Supporting Information

Supplementary material

This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.

Appendix to: Shipley J, Beharry J, Yeh W, et al. Consensus recommendations on multiple sclerosis management in Australia and New Zealand: part 1. *Med J Aust* 2024; doi: 10.5694/mja2.52578.

Table 1. Consensus recommendations for multiple sclerosis (MS) management in Australia and New Zealand

Number	Consensus recommendation/statement[a]	Level of consensus	GRADE[b]
Disease-modifying therapy (DMT) counselling and selection			
DMT counselling			
R1	Prior to commencing DMT, patients should be counselled about the nature of the disease, what to expect, and implications for day-to-day life and life choices such as pregnancy. Patients should also be counselled about the aims of DMT, the DMTs available, the associated risks and benefits, the importance of early treatment, and modifiable risk factors for disease progression (see *Table 1* and '*general lifestyle measures*').	96.3%	GPP
R2	Where available, a second consultation with an MS nurse specialist should also occur to further discuss DMTs, mode of administration, and to address any further questions.	88.5%	GPP
R3	DMTs for MS should be initiated and supervised by a neurologist and selection individualised to the person with MS (PwMS). The choice of DMT is determined by considerations including disease phenotype, disease activity, drug efficacy, drug risk profile, John Cunningham virus (JCV) antibody status, patient comorbidities, pregnancy considerations, local accessibility, route of administration, and patients' personal preferences, values, and goals.	100%	GPP
Relapsing-remitting MS (RRMS)			
R4	In RRMS, it is recommended that DMT is started as early as possible after diagnosis to limit irreversible disease progression. 'International consensus on quality standards for brain health-focused care in multiple sclerosis' suggests the process of discussing and commencing DMT should be complete within 3 months ('core') (with approximately 5 weeks being 'achievable' and 17 days being 'aspirational').	100%	A1
R5	In Australia and New Zealand, high-efficacy therapy (particularly natalizumab, ocrelizumab, ofatumumab, or cladribine) is generally favoured as first-line DMT in people with RRMS.	96.2%	A1
R6	Following an informed discussion between the patient and consultant, there are circumstances where intermediate or low-efficacy therapy is indicated.	88.2%	B2
Progressive MS			
R7	The evidence of effectiveness of DMTs in progressive MS is limited. Therefore, when considering therapy for progressive MS, the risk of adverse effects needs to be carefully weighed against the likelihood of slowing disease progression.	100%	B1
Clinically isolated syndrome (CIS)			
R8	In individuals with CIS meeting criteria for dissemination in space on magnetic resonance imaging (MRI) but not fulfilling criteria for dissemination in time, lumbar puncture for intrathecally-restricted oligoclonal bands can be offered as a probabilistic substitute for dissemination in time. This allows the diagnosis of MS and treatment according to the recommendations for RRMS (refer to *'RRMS'*).	85.2%	B1
R9	Individuals with a first demyelinating event with MRI abnormalities typical of MS should be considered for DMT, especially those with intrathecally-restricted oligoclonal bands.	94.4%	B2
Radiologically isolated syndrome (RIS)			
R10	In general, people with RIS should be monitored for the development of clinical manifestations and new demyelinating lesions on MRI at least annually for at least 5 years.	88.4%	B2
R11	Advice from MS specialist neurologists should be sought in treatment decisions in radiologically-isolated MS.	94.1%	GPP
Evaluation prior to commencing DMT			

Pre-immunotherapy screen			
R12	Prior to commencing DMT, perform a pre-immunotherapy screen to identify active and latent infections at risk of worsening with immunotherapy and to assess immunisation status (see *Table 2*).	100%	GPP
R13	If an important active or latent infection is identified, the patient should be referred to an appropriate specialist (e.g., infectious diseases or hepatologist) for assessment and treatment prior to initiation of DMT.	92.3%	GPP
R14	Patients with serological evidence of chronic active hepatitis B infection (HbsAg positive, HBV DNA positive) or evidence of prior exposure (anti-Hbcore Ab positive, HbsAg negative) should be referred to an infectious diseases physician or hepatologist prior to DMT commencement. The specialist will consider antiviral therapy (e.g., entecavir) for those with chronic infection and consider antiviral therapy or surveillance for those with evidence of prior exposure to minimise the risk of reactivation.	81.5%	B1
R15	Patients receiving anti-CD20 monoclonal antibodies are at highest risk of hepatitis B reactivation and anti-CD20 therapy is contraindicated without prophylaxis. Prophylaxis should continue for up to 18 to 24 months after cessation of anti-CD20 monoclonal antibodies.	85.2%	B1
Immunisations			
R16	Review the patient's immunisation history and aim to ensure that they up to date with the Australian National Immunisation Program Schedule (NIPS) or New Zealand National Immunisation Schedule, as relevant. Particular attention should be paid to varicella zoster and hepatitis B vaccinations. However, delaying DMT to complete vaccinations may not be feasible in all cases, especially in the setting of severe or aggressive MS.	84.6%	B1
R17	All indicated live and live-attenuated vaccinations should be given at least 4 to 6 weeks prior to starting certain immunosuppressant DMT (e.g., anti-CD20 monoclonal antibodies) to ensure the vaccines are safe and effective.	84.6%	B2
R18	To allow time for a vaccine response, non-live vaccines should be completed 2 to 6 weeks prior to some DMT, as per Therapeutic Goods Administration (TGA) guidelines.	80.7%	B2
Baseline laboratory tests and examinations			
R19	Perform baseline laboratory tests relevant to the particular DMT (e.g., full blood examination, creatinine, liver function tests, quantitative serum immunoglobulins, pregnancy test, urinalysis, electrocardiogram, optical coherence tomography) and relevant examinations (e.g., skin, ophthalmic, cervical smear) (see *Table 1*). These tests are not required prior to all therapies.	92.3%	GPP
Monitoring disease activity on DMT			
R20	Monitor PwMS on DMT for symptoms and/or signs of disease activity, including acute clinical relapses and progression of disability.	100%	A1
R21	Obtain a re-baselining MRI of the brain and/or spine within 3 to 6 months of treatment commencement.	92.6%	GPP
R22	If there are new lesions on the re-baselining MRI, arrange an interval MRI in 3 to 6 months to ensure radiological disease stability.	92.6%	GPP
R23	In patients with long-term disease stability and low risk of progressive multifocal leukoencephalopathy (PML), interval MRI is generally performed every 12 months (see '*progressive multifocal leukoencephalopathy'*). In patients with active disease or moderate to high risk of PML, MRI is generally performed 3- to 6-monthly.	84.5%	GPP
Switching DMT			
Indications for switching			
R24	Switching to another DMT is recommended if there is evidence of breakthrough clinical disease activity (one or more clinical relapses) or radiological disease activity (one or more new T2-	92.3%	B1

	hyperintense lesions) after being on and adherent to a DMT for a sufficient time for it to be fully effective.		
R25	Switching DMT should also be considered if the risk of continuing outweighs the benefit or the patient develops serious or intolerable adverse effects.	96.2%	GPP
Sequential DMT selection and washout period			
R26	In addition to considerations outlined in '*DMT counselling and selection*', choice of sequential DMT is determined by considerations such as implications of previous immunosuppressive therapies and comparative drug efficacy.	100%	B2
R27	There is limited evidence to guide the optimal duration of washout periods. A washout period of more than 4 to 8 weeks should be avoided for natalizumab and sphingosine 1-phosphate (S1P) receptor modulators.	100%	A1
Autologous haematopoietic stem cell transplant (aHSCT)			
R28	aHSCT is used in a small number of carefully selected patients with severe refractory active RRMS without high levels of disability. It is generally reserved for younger adults (<65 years old) with lower baseline disability (Expanded Disability Status Scale (EDSS) ≤6.5) who have failed two or more high-efficacy DMTs due to continued clinical and radiological disease activity. Neurologists can consider referring appropriate PwMS for assessment by an MS neurologist in a major tertiary centre with experience in aHSCT for MS where cases are reviewed by the national aHSCT committee and their follow up trajectory monitored as per national standards. Appropriate PwMS in New Zealand can be referred for review by the aHSCT committee of Australia.	96.3%	C1
Discontinuing DMT			
R29	In general, it is recommended that patients with RRMS continue DMT if they are clinically stable and not experiencing significant adverse effects. For those of older age (>65 years) and at greater risk of side effects, careful consideration should be given to DMT cessation or de-escalation.	96.2%	C1
R30	For patients who decide to discontinue DMT, close clinical and radiological monitoring is recommended.	96.2%	B1
R31	In patients with progressive MS, consider discontinuing DMT if the risks outweigh the benefits or there is significant disability progression (Expanded Disability Status Scale (EDSS) ≥7).	84.7%	C2
Risk mitigation strategies during treatment with DMT			
Laboratory monitoring			
R32	Monitor relevant laboratory tests in patients on DMT, as summarised in *Table 1*. Switching DMT might be warranted if significant or serious abnormalities occur.	96.2%	GPP
Progressive multifocal leukoencephalopathy (PML)			
R33	Prior to commencing natalizumab therapy and during treatment, the risk-benefit balance of natalizumab **(**specifically the risk of PML) should be discussed.	100%	GPP
R34	To aid in quantifying the risk of PML on natalizumab, perform anti-JCV antibody testing 6-monthly and utilise established risk algorithms.	100%	A1
R352	Patients on natalizumab should be monitored for clinical and radiological evidence of PML. Therapy should be suspended immediately if there is any concern for PML and the patient should be referred to a specialist centre.	100%	A1
R36	In the setting neurological deterioration associated with immune reconstitution inflammatory syndrome (IRIS), high-dose corticosteroids (often 1g intravenous (IV) methylprednisolone for 5 days followed by tapering oral steroids) are recommended.	88.9%	C2
Mitigating infection risk			

R37	While on therapy, it is recommended that all patients are up to date with the relevant national immunisation schedule, including annual influenza vaccination (non-live formulation) and COVID-19 vaccinations in line with national guidelines.	96.2%	GPP
R38	In general, live and live-attenuated vaccines should not be administered during treatment with immunosuppressive DMTs. However, there are exceptions for which infectious diseases consultation should be sought.	94.4%	B2
Cancer screening			
R39	For all PwMS on DMT, it is recommended that standard age-appropriate national cancer screening guidelines are followed.	96.2%	A1
R40	However, in women on moderate to high-efficacy therapy in whom an oncogenic human papilloma virus (HPV) type has not been detected, cervical cancer screening with an HPV test is recommended 3-yearly instead of 5-yearly.	81.4%	C2
R41	Skins checks are recommended at least annually for patients on S1P receptor modulators.	96.3%	C1
Managing DMT in special situations			
Pregnancy			
R42	Pregnancy plans should be discussed with women of childbearing potential prior to commencing DMT and regularly thereafter to carefully plan the best approach to DMT selection and management.	100%	GPP
R43	The decision to continue or temporarily discontinue DMTs during pregnancy is individualised based on factors such as the individual's clinical and radiological disease activity and severity, DMT safety in pregnancy, the risk of rebound activity after DMT discontinuation, and personal preferences and values.	100%	GPP
R44	DMT associated with significant risks in pregnancy, including teriflunomide, fingolimod, siponimod, and ozanimod, should not be given to pregnant women or women of childbearing age who are not using highly effective contraception.	88.9%	B2
R45	If a PwMS has an unplanned pregnancy on one of these teratogenic DMTs, discontinue the DMT immediately and refer to an obstetrician for further assessment.	88.9%	A2
R46	If a PwMS becomes pregnant on teriflunomide, discontinue the drug immediately, initiate an accelerated elimination procedure (e.g., a cholestyramine washout or activated charcoal), and arrange a referral to an obstetrician for further assessment.	100%	A1
R47	Cladribine is another teratogenic DMT and should not be administered during pregnancy. Individuals can consider conception 6 months after completing the last course of cladribine. If pregnancy occurs after the year 1 course of cladribine, the second-year course should be delayed until after delivery and breastfeeding.	88.9%	B2
R48	If an individual wishes to discontinue another DMT prior to pregnancy, the risk-benefit considerations should be discussed. This includes the potential risks associated with fetal DMT exposure and the risk of MS disease activity and disability accrual with discontinuation. Following a careful risk-benefit discussion with the patient, discontinuing DMT prior to pregnancy can be considered in individual circumstances taking into consideration the personal preferences, recent disease activity, and DMT type.	96.3%	GPP
R49	In people with highly active MS, briefly delaying pregnancy to allow disease control should generally be discussed. Pregnancy outcomes are improved in women with stable disease pre-conception and therefore a period of disease stability is generally preferred prior to pregnancy. However, individualised circumstances should always be considered.	81.4%	C2
R50	In people with active disease or adverse prognostic factors who wish to become pregnant, a shared decision can be made to continue certain DMT where the risk of disease activity outweighs the risk associated with DMT exposure during pregnancy.	88.5%	B2
R51	Natalizumab can be continued until the third trimester and extended interval dosing (6-weekly) up to 30 to 34 weeks can be considered.	88.9%	B2

R52	While it was previously recommended that ocrelizumab be ceased 6 to 12 months prior to planned conception, aiming for conception 3 months after the last infusion can be considered.	88.9%	B2
R53	Glatiramer acetate is considered safe in pregnancy.	100%	B1
R54	Treatment of MS relapses during pregnancy is only recommended when symptoms are functionally disabling. A short course of non-fluorinated corticosteroids (such as methylprednisolone) is generally considered low risk after the first trimester (refer to *'acute relapses'* for approach).	85.1%	C2
R55	If MRI is required, gadolinium contrast should generally be avoided due to potential risks associated with fetal exposure.	96.3%	B1
Postpartum and breastfeeding			
R56	Early resumption of DMT is generally recommended to reduce the risk of postpartum relapse. Timing of DMT recommencement varies based on disease activity prior to and during pregnancy, risk of rebound disease activity off DMT**,** and safety considerations surrounding breastfeeding.	100%	B1
R57	Aim to recommence natalizumab within 2 weeks after birth due to the risk of rebound disease activity after natalizumab withdrawal.	92.6%	B2
R58	The benefits of breastfeeding should be discussed with women along with safety considerations related to DMTs during breastfeeding.	100%	GPP
R59	Glatiramer acetate and interferon beta are considered safe during breastfeeding.	96.2%	B1
R60	Natalizumab is likely safe during breastfeeding, with no increased risk of adverse effects in small studies of newborns exposed to natalizumab in breastmilk.	85.1%	C2
R61	Ocrelizumab and ofatumumab are likely safe during breastfeeding, though there may be a very low risk of neonatal B-cell depletion, infection, and impaired vaccine response.	92.3%	C2
R62	In neonates with B-cell depletion from anti-CD20 therapy, live vaccines should be delayed until B-cell counts have recovered.	96.3%	C1
R63	DMTs comprised of small molecules, including fingolimod, siponimod, ozanimod, teriflunomide, and cladribine, are not considered safe in breastfeeding.	92.5%	B1
Active infection			
R64	Administration of immunosuppressive DMT should be temporarily delayed if a PwMS develops a life-threatening infection or there is poor response to initial anti-microbial therapy. However, withholding therapy provides minimal short-term protective benefit due to the long half-lives of many DMTs and the latency of the impact on white cell function and reconstitution. Risk of significant rebound disease activity as a result of suspending DMT (such as S1P receptor inhibitors) should also be carefully considered.	100%	C1
R65	In PwMS with severe or recurrent serious infections, switching to a DMT with a lower risk of infection should be considered.	96.2%	B1
COVID-19 infection			
R66	Patients should be counselled about the importance of COVID-19 vaccinations and general behavioural modification strategies to reduce the risk of COVID-19 infection.	96.2%	GPP
R67	In PwMS who are on immunosuppressive therapies and experience acute COVID-19 infection, COVID-19 specific treatments (i.e., anti-virals) should be commenced promptly as per up-to-date protocols.	96.3%	GPP
R68	In the case of severe COVID-19 infection, administration of immunosuppressive DMT should generally be delayed until the infection has resolved, although the lack of acute protective benefit from delaying DMT and the risk of rebound disease activity should be considered.	81.4%	C2
Current or previous malignancy			
R69	When a patient has a current or past malignancy, decisions regarding DMT management are made on a case-by-case basis taking into consideration factors such as the type, recency, and grade of	100%	GPP

	malignancy and risk of DMT. Caution should be exercised in patients with a current or previous malignancy and specialist advice sought. People at high risk of skin cancers should avoid S1P receptor inhibitors.		
General lifestyle measures			
Exercise			
R70	PwMS are recommended to participate in regular exercise, including aerobic and resistance training, to a minimum weekly total of 2.5 hours.	100%	B1
R71	At higher disability levels, guidance from allied health clinicians such as physiotherapists, occupational therapists, and exercise physiologists with experience in MS is recommended to develop individualised exercise programs that are safe and effective.	96.3%	GPP
Smoking cessation			
R72	PwMS should be strongly counselled and supported to cease and avoid smoking, including vaping.	100%	B1
Vitamin D supplementation			
R73	While there is no benefit in modulation of disease activity, maintaining adequate serum vitamin D levels is recommended to promote bone health through adequate safe sun exposure and vitamin D supplementation where required.	85.1%	C2
Acute MS relapses			
Pseudorelapses			
R74	When a patient presents with neurological symptoms suggesting a clinical relapse of MS, assess for causes of a pseudorelapse such as infection that might explain the deterioration. However, differentiating relapses and pseudorelapses can be difficult. A comprehensive assessment, including a thorough history, neurological examination, and in some instances imaging, is required for accurate differentiation.	100%	GPP
R75	Manage a pseudorelapse by treating the underlying cause.	100%	GPP
MS relapses			
R76	After infection or other intercurrent medical illness is excluded, acute or subacute symptomatic neurological episodes with functionally disabling symptoms lasting more than 24 hours are treated with IV or oral methylprednisolone 1g for three to five days. Mild relapses, particularly those characterised by isolated sensory symptoms, generally do not warrant steroid treatment.	100%	B1
R77	In severe refractory relapses, a second course of methylprednisolone or plasma exchange can be considered.	96.2%	C1
R77	Acute clinical relapses should be evaluated with MRI of the brain or spine with gadolinium contrast, but treatment need not be delayed for this.	84.7%	C2
Symptomatic treatments			
R79	Support from a multidisciplinary team of allied health clinicians with experience in MS, such as physiotherapists, occupational therapists, continence specialists, exercise physiologists, speech pathologists, dieticians, psychologists, and neuropsychologists, is important in managing specific symptoms in select individuals with MS.	92.6%	GPP
R80	Clinicians should exclude other causes of symptoms such as fatigue (e.g., infection, depression, anaemia, iron deficiency, and thyroid dysfunction) and consider non-pharmacological approaches (e.g., exercise therapy for fatigue) prior to prescribing pharmacological therapy.	96.3%	GPP

a Please see main text for additional context and references to supporting evidence for each of the recommendations

b Recommendations were graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The quality of the supporting evidence was defined as high (A), moderate (B), or low (C) and the strength of the recommendations was classified as strong (1) or conditional (2). Where specific evidence is lacking and recommendations are based on best-practice standard of care, consensus recommendations were designated as Good Practice Points (GPP). Based on the GRADE framework, high quality evidence (A) was assigned when it was assessed that 'further research is very unlikely to change our confidence in the estimate of effect', moderate (B) when 'further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate', and low (C) (combining the 'low' and 'very low' categories of the standard GRADE system) when 'further research is very

likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate' or 'any estimate of effect is very uncertain'. Recommendations were assigned as strong (1) when a 'guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects',[1] and conditional (or weak) (2) when 'the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists'.[2] The strength of the evidence and recommendations was determined through consideration of the balance of benefits and harms, level of certainty, quality of the supporting evidence, associated costs, resource implications, and patients' personal values and preferences.

Table 2. Characteristics of the Delphi Panel

	n
Delphi Panelists	26[a]
Regularly see MS patients in their practice	25/26 (96.2%)
Level of experience	
<5 years neurology trained	5/26 (19.2%)
6-10 years neurology trained	13/26 (50%)
>11 years neurology trained	8/26 (30.8%)

a Panelists that completed the first anonymised multiple-choice survey

Table 3. Summary of results of Delphi review rounds

	Number of recommendations	Level of consensus	Total consensus	Number of panelists	Medium
Round 1a[a]	70	56/70 (80%)	56/70 (80%)	26	Multiple-choice survey with a 5-point Likert scale
Round 1b[a]	70	-	-	32	Free-text feedback
Review process	• Consensus reached: 49 retained, 7 removed (consolidated), 6 modified • Consensus not reached: 11 revised, 3 removed • New: 30				
Round 2	47, including 6 modified consensus recommendations, 11 revised non-consensus recommendations, and 30 new recommendations	34/47 (72.3%)	77/90 (85.6%)	27	Multiple-choice survey with a 5-point Likert scale
Review process	• Consensus reached: 34 retained • Consensus not reached: 7 revised, 6 removed • New: 1				
Round 3	8, including 7 non-consensus recommendations and 1 new recommendation	7/7 (100%)	84/84 (100%)	18	Online meeting and multiple-choice poll with a 5-point Likert scale
Review process	• Consensus reached: 7 retained, 4 previous recommendations removed (consolidated) • Consensus not reached: Panel decision to remove 1 recommendation during the meeting prior to voting				
Final	80 consensus recommendations				

5-point Likert scale: 1 – strongly disagree, 2 – disagree, 3 – neutral, 4- agree, 5- strongly agree
a Took place concurrently

References

1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
2. Schünemann H, Brożek J, Guyatt G, et al. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, 2013. guidelinedevelopment.org/handbook (viewed June 2024).

Table 4. Summary of DMTs currently available on the PBS in Australia and Pharmac in New Zealand

DMT	Administration	Mechanism of action	MS phenotype	Subsidised in AU and/or NZ	Efficacy (relative reduction in ARR)[a]	Contraindications	Interval between vaccines and DMT	Laboratory and clinical assessments prior to commencement[b]	Risk profile (see full PI)	Washout period[c]	TGA pregnancy category	Interval between DMT exposure and pregnancy[1,d]	Monitoring during treatment
Alemtuzumab (Lemtrada®)	2 courses 12 months apart: 12mg IV daily for 5 consecutive days year one, 12mg IV daily for 3 days 12 months later	Humanised anti-CD52 monoclonal antibody that depletes B and T lymphocytes	RRMS	AU	49-72% (vs interferon beta)[2-4]	• Serious hypersensitivity to alemtuzumab or excipients • Active systemic infections (e.g., HIV) • Uncontrolled hypertension • Stroke, arterial dissection of the cervicocephalic arteries, angina pectoris or AMI • Coagulopathy or anticoagulant therapy	All necessary vaccines at least 6 weeks prior to commencement[5]	• FBE, Cr, LFTs, TSH, consider pregnancy test • Urinalysis with cell counts, urine protein-creatinine ratio • Skin exam • HPV screening in females	• Hypersensitivity and infusion reactions • Autoimmune disorders (e.g., thyroid (36.8%), ITP (1%) including fatal ICH, glomerular nephropathies (0.4%))[5] • Lymphopaenia (nadir 1 month post-treatment; may persist for years) • Infection (e.g., herpesvirus, Listeria including Listeria meningitis, PJP) • Stroke, arterial dissection • May increase the risk of malignancy • PML (very rare)	12 months	B2	4 months	• During treatment and for 4 years after the last infusion: Monthly FBE, Cr, urinalysis with cell counts and 3-monthly TSH and fT3/fT4 if TSH abnormal[5] • Anti-herpes prophylaxis (e.g., oral acyclovir 200mg BD) from day 1 of each course for a minimum of 1 month or until CD4+ lymphocytes ≥200 cells/μL (whichever occurs later)[5] • Consider Listeria prophylaxis with trimethoprim sulfamethoxazole for 1 month after treatment and discuss dietary modification to reduce the risk of listeriosis[6]

Natalizumab (Tysabri®)	300mg IV 4-weekly	Humanised monoclonal antibody that binds to α4-integrin and inhibits lymphocyte migration into the CNS	RRMS	AU, NZ	68% (vs placebo)[7]	• Serious hypersensitivity to natalizumab or excipients • Current or previous PML • Immunocompromised state, including current or recent treatment with other immunosuppressants (e.g., azathioprine, cyclophosphamide, methotrexate) and systemic medical conditions (e.g., HIV, organ transplant, active malignancy)	No special interval[8]	JCV serology	• Hypersensitivity and infusion reactions (e.g., headache, dizziness, fatigue) • PML (see *'progressive multifocal leukoencephalopathy'* in Part 2) • Transaminitis • Infection	1 month (consider risk of rebound disease activity)	C	Consider continuing up to the third trimester	• Anti-JCV IgG 6-monthly
Ocrelizumab (Ocrevus®)	Initially 300mg followed by 300mg two weeks later then 600mg IV 6-monthly	Humanized anti-CD20 monoclonal antibody that depletes CD20-expressing B lymphocytes	RRMS; in NZ, subsidised for PPMS	AU, NZ	46-47% (vs interferon beta)[9]	• Serious hypersensitivity to the active substance or excipients • Active hepatitis B infection	• Live and live-attenuated vaccines at least 4-6 weeks prior to commencement • Non-live vaccines at least 2 weeks prior	• Hepatitis B serology • Quantitative serum immunoglobulins (if low, consult immunology prior to anti-CD20 therapy)[10]	• Hypersensitivity and infusion reactions (e.g., pruritus, rash, bronchospasm; 34%)[9] • Infection (e.g., respiratory, skin, urinary tract, herpesvirus, hepatitis B reactivation) • Reduction in immunoglobulins • Neutropaenia (may be delayed) • Immune-mediated colitis • May increase the risk of malignancy	3-6 months	C	3 months	• Quantitative serum immunoglobulins • Consider discontinuing anti-CD20 therapy or supplementing with IVIG or SCIG in consultation with immunology if low serum IgG (<6 g/L) and serious or recurrent infections[10]
Ofatumumab (Kesimpta®)	Initially 20mg SC at 0, 1, 2, 4 weeks followed by monthly dosing	Fully humanised anti-CD20 monoclonal antibody that depletes CD20-expressing B lymphocytes	RRMS	AU	51-58% (vs teriflunomide)[11]					2-4 weeks	C	Stop when trying to conceive	

									• PML (very rare)				
Cladribine (Mavenclad®)	Total dose of 3.5mg/kg PO over 2 treatment courses 12 months apart with each treatment course divided into 2 cycles: 1.75 mg/kg per treatment course, half over 5 days in week 1, remainder in week 5, then repeat 12 months later	Cytotoxic drug that impairs DNA synthesis leading to a reduction in circulating B and T lymphocytes	RRMS	AU	58% (vs placebo)[12]	• Serious hypersensitivity to cladribine or excipients • Pregnancy • Women or men of reproductive potential not using effective contraception during therapy and for 6 months after each treatment course • Breastfeeding • Active chronic infection (e.g., HIV, tuberculosis, hepatitis B or C) • Immunocompromised state, including other current immuno- or myelosuppressive medications (e.g., azathioprine, cyclosporin, methotrexate) • Moderate or severe renal impairment (CrCl <60 ml/min)	Live and live-attenuated at least 4-6 weeks prior to commencement	FBE, LFTs, consider pregnancy test	• Lymphopenia (nadir 2-3 months after the first dose of each treatment course) • Infection (e.g., herpes zoster, oral herpes) • GVHD with blood transfusions (if blood transfusion required, use irradiated blood products and consult haematology)[65] • Liver injury • Heart failure • May increase the risk of malignancy • Hypersensitivity	4-12 months depending on lymphocyte count (aim >800 cells/µL)	D	6 months in men and women	• FBE prior to each treatment course and 2 and 6 months after the start of each treatment course. If lymphocytes <200 cells/µL at 2 months, monitor monthly until month 6 • If lymphocytes <500 cells/µL, monitor closely for infection. If lymphocytes <200 cells/µL, consider herpes prophylaxis[13] • Lymphocytes must be ≥800 cells/µL before the second course which can be delayed up to 6 months to allow lymphocyte recovery[13] • LFTs prior to each treatment course and repeat if any clinical concerns

Fingolimod (Gilenya®)	0.5mg PO daily (for weight >40kg, otherwise 0.25mg PO daily)	S1P receptor modulator leading to retention of lymphocytes in lymphoid tissue	RRMS	AU, NZ	52% (vs interferon beta)[14], 48-55% (vs placebo)[15,16]	• Serious hypersensitivity to the active substance or excipients • Recent (within 6 months) AMI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation or NYHA III/IV heart failure • Mobitz II 2nd or 3rd degree AV block or sick sinus syndrome (unless pacemaker) • QTc ≥500ms • Class Ia or III antiarrhythmic drugs • Pregnancy • Women of reproductive potential not using effective contraception • Breastfeeding	Live and live-attenuated vaccines at least 4-6 weeks prior to commencement	• FBE, LFTs, consider pregnancy test • ECG prior to first dose • Ophthalmic review to screen for macular oedema	• Transient bradycardia or bradyarrhythmia (2:1 AV block) with first dose • Headache, flu-like symptoms, cough, dyspnoea, GI symptoms • Macular oedema (usually after 3-4 months) • Hypertension • Lymphopaenia • Infection (e.g., respiratory, herpes zoster, cryptococcal meningitis, HPV) • Transaminitis • May increase the risk of malignancy, particularly cutaneous malignancy • PRES • Seizures • PML (very rare) • Hypersensitivity	0-1 month depending on lymphocyte count (aim >600 cells/μL; consider risk of rebound disease activity)	D	≥2 months	• First-dose monitoring for at least 6 hours including hourly blood pressure, heart rate, and repeat ECG after 6 hours (for all patients starting fingolimod and those with sinus bradycardia <55 beats per minute, 1st or 2nd-degree Mobitz I AV block, or history of AMI or heart failure starting siponimod if not contraindicated; not routinely done for ozanimod)[17-19] • Ophthalmic assessment for macular oedema 3-4 months after commencement and if visual disturbance develops[17] • LFTs within 6 months of commencement and periodically thereafter • Annual skin check • Consider herpesvirus prophylaxis in those with frequent oral or genital herpes simplex infections[20]
Siponimod (Mayzent®)	Up-titration to 1mg or 2mg PO daily (depending on CYP2C9 genotype)		RRMS; SPMS	AU	In SPMS, 21% relative reduction in patients with 3-month CDP (vs placebo)[21]	• As for fingolimod (consult cardiology if prolonged QTc or on QT-prolonging drugs)[71] • CYP2C9*3/*3 genotype		• As for fingolimod • CYP2C9 enzyme status				≥10 days	

Ozanimod (Zeposia®)	Up-titration to 0.92mg PO daily		RRMS	AU	38-48% (vs interferon beta)[25,26]	• As for fingolimod (consult cardiology if prolonged QTc or antiarrhythmic drugs)[18] • Severe untreated sleep apnoea • MAO inhibitors		As for fingolimod				≥3 months	
Dimethyl fumarate (Tecfidera®)	Up-titration to 240mg PO BD	Modulates the Nrf2 pathway leading to antioxidant, immunomodulatory, and ant-inflammatory effects	RRMS	AU, NZ	41-53% (vs placebo)[24,25]	Serious hypersensitivity to the active substance, other fumaric acid derivatives, or excipients	No special interval	FBE	• Flushing • GI symptoms (e.g., nausea, vomiting, abdominal pain, diarrhoea; lower rate with diroximel fumarate)[26] • Lymphopaenia • Transaminitis • Infection (e.g., herpes zoster) • PML (very rare, reported with dimethyl fumarate) • Hypersensitivity	0-4 weeks depending on lymphocyte count (aim >800 cells/µL)	B1	Cease at positive pregnancy test	• FBE 6 months after initiation of treatment, then 6-12 monthly thereafter. Consider interruption of treatment if lymphocytes <500 cells/µL persisting for ≥6 months[27] • LFTs, as clinically indicated
Diroximel fumarate (Vumerity®)	Uptitration to 462mg PO BD		RRMS	AU	Interim efficacy data similar to dimethyl fumarate[28]						B3	-	
Teriflunomide	14mg PO daily	Pyrimidine synthesis inhibitor leading to impaired lymphocyte proliferation and function	RRMS	AU, NZ	32-36% (vs placebo)[29,30]	• Serious hypersensitivity to teriflunomide, leflunomide, or excipients • Pregnancy • Women of reproductive potential not using effective contraception during treatment and while plasma levels of the active metabolite are	No special interval	• FBE, LFTs, consider pregnancy test • Blood pressure	• Alopecia • GI symptoms (e.g., nausea, diarrhoea) • Peripheral neuropathy • Neutropaenia, lymphopaenia • Liver injury including fatal liver failure • Acute renal impairment • Hypertension • Infection (e.g., respiratory, GI,	No washout	X	24 months	• Monthly LFTs for 6 months, then 6 monthly (consider drug discontinuation if ALT >3 times ULN)[31] • FBE if suspected infection • Blood pressure

						>0.02 mg/L unless undergoing washout • Breastfeeding • Leflunomide • Severe liver impairment • Severe immunodeficiency • Severe uncontrolled infections • Severe bone marrow dysfunction • Severe hypoproteinaemia			urinary) • Hypersensitivity				
Interferon β-1b (Betaferon®)	Up-titration to 0.25mg SC every second day	Anti-inflammatory effects and decreased lymphocyte trafficking into the CNS	RRMS	AU, NZ	34% (vs placebo)[32]	• Serious hypersensitivity to interferon β, albumin, mannitol or other excipients	No special interval	FBE	• Flu-like symptoms (especially first 3 months) • Hypersensitivity and injection site reactions and necrosis • GI symptoms (e.g., nausea, abdominal pain) • Anaemia, leukopaenia • Liver injury • Depression and suicidal ideation • Hypertension • Heart failure • Thrombotic microangiopathy • Nephrotic syndrome • Seizures	No washout	D	Can be continued during pregnancy	FBE and LFTs at 1, 3 and 6 months then annually
Interferon β-1a (Plegridy®)	Up-titration to 0.125mg SC every second week		RRMS	AU, NZ (Avonex® in NZ)	36% (vs placebo)[33,34]	• Serious hypersensitivity to interferon β, albumin, mannitol or other excipients • Current severe depression and/or suicidal ideation							
Glatiramer acetate	40mg SC 3 times per	Synthetic polypeptide	RRMS	AU,	29% (vs	Serious hypersensitivity to	No special		• Hypersensitivity and injection site	No washou	B1	Can be continued	None

(Copaxone®)	week	that reduces the immune response to myelin	NZ	placebo)[35]	glatiramer acetate or mannitol	interval	reactions (e.g., localised lipoatrophy) • Immediate post-injection reaction (e.g., flushing, dyspnoea, chest pain, palpitations)	t	during pregnanc y

ALT: alanine transaminase; AMI: acute myocardial infarction; ARR: annualised relapse rate; AU: Australia; AV: atrioventricular; BD: twice per day; CDP: confirmed disability progression; Cr: creatinine; CrCl: creatinine clearance; ECG: electrocardiogram; FBE: full blood examination (with differential); fT3: free tri-iodothyronine; fT4: free thyroxine; GI: gastrointestinal; GVHD: graft-versus-host disease; HIV: human immunodeficiency virus; HPV: human papilloma virus; ICH: intracerebral haemorrhage; ITP: immune thrombocytopaenia; IV: intravenous; IVIG: intravenous immunoglobulin; LFTs: liver function tests; MAO: monoamine oxidase; Nrf2: nuclear factor erythroid 2–related factor 2; NYHA: New York Heart Association; NZ: New Zealand; PI: product information; PJP: Pneumocystis jirovecii pneumonia; PML: progressive multifocal leukoencephalopathy; PO: oral; PPMS: primary progressive MS; PRES: posterior reversible encephalopathy syndrome; QTc: corrected QT interval; RRMS: relapsing-remitting MS; S1P: sphingosine 1-phosphate; SC: subcutaneous; SCIG: subcutaneous immunoglobulin; SPMS: secondary progressive MS; TGA: Therapeutic Goods Administration; TIA: transient ischaemic attack; TSH: thyroid stimulating hormone; ULN: upper limit of normal

a These data are directly reported from different randomised-controlled trials with different inclusion criteria, cohort demographics, and definitions of outcomes. They should not be compared directly

b In addition to a pre-immunotherapy screen (see '*pre-immunotherapy screen'*)

c See '*switching DMT'*

d Recommended interval between drug exposure/discontinuation and conception based on recommendations by Krysko et al. (2023).[1] See *'pregnancy'* in Part 2[36]

References

1 Krysko KM, Dobson R, Alroughani R, et al. Family planning considerations in people with multiple sclerosis. *Lancet Neurol* 2023; 22: 350-366.
2 CAMMS223 Trial Investigators; Coles AJ, Compston DA, Selmaj KW, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Eng J Med* 2008; 359: 1786-1801.
3 Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1819-1828.
4 Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829-1839.
5 Therapeutic Goods Administration. Australian product information: Lemtrada (alemtuzumab). Canberra: TGA, 2024. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02549-1&d=20240327172310101 (viewed Feb 2024).
6 Australian Medicines Handbook. Alemtuzumab (neurology). Adelaide: AMH, 2024. https://amhonline.amh.net.au.acs.hcn.com.au/chapters/neurological-drugs/drugs-multiple-sclerosis/alemtuzumab-neurology (viewed Jan 2024).
7 Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Eng J Med* 2006; 354: 899-910.
8 Kaufman M, Pardo G, Rossman H, et al. Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis. *J Neurol Sci* 2014; 341: 22-27.
9 Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Eng J Med* 2017; 376: 221-234.
10 Otani IM, Lehman HK, Jongco AM, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: a work group report of the AAAAI primary immunodeficiency and altered immune response committees. *J Allergy Clin Immunol* 2022; 149: 1525-1560.
11 Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Eng J Med* 2020; 383: 546-557.
12 Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Eng J Med* 2010; 362: 416-426.
13 Therapeutic Goods Administration. Australian product information: Mavenclad (cladribine) tablets. Canberra: TGA, 2024. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-07339-3 (viewed Jan 2024).
14 Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Eng J Med* 2010; 362: 402-415.
15 Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Eng J Med* 2010; 362: 387-401.
16 Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; 13: 545-556.
17 Therapeutic Goods Administration. Australian product information: Gilenya (fingolimod) capsules. Canberra: TGA, 2021. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-01890-3 (viewed Jan 2024).
18 Therapeutic Goods Administration. Australian product information: Zeposia (ozanimod) capsules. Canberra: TGA, 2023. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-01969-1 (viewed Jan 2024).
19 Therapeutic Goods Administration. Australian product information: Mayzent (siponimod) tablets. Canberra: TGA, 2023. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-02212-1&d=20231205172310101 (viewed Jan 2024).
20 Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. *Open Forum Infect Dis* 2018; 5: ofy174.
21 Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018; 391: 1263-1273.
22 Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet Neurol* 2019; 18: 1021-1033.
23 Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol* 2019; 18: 1009-1020.
24 Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Eng J Med* 2012; 367: 1087-1097.
25 Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Eng J Med* 2012; 367: 1098-1107.
26 Naismith RT, Wundes A, Ziemssen T, et al. Diroximel fumarate demonstrates an improved gastrointestinal tolerability profile compared with dimethyl fumarate in patients with relapsing–remitting multiple sclerosis: results from the randomized, double-blind, phase III EVOLVE-MS-2 study. *CNS Drugs* 2020; 34: 185-196.
27 Therapeutic Goods Administration. Australian product information: Tecfidera (dimethyl fumarate) modified release capsules. Canberra: TGA, 2023. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01953-1 (viewed Jan 2024).
28 Naismith RT, Wolinsky JS, Wundes A, et al. Diroximel fumarate (DRF) in patients with relapsing–remitting multiple sclerosis: interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study. *Mult Scler* 2020; 26: 1729-1739.
29 O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Eng J Med* 2011; 365: 1293-1303.
30 Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; 13: 247-256.
31 Therapeutic Goods Administration. Australian product information: Aubagio (teriflunomide). Canberra: TGA, 2012. https://www.tga.gov.au/sites/default/files/auspar-teriflunomide-130521-pi.pdf (viewed Dec 2023).
32 IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; 43: 655-661.
33 Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon β-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014; 13: 657-665.
34 Newsome SD, Scott TF, Arnold DL, et al. Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN. *Ther Adv Neurol Disord* 2018; 11: 1756286418791143.
35 Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing–remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. *Neurology* 1995; 45: 1268-1276.
36 Shipley J, Beharry J, Yeh W, et al. Consensus recommendations on multiple sclerosis management in Australia and New Zealand: part 2. *Med J Aust* 2024; doi: 10.5694/mja2.52577.