250 mcg/1mL x15 vials	SC, every second day	8101J	November 1996	Current	$1,448.04	$763.87	N	N
Interferon beta 1a (IM)	Avonex	30 mcg/2mL x4 vials	IM, weekly	8289G	February 1999	February 2017	$1,112.14	$998.03	N	N
	Avonex	30 mcg/0.5mL x4 vials	IM, weekly	8805K	April 2005	April 2023	$1,090.93	$667.25	N	N
Glatiramer acetate	Copaxone	20 mg/mL x28 vials	SC, daily	8352N	November 1999	August 2004	$1,112.14	$1,090.89	N	N
	Copaxone	20 mg/mL x28 syringes	SC, daily	8726G	May 2004	July 2019	$1,090.89	$885.88	N	N
	Copaxone	40 mg/mL x12 pens	SC, three times weekly	13110B	September 2022	Current	$667.25	$599.19	N	N
	Copaxone	40 mg/mL x12 syringes	SC, three times weekly	10416F	August 2015	Current	$1,054.87	$563.85	N	N
Interferon beta 1a (SC 22)	Rebif 22	22 mcg/0.5 mL x12 syringes	SC, three times weekly	8402F	May 2000	July 2002	$1,050.39	$1,040.21	N	N
Interferon beta 1a (SC 44)	Rebif 44	44 mcg/0.5 mL x12 syringes	SC, three times weekly	8403G	May 2000	December 2022/ April 2023	$1,346.68	$865.68	N	N
	Rebif 44	44 mcg/0.5 mL x12 pen	SC, three times weekly	8968B	May 2011	December 2022/ April 2023	$1,056.77	$865.68	N	N
	Rebif 44	132 mcg/1.5 mL x4 cartridge	SC, monthly	9332E	May 2010	December 2022/ April 2023	$1,056.77	$865.68	N	N
Natalizumab	Tysabri	300 mg/15mL x1 infusion	IV, every 4 weeks	9624M	July 2008	Current	$2,038.46	$637.97	Y	N
	Tysabri	300 mg/15mL x1 infusion	IV, every 4 weeks	9505G	November 2010	Current	$2,038.46	$604.89	Y	N
	Tysabri	150 mg/mL x2 syringes	SC (x2), every 4 weeks	13820J	February 2024	Current	$1,316.71	$637.97	Y	N
	Tysabri	150 mg/mL x2 syringes	SC (x2), every 4 weeks	13825P	February 2024	Current	$1,268.34	$604.89	Y	N

DMT	Brand	Strength/pack	Mode of administration & frequency	PBS item number	Listing date	Listing status (date of delisting)	DPMQ at listing	DPMQ June 2026 (or latest available)	SPA at time of listing	SPA June 2026 (or latest available)
Fingolimod	Gilenya	250 mcg capsule x28	Oral, daily	11818B	November 2019	Current	$2,210.41	$1,064.24	Y	N
	Gilenya	500 mcg capsule x28	Oral, daily	5262Y	September 2011	Current	$2,312.98	$794.21	Y	N
Dimethyl fumarate	Tecfidera	120 mg capsule x14	Oral, twice daily loading dose	2896K	December 2013	Current	$491.18	$213.28	Y	N
	Tecfidera	120 mg capsule x14	Oral, twice daily loading dose	2943X	December 2013	Current	$491.18	$213.28	Y	N
	Tecfidera	240 mg capsule x56	Oral, twice daily	2966D	December 2013	Current	$1,879.87	$348.18	Y	N
Teriflunomide	Aubagio	14 mg tablet x28	Oral, daily	2898M	December 2013	Current	$1,847.13	$99.95	Y	N
Alemtuzumab	Lemtrada	12 mg/1.2 mL x5 vials	IV, yearly for 2 years*	10228H	April 2015	Current	$56,970.00	$51,415.45	Y	Y
	Lemtrada	12 mg/1.2 mL x3 vials	IV, yearly for 2 years*	10232M	April 2015	Current	$34,182.00	$30,849.27	Y	Y
	Lemtrada	12 mg/1.2 mL x5 vials	IV, yearly for 2 years*	10243D	April 2015	Current	$57,016.76	$51,464.33	Y	Y
	Lemtrada	12 mg/1.2 mL x3 vials	IV, yearly for 2 years*	10246G	April 2015	Current	$34,228.75	$30,898.14	Y	Y
Peginterferon beta 1a	Plegridy	125 mcg/0.5 mL x2 pen	SC, fortnightly	10212L	March 2015	Current	$1,057.11	$635.89	N	N
	Plegridy	125 mcg/0.5 mL x2 pen	SC, fortnightly	10220X	March 2015	Current	$1,057.11	$635.89	N	N
	Plegridy	63 mcg/0.5 mL&94 mcg/0.5 mL x1 pen	SC, loading dose	10218T	March 2015	Current	$1,057.11	$635.89	N	N
Daclizumab	Zinbryta	150 mg/mL x1 injection	SC, monthly	11101G	May 2017	June 2018	$2,231.21	$2,232.85	Y	Y

DMT	Brand	Strength/pack	Mode of administration & frequency	PBS item number	Listing date	Listing status (date of delisting)	DPMQ at listing	DPMQ June 2026 (or latest available)	SPA at time of listing	SPA June 2026 (or latest available)
Ocrelizumab	Ocrevus SC	920 mg/23 mL x1 vial	SC, 6 monthly	15113K	December 2025	Current	$16,705.24	$16,705.24	Y	Y
	Ocrevus SC	920 mg/23 mL x1 vial	SC, 6 monthly	15120T	December 2025	Current	$16,656.36	$16,656.36	Y	Y
	Ocrevus	300 mg/10 mL x2 vials	IV, 6 monthly	11237K	February 2018	Current	$17,580.15	$16,705.24	Y	Y
	Ocrevus	300 mg/10 mL x2 vials	IV, 6 monthly	11242Q	February 2018	Current	$17,533.00	$16,656.36	Y	Y
Cladribine	Mavenclad	10 mg tablet x1	Oral, short course yearly for 2 years**	11603Q	January 2019	Current	$3,984.08	$1,243.40	Y	N
	Mavenclad	10 mg tablet x4x2	Oral, short course yearly for 2 years**	11604R	January 2019	Current	$30,815.37	$9,136.38	Y	N
	Mavenclad	10 mg tablet x6	Oral, short course yearly for 2 years**	11611D	January 2019	Current	$23,149.28	$6,893.01	Y	N
Siponimod	Mayzent	1 mg tablet x28	Oral, daily	14607T	October 2024	Current	$2,082.44	$1,981.92	Y	Y
	Mayzent	250 mcg tablet x12	Oral, titration	12172P	November 2020	Current	$239.40	$229.54	Y	Y
	Mayzent	250 mcg tablet x120	Oral, daily	12160B	November 2020	May 2025/ November 2025	$2,235.26	$2,220.90	Y	Y
	Mayzent	2 mg tablet x28	Oral, daily	12158X	November 2020	Current	$2,235.25	$2,118.31	Y	Y
Ozanimod	Zeposia	920 mcg capsule x28	Oral, daily	12271W	March 2021	Current	$2,219.45	$2,118.31	Y	Y
	Zeposia	230 mcg x4 & 460 mcg x3 capsules	Oral, titration	12278F	March 2021	Current	$587.95	$560.67	Y	Y

DMT	Brand	Strength/pack	Mode of administration & frequency	PBS item number	Listing date	Listing status (date of delisting)	DPMQ at listing	DPMQ June 2026 (or latest available)	SPA at time of listing	SPA June 2026 (or latest available)
Ofatumumab	Kesimpta	20 mg/0.4 mL x1 pen	SC, monthly	12641H	October 2021	Current	$2,183.42	$2,185.13	Y	Y
	Kesimpta	20 mg/0.4 mL x3 pen	SC, loading dose	12642J	October 2021	Current	$6,336.10	$6,337.80	Y	Y
Diroximel fumarate	Vumerity	231 mg x120 capsules	Oral, twice daily	13059H	August 2022	Current	$714.41	$716.06	N	N
Ublituximab	Briumvi	150 mg/6 mL x3 vials	IV, 6 monthly	15175Q	January 2026	Current	$11,583.00	$11,583.00	Y	Y
	Briumvi	150 mg/6 mL x4 vials	IV, loading dose	15176R	January 2026	Current	$15,444.00	$15,444.00	Y	Y
	Briumvi	150 mg/6 mL x3 vials	IV, 6 monthly	15197W	January 2026	Current	$11,631.87	$11,631.87	Y	Y
	Briumvi	150 mg/6 mL x4 vials	IV, loading dose	15187H	January 2026	Current	$15,492.88	$15,492.88	Y	Y

Abbreviations: DMT, disease-modifying therapy; DPMQ, dispensed price for maximum quantity; IM, intramuscular; IV, intravenous; mcg, microgram; mg, milligram; mL, millilitre; PBS, Pharmaceutical Benefits Scheme; SC, subcutaneous; SPA, Special Pricing Arrangement

*5 consecutive days in Year 1, 3 consecutive days in Year 2, as-needed treatment courses in Years 3&4.

**Two treatment weeks a year (4–5 days per week), at the start of the first and second months of each year for a maximum of 2 treatment courses over two consecutive years.

Appendix B: TGA indications for DMTs subsidised for MS

Drug (originator brand)	Treatment class	ATC Code	Date of first registration	Current Therapeutic Goods Administration (TGA) approved therapeutic indication(s) [as of June 2026]
Interferon beta-1b (Betaferon)	Interferons	L03AB08	9 Aug 2002 (currently registered formulation; first formulation registered in 1995)	Betaferon is indicated for: the treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent magnetic resonance imaging (MRI) lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded, 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, the reduction of frequency and severity of clinical relapses, and for the slowing of progression of disease in patients with secondary progressive multiple sclerosis.
Interferon beta-1a (Avonex)	Interferons	L03AB07	4 May 2004 (PFS)	AVONEX is indicated for the treatment of relapsing forms of multiple sclerosis (MS). AVONEX is indicated in patients who have experienced a single demyelinating event and are at risk of developing clinically definite MS based on the presence of brain MRI abnormalities characteristic of MS. AVONEX 60 µg is indicated for the treatment of secondary progressive MS in patients in whom relapse is still a feature of the disease. AVONEX 60 µg should not be initiated in patients with secondary progressive MS who have not experienced a relapse in the previous 12 months.
Glatiramer acetate (Copaxone)	Immunomodulator	L03AX13	17 Dec 2003 (20 mg)	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 (Rebif)	Interferons	L03AB07	31 Jan 2000 (Rebif 22 vial)	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 therapy should not be initiated in secondary progressive MS patients who no longer experience relapses.
Natalizumab (Tysabri)	Monoclonal antibody (α4 integrin)	L04AG03	1 Nov 2006	TYSABRI 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.
Fingolimod (Gilenya)	Sphingosine 1-phosphate receptor modulator	L04AE01	1 Feb 2011	GILENYA is indicated for the treatment of adult and paediatric patients of 10 years of age and above with relapsing forms of multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.
Dimethyl Fumarate (Tecfidera)	Immunomodulator	L04AX07	11 Jul 2013	TECFIDERA is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.
Teriflunomide (Aubagio)	Pyrimidine synthesis inhibitor	L04AK02	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.

Drug (originator brand)	Treatment class	ATC Code	Date of first registration	Current Therapeutic Goods Administration (TGA) approved therapeutic indication(s) [as of June 2026]
Alemtuzumab (Lemtrada)	Monoclonal antibody (CD52)	L04AG06	18 Dec 2013	Lemtrada 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.
Peginterferon beta-1a (Plegridy)	Interferons	L03AB13	10 Nov 2014	PLEGRIDY is indicated for the treatment of relapsing forms of Multiple Sclerosis (MS).
Daclizumab (Zinbryta)	Interleukin inhibitor	L04AC01	22 Sep 2016	N/A*
Ocrelizumab (Ocrevus)	Monoclonal antibody (CD20)	L04AG08	13 July 2017	Ocrevus is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and to reduce the frequency of relapse. Ocrevus is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay the progression of physical disability.
Cladribine (Mavenclad)	Purine antimetabolite	L04AA40	9 Sep 2010	MAVENCLAD is indicated for the treatment of relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical relapses and to delay the progression of physical disability.
Siponimod (Mayzent)	Sphingosine 1-phosphate receptor modulator	L04AE03	1 Nov 2019	Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS).
Ozanimod (Zeposia)	Sphingosine 1 phosphate receptor modulators	L04AE02	17 July 2020	[Multiple Sclerosis]: ZEPOSIA is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis. [Ulcerative Colitis]: ZEPOSIA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.
Ofatumumab (Kesimpta)	Monoclonal antibody (CD20)	L04AG12	4 Mar 2021	Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and reduce the frequency of relapse
Diroximel fumarate (Vumerity)	Immunomodulator	L04AX09	21 Mar 2022	VUMERITY is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.
Ublituximab (Briumvi)	Monoclonal antibody (CD20)	L04AG14	11 June 2025	BRIUMVI is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

Notes: *No longer listed on the ARTG ^Originator brand of teriflunomide (Aubagio) no longer listed on the ARTG; indication sourced from the Product Information of a generic brand.

Source: Australian Register of Therapeutic Goods: https://www.ebs.tga.gov.au/; ATC classification: https://atcddd.fhi.no/atc_ddd_index