OPTUMRx

Therapeutic Class Overview
Multiple Sclerosis Agents

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is among the most common causes of neurological disability in young adults *(MS Coalition 2019; National Institutes of Health MS 2018)*. Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes. Most patients with MS experience relapses and remissions of neurological symptoms, usually early in the disease process, with clinical events that are generally associated with CNS inflammation. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for an estimated 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 15% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Clinically isolated syndrome (CIS) refers to the first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS. Patients who experience a CIS may or may not develop MS *(Sanvito et al 2011, National MS Society 2019[a])*.
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the historical category of progressive-relapsing multiples sclerosis (PRMS) can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 1 million adults in the United States are affected by MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is at least 2 to 3 times more common in women than in men *(National MS Society 2019[b])*.
- Diagnosis of MS requires evidence that demonstrates lesions in the CNS showing “dissemination in space” (ie, suggestions of damage in > 1 place in the nervous system) and “dissemination in time” (ie, suggestions that damage has occurred more than once). It is a diagnosis of exclusion, after consideration of and elimination of more likely diagnoses *(Thompson et al 2018)*.
- The patient evaluation includes an extensive history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and possibly lumbar puncture (*Thompson et al 2018*).
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that lead to damage to the myelin and slowing or blocking of transmission of nerve impulses. A true MS exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of disease-modifying therapies (DMTs) to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018[b])*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) guidelines recommend initiation of DMTs early on in the patient’s disease course (*Rae Grant et al 2018[b], Montalban et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) *(Miller et al 2012, Armoiry et al 2018)*.The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to available DMTs for patients with MS. While there are no precise algorithms to determine the order of product selection, therapy should be individualized and patients’ clinical response and tolerability to medications should be monitored (*Corboy et al 2015, MS Coalition 2019, Scolding et al 2015*).

- Pediatric-onset MS is rare, with the vast majority of cases demonstrating a relapsing-remitting disease course (*Otallah et al 2018*). Gilenya (fingolimod) is the first FDA-approved agent for pediatric patients. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*).
- Cladribine injection is indicated for the treatment of active hairy-cell leukemia (*Clinical Pharmacology 2019*). This oncology indication is not related to the treatment of MS and will not be discussed in this review.
- The most recently approved agent in this review, Vumerity (diroximel fumarate), is rapidly converted to monomethyl fumarate (MMF), which also is the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved gastrointestinal (GI) tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019*).
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review§

Drug	Generic Availability
Ampyra (dalfampridine)	✔
Aubagio (teriflunomide)	✔ *
Avonex (interferon β-1a)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	✔ *
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)	-
Mayzent (siponimod)	-
mitoxantrone‡	✔
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-
Vumerity (diroximel fumarate)	-

*Generics have received FDA-approval; however, settlement agreements will delay launch.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate); it is available in 20 mg/mL and 40 mg/mL injections. Mylan launched generic versions of the 20 mg/mL and the 40 mg/mL strengths of Copaxone on October 5, 2017.
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§As of April 30, 2018, the manufacturer has voluntarily withdrawn Zinbryta (daclizumab) from the market; cases of encephalitis and meningoencephalitis have been reported in patients treated with Zinbryta.

(*Drugs@FDA 2019, FDA Web Site 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019, Purple Book 2019*)

INDICATIONS

- In 2019, the FDA requested all manufacturers of drugs indicated for treatment of MS to revise the language of the indications to conform to contemporary nomenclature. As of October 31, 2019, all drugs have received revised FDA-approved indications except Lemtrada and mitoxantrone (*Drugs@FDA.gov 2019*).

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS	Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease	Primary Progressive MS in adults	Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting MS	Relapsing forms of MS
Ampyra (dalfampridine)	✔ *	-	-	-	-	
Aubagio (teriflunomide)	-	✔	-	-	-	
Avonex (interferon β-1a)	-	✔	-	-	-	
Betaseron/Extavia (interferon β-1b)	-	✔	-	-	-	
Copaxone (glatiramer acetate)	-	✔	-	-	-	
Gilenya (fingolimod)	-	✔ †	-	-	-	
Lemtrada (alemtuzumab)	-	-	-	-	-	✔ ‡ (3rd line)
Mavenclad (cladribine)	-	-	✔ §	-	-	
Mayzent (siponimod)	-	✔	-	-	-	
mitoxantrone	-	-	-	-	✔ ‖	
Ocrevus (ocrelizumab)	-	✔	-	✔	-	
Plegridy (peginterferon β-1a)	-	✔	-	-	-	
Rebif (interferon β-1a)	-	✔	-	-	-	
Tecfidera (dimethyl fumarate)	-	✔	-	-	-	
Tysabri (natalizumab)	-	✔ ¶	-	-	-	
Vumerity (diroximel fumarate)		✔				

IM=intramuscular; SC=subcutaneous

*Ampyra is indicated as a treatment to improve walking in adult patients with MS. This was demonstrated by an increase in walking speed.

†Approved in patients 10 years of age and older.

‡Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS

§ Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with CIS because of its safety profile.

‖Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications including pain related to advanced hormone-refractory prostate cancer and initial therapy of acute nonlymphocytic leukemia (includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias).

¶Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. In CD, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF- α.

(Prescribing information: Ampyra 2017, Aubagio 2019, Avonex 2019, Betaseron 2019, Copaxone 2019, Extavia 2019, Gilenya 2019, Glatopa 2019, Lemtrada 2019, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Ocrevus 2019, Plegridy 2019, Rebif 2019, Tecfidera 2019, Tysabri 2019, Vumerity 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- In the management of MS, numerous clinical trials have established the safety and efficacy of the biological response modifiers in reducing the frequency of relapses, lesions on MRI scans, and possibly delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on MRI, and disability progression for the interferons (IFNs) and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al 1995, The interferon beta [IFNβ] Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995)*. Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.
- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a SC), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. Results from several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg IM once weekly) may be less efficacious while being more tolerable compared to Rebif (IFNβ-1a SC 3 times weekly) or Betaseron (IFNβ-1b every other day) or glatiramer acetate *(Barbero et al 2006, Durelli et al 2002, Khan et al 2001[a], Khan et al 2001[b], Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing IFNs with glatiramer acetate, there were no significant differences between IFNs and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.
  - At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given IFNs than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; p = 0.002). While a MRI outcomes analysis showed that effects on newer enlarging T2 or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI: −0.99 to −0.18; p = 0.004, and MD −0.20, 95% CI: −0.33 to −0.07; p = 0.003, respectively).
- In a network meta-analysis of 24 studies comparing IFNs and glatiramer acetate, both drugs were found to reduce the annualized relapse rate (ARR) as compared to placebo but did not differ statistically from each other (*Melendez-Torres et al 2018*). Ranking of the drugs based on SUCRA (surface under the cumulative ranking curve) indicated that glatiramer acetate 20 mg once daily had the highest probability for superiority, followed by peginterferon β-1a 125 mcg every 2 weeks.
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and SPMS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N = 368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly for 4 years was

associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI: 1.12 to 1.78; p = 0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (p < 0.001).

- In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of IFN NAb *(Govindappa et al 2015)*. NAb development was most frequent with IFN β-1b, followed by IFN β-1a SC, and lowest with IFN β-1a IM. Higher doses were associated with a higher rate of NAb development.
- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The ARR for the combination therapy (IFNβ-1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (p = 0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a + glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 25% (p = 0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another recommended therapy is safe and effective *(Caon et al 2006, Zwibel 2006, Carra et al 2008)*. Patients switching to glatiramer acetate after experiencing an inadequate response to IFNβ-1a therapy had a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.
- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27 *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon β-1a) in adult patients with MS (n = 1516) were evaluated in ADVANCE, a Phase 3, multicenter, randomized, placebo-controlled trial. Eligible adult patients had RRMS with a baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon β-1a every 2 week group (ARR = 0.256; p = 0.0007) and peginterferon β-1a every 4 week group (ARR = 0.288; p = 0.0114) compared to placebo (ARR = 0.397).
  - There were also significant differences between the peginterferon β-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (p = 0.0003 and p = 0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period were significantly lower in the peginterferon β-1a groups (both 6.8%; p = 0.0383 for every 2 weeks group; p = 0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; p < 0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β-1a every 2 weeks compared to placebo (p < 0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β-1a groups compared to placebo *(Calabresi et al 2014b)*.
  - NAb to interferon β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a every 2 weeks, 4 patients; peginterferon β-1a every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014b)*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.
- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the “placebo-switch group”). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a every 2 weeks group (ARR 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4

week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β-1a every 4 week group (ARR 0.291). The peginterferon β-1a every 4 week group (ARR 0.291; p = NS vs placebo-switch group) was not significantly different from the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weighted hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014b, Kieseier et al 2015)*.

- The ATTAIN study was an open-label extension of the ADVANCE study, where patients were followed for an additional 2 years (*Newsome et al 2018*). Of the original ADVANCE patients, 71% continued into the ATTAIN study, and 78% of those patients completed the extension study. The primary objective of the study was to evaluate the long-term safety of peginterferon β-1a. During the study, the common adverse events were influenza-like illness (43%), injection site erythema (41%), and headache (29%). The rate of treatment-related serious adverse events was 1%. The adjusted ARR and risk of relapse was reduced significantly with the every 2 weeks compared to the every 4 weeks dosing group (0.188 vs 0.263 and 36% vs 49%, respectively).

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) in adults against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; $p < 0.001$ for both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly ($p < 0.001$ for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IFNβ-1a IM were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IFNβ-1a IM. Patients switched from IFNβ-1a IM to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a IM in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; p values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; p values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.
- In the FREEDOMS II study, a 24-month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both $p < 0.0001$) *(Calabresi et al 2014a)*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.
- Fingolimod has also been evaluated in pediatric patients with relapsing MS (*Chitnis et al 2018*). The PARADIGMS trial randomized patients between 10 and 17 years of age to fingolimod 0.5 mg daily (0.25 mg for patients ≤ 40 kg) or IFNβ-1a IM 30 mcg weekly for up to 2 years. Fingolimod significantly reduced ARR compared to IFNβ-1a IM (adjusted rates, 0.12 vs 0.67; relative difference of 82%; $p < 0.001$). Fingolimod was also associated with a 53% relative reduction in the annualized rate of new or newly enlarged lesions. However, serious adverse events occurred more frequently with fingolimod than IFNβ-1a IM (16.8% vs 6.5%).

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio were evaluated in two Phase 3, randomized, double-blind, placebo-controlled trials – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (CDP) was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; p = 0.03) *(O'Connor et al 2011)*.
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.

- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability *(Confavreux et al 2014)*.
- Teriflunomide and Rebif (IFNβ-1a SC) were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Gold et al 2012, Fox et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in patients with RRMS. There were 1237 patients enrolled, and the trial duration was 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of disability progression. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab plus IFNβ-1a IM resulted in a significant reduction in ARR at year 1 and 2 and significant reduction in cumulative probability of sustained disability progression at year 2. Lesion burden on MRI was also significantly reduced with the combination therapy. Two cases of PML were reported in the SENTINEL patient population resulting in the early termination of the trial *(Rudick et al 2006)*.

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two randomized, Phase 3, open-label trials in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (n = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.
  - Patients (n = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
  - The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
  - In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC ($p < 0.0001$). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) ($p = 0.22$).
  - In the CARE-MS II trial, alemtuzumab significantly reduced the relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab ($p < 0.0001$). The

percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab (p = 0.0084).
  - Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
  - During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year *(Garnock-Jones 2014)*.
- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.60, 95% CI: 0.52 to 0.70); preventing disease progression (RR = 0.60, 95% CI: 0.45 to 0.79); and developing new T2-weighted lesions on MRI (RR = 0.75, 95% CI: 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD = -0.35, 95% CI: -0.73 to 0.03). In the alemtuzumab 24 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.38, 95% CI: 0.23 to 0.62); preventing disease progression (RR = 0.42, 95% CI: 0.21 to 0.84); and the changes of EDSS score (MD = -0.83, 95% CI: -1.17 to -0.49) after 36 months' follow-up. The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017[a], Montalban et al 2017)*.
  - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multicenter, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a; 44 mcg administered by SC injection 3 times per week) in 1656 patients with relapsing MS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
    - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
    - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif (IFNβ-1a SC) across both trials (primary endpoint).
      - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; p < 0.001)
      - OPERA II (0.16 vs 0.29; 47% lower rate; p < 0.001)
    - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; hazard ratio [HR] = 0.60, 95% CI: 0.45 to 0.81; p < 0.001). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs 10.5%; HR = 0.60, 95% CI: 0.43 to 0.84; p = 0.003. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; p = 0.02).
    - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).
      - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; p < 0.001)
      - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; p < 0.001)
    - The most common adverse events were infusion-related reactions and infections.
  - No opportunistic infections, including PML, were reported in any group over the duration of either trial.
    - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.
    - Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.

- Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.

o ORATORIO was an event-driven, Phase 3, double-blind, multicenter, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.

- The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*Ocrevus FDA Medical and Summary Reviews 2017*).
- The percentages of patients with 12-week confirmed disability progression (primary endpoint) were 32.9% with ocrelizumab vs 39.3% with placebo (HR = 0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; p = 0.03).
- The percentages of patients with 24-week CDP (secondary endpoint) were 29.6% with ocrelizumab vs 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; p = 0.04).
- Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
  - The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
  - From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients (p < 0.001).
  - From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo (p = 0.02).
- Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.
- Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
  - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

Mayzent (siponimod)

- The Phase 3 EXPAND trial was a double-blind, randomized, parallel-group, placebo-controlled, time-to-event study in patients with SPMS who had evidence of disability progression in the previous 2 years (*Kappos et al 2018*).
  - o A total of 1651 patients were randomized to treatment with either siponimod 2 mg (n = 1105) or placebo (n = 546).
  - o A total of 82% of the siponimod-treated patients and 78% of placebo-treated patients completed the study.
    - The median age of patients was 49.0 years, 95% of patients were white, and 60% were female.
  - For the primary endpoint, 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had a 3-month CDP (HR 0.79: 95% CI: 0.65 to 0.95: RR reduction, 21%; p = 0.013).
  - Key secondary endpoints included time to 3-month confirmed worsening of at least 20% from baseline in timed 25-foot walk (T25FW) and change from baseline in T2 lesion volume on MRI. Siponimod did not show a significant difference in T25FW.
  - Patients treated with siponimod had a 55% relative reduction in ARR (0.071 vs 0.16), compared to placebo (nominal p < 0.01). The absolute reduction in the ARR was 0.089 with siponimod.

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter trial to evaluate the safety and efficacy of oral cladribine in 1326 patients with RRMS (*Giovannoni et al 2010*, *Giovannoni 2017*).
  - Patients were required to have at least 1 relapse in the previous 12 months. The median patient age was 39 years and the female-to-male ratio was 2:1. The mean duration of MS prior to study reenrollment was 8.7 years.
  - Patients were randomized to receive either placebo (n = 437), or a cumulative oral dose of cladribine 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) over the 96-week study period in 2 treatment courses.
  - The primary outcome was ARR:
    - ARRs at 96 weeks were reduced in both cladribine treatment groups vs placebo (0.14, 0.15, and 0.33 in the 3.5 mg/kg, 5.25 mg/kg and placebo groups, respectively; each $p < 0.001$).
  - A significantly higher percentage of patients remained relapse-free at 96 weeks in both cladribine treatment groups vs placebo; a total of 79.7% and 78.9% of patients in the 3.5 mg/kg and 5.25 mg/kg groups, respectively, were relapse free vs 60.9% in the placebo group (each $p < 0.001$ vs placebo).
  - Cladribine 3.5 mg/kg significantly lowered the ARR vs the 5.25 mg/kg treatment group.

Vumerity (diroximel fumarate)

- The efficacy of diroximel fumarate was established through bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing oral dimethyl fumarate to diroximel fumarate (*Vumerity Prescribing Information 2019*).
- In a Phase 3, open-label, long-term safety study, 696 patients with RRMS (EVOLVE-MS-1) were administered diroximel fumarate 462 mg twice daily for up to 96 weeks (*Palte et al 2019*). Interim results revealed that GI treatment-emergent adverse events occurred in 215 (30.9%) of patients; the vast majority of these events (207 [96%]) were mild or moderate in severity. Gastrointestinal events occurred early in therapy, resolved (88.8%; 191/215), and were of short duration (median 7.5 days) in most patients. Discontinuation of treatment due to a GI treatment-emergent adverse event occurred in <1% of patients.
- Topline results from the randomized, double-blind, 5-week, Phase 3, EVOLVE-MS-2 study also demonstrated significantly improved GI tolerability with diroximel fumarate vs dimethyl fumarate in 506 patients with RRMS (*Selmaj et al 2019*). In this study, patients were randomized to diroximel fumarate 462 mg twice daily or dimethyl fumarate 240 mg twice daily. The primary endpoint was the number of days patients reported GI symptoms with a symptom intensity score ≥ 2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) rating scale. Results revealed that patients treated with diroximel fumarate self-reported significantly fewer days of key GI symptoms with intensity scores ≥ 2 as compared to dimethyl fumarate ($p = 0.0003$). The most commonly reported adverse events for both groups were flushing, diarrhea, and nausea.

Symptomatic MS

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the walking speed by about 25% in approximately one-third of MS patients as measured by the T25FW *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.
  - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- Avonex (IFNβ-1a IM) and Betaseron (IFNβ-1b) are FDA-approved for the treatment of the first clinical episode with MRI features consistent with MS. Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.

- In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a CDMS diagnosis by 45% compared to placebo in patients with CIS (p = 0.005). In addition, the time for 25% of patients to convert to CDMS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; p = 0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of CDMS compared to delayed glatiramer acetate (HR: 0.59; 95% CI: 0.44 to 0.8; p = 0.0005). Over the 2 year extension, the baseline-adjusted proportions of patients who developed CDMS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; p = 0.0002) *(Comi et al 2012)*.
- A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of CDMS with IFN therapy compared to placebo (p < 0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, randomized clinical trial with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR = 0.6; 95% CI: 0.39 to 0.92; p = 0.022).
- A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to clinically definite multiple sclerosis (CDMS) in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI: 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that 1 active treatment was superior to another when compared indirectly. The authors noted that there was insufficient information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR = 0.64, 95% CI: 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.
- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining CDMS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to CDMS by 42.6% compared to placebo (HR, 0.574; 95% CI: 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to CDMS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; p = 0.0271).

Progressive MS

- Limited treatment options are available for patients with non-active SPMS and PPMS. Mitoxantrone is FDA-approved for treating SPMS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, SPMS, and PRMS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd enhancement or at month 12 for the number of lesions on T2-weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data, including cohort data, for mitoxantrone. An evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.
- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS, and due to being off-label, these uses are not included in Table 2. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*. Results from the ASCEND trial, evaluating natalizumab in SPMS, found no significant difference in the rate of confirmed disability progression compared to placebo (*Kapoor et al 2018*).
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N = 3082) of IFNβ compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression

with IFNβ was 0.98 (95% CI: 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I^2 = 57%) *(La Mantia et al 2013)*.

Timing of DMT initiation

- A 2017 systematic review by Merkel et al (2017) evaluated the effect of high-efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS. Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high-efficacy DMTs for RRMS. A number of these studies suggested that earlier commencement of high-efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high-efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

- Patients with RRMS eventually progress to SPMS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for non-active SPMS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued therapy vs discontinued therapy for MS in comparable populations. Based on a low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFNβ-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy (*Rae-Grant et al 2018[b]*).

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between 15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- RCTs (n = 39) evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFNβ-1a, azathioprine, and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.
  - Relapses: alemtuzumab, mitoxantrone, natalizumab, and fingolimod were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
    - alemtuzumab: RR = 0.40, 95% CI: 0.31 to 0.51; moderate quality evidence
    - mitoxantrone: RR = 0.40, 95% CI: 0.20 to 0.76; low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.43 to 0.73; high quality evidence
    - fingolimod: RR = 0.63, 95% CI: 0.53 to 0.74; low quality evidence
    - dimethyl fumarate: RR = 0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
    - daclizumab (no longer on the market): RR = 0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
    - glatiramer acetate: RR = 0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
  - Relapses over 24 months vs placebo (26 studies; N = 16,800):
    - alemtuzumab: RR = 0.46, 95% CI: 0.38 to 0.55; moderate quality evidence
    - mitoxantrone: RR = 0.47, 95% CI: 0.27 to 0.81; very low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.47 to 0.66; high quality evidence
    - fingolimod: RR = 0.72, 95% CI: 0.64 to 0.81; moderate quality evidence

- Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
  - mitoxantrone: RR = 0.20, 95% CI: 0.05 to 0.84; low quality evidence
  - alemtuzumab: RR = 0.35, 95% CI: 0.26 to 0.48; low quality evidence
  - natalizumab: RR = 0.64, 95% CI: 0.49 to 0.85; moderate quality evidence
- Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
- Acceptability: Higher rates of withdrawal due to adverse events compared to placebo over 12 months were reported for teriflunomide (RR = 2.24, 95% CI: 1.5 to 3.34); peginterferon beta-1a (RR = 2.8, 95% CI: 1.39 to 5.64); Avonex (RR = 4.36, 95% CI: 1.98 to 9.6); Rebif (RR = 4.83, 95% CI: 2.59 to 9); and fingolimod (RR = 8.26, 95% CI: 3.25 to 20.97).
- Over 24 months, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR vs placebo = 1.69, 95% CI: 1.32 to 2.17).
  - mitoxantrone: RR = 9.82, 95% CI: 0.54 to 168.84
  - natalizumab: RR = 1.53, 95% CI: 0.93 to 2.53
  - alemtuzumab: RR = 0.72, 95% CI: 0.32 to 1.61

- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, natalizumab and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32, 95% CI: 0.24 to 0.43; OR = 0.45, 95% CI: 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28, 95% CI: 0.22 to 0.36; OR = 0.19, 95% CI: 0.06 to 0.6, respectively).
  - Based on moderate quality evidence, natalizumab and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
  - Natalizumab and Betaseron were significantly more effective (OR = 0.62, 95% CI: 0.49 to 0.78; OR = 0.35, 95% CI: 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
  - The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N= 16,998) (*CADTH 2013).* Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for natalizumab and alemtuzumab, 50% for fingolimod or dimethyl fumarate, and 30% for SC IFNs, glatiramer acetate, or teriflunomide.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI: 0.54 to 0.87); Rebif (0.76, 95% CI: 0.59 to 0.98); and fingolimod (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for dimethyl fumarate (0.76, 95% CI: 0.62 to 0.93) compared with glatiramer acetate.
  - Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for natalizumab to 0.74 (95% CI: 0.57 to 0.96) for teriflunomide. Between-treatment differences were less apparent.
  - Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab (0.59, 95% CI: 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI: 0.2 to 0.80) compared with Avonex.
  - Among active comparisons, MRI findings were more favorable for alemtuzumab compared with Rebif, and more favorable for all 3 of fingolimod, Betaseron, and Rebif compared with Avonex. Compared with glatiramer acetate, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
  - The incidence of serious adverse events and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and alemtuzumab.
- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, IFNs, peginterferon, glatiramer acetate, natalizumab, fingolimod, and

alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR = 0.29, 95% CI: 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 24 mg (RR = 0.36, 95% CI: 0.16 to 0.7; low quality evidence) and alemtuzumab 12 mg (RR = 0.40, 95% CI: 0.27 to 0.60; very low quality evidence) were the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.5, 95% CI: 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.46, 95% CI: 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.45, 95% CI: 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.65, 95% CI: 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.71, 95% CI: 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.71, 95% CI: 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR = 2.21, 95% CI: 1.42 to 2.5; moderate quality evidence), and Rebif 44 mcg (RR = 2.21, 95% CI: 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.
  - Alemtuzumab 24 mg (mean difference = -0.91; 95% CI: -1.48 to -0.40), and 12 mg (mean difference = -0.6; 95% CI: -1.02 to -0.24) were more effective than other therapies in lowering the EDSS.
  - No treatments were found to significantly increase serious adverse events; peginterferon β-1a was associated with more adverse events overall when compared with other medications (RR = 1.66, 95% CI: 1.21 to 2.28).
  - None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.
- A Bayesian network meta-analysis evaluating DMTs for RRMS ranked the most effective therapies based on SUCRA analysis (*Lucchetta et al 2018*). A total of 33 studies were included in the analysis. For the ARR, alemtuzumab (96% probability), natalizumab (96%), and ocrelizumab (85%) were determined to be the most effective therapies (high-quality evidence).
- A meta-analysis of randomized controlled trials was conducted to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (*Xu et al 2016*). The results showed that teriflunomide (7 and 14 mg) reduced the ARR and teriflunomide 14 mg decreased the disability progression in comparison to placebo (RR = 0.69, 95% CI: 0.55 to 0.87).

CLINICAL GUIDELINES

- The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*).
- The main recommendations reported were the following:
  - The entire spectrum of DMTs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive patient assessment, detection of adverse effects, and the capacity to address adverse effects properly if they occur. (Consensus statement)
  - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
  - Offer early treatment with DMTs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)
  - For active RRMS, choosing among the wide range of available drugs from the modestly to highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
  - Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile. (Weak)

- Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
- Consider ocrelizumab for patients with active SPMS. (Weak)
- Consider ocrelizumab for patients with PPMS. (Weak)
- Always consult the summary of product characteristics for dosage, special warnings, precautions, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
- Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
- When monitoring treatment response in patients treated with DMTs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
- When monitoring treatment response in patients treated with DMTs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)
- When monitoring treatment safety in patients treated with DMTs, perform a standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
- Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
- When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
- When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
- Consider continuing a DMT if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
- Advise all women of childbearing potential that DMTs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)
- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

- The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae Grant et al 2018[a]*). The results of the systematic review were used to assist in formulating updated AAN treatment guidelines (*Rae Grant et al 2018[b]*). The main recommendations were as follows:
  - Starting DMT
    - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
    - Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
    - Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT in women of childbearing potential who have MS. (Level B)

- Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
- Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
- Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
- Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
- Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)

o Switching DMTs

- Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
- Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)
- Clinicians should discuss a change to non-injectable or less frequently injected DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs. (Level B)
- Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
- Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
- Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
- Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)
- Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
- Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
- Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)

o Stopping DMTs

- In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability

progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
    - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
    - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)
- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses, and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- With an increasing number of options for the treatment of RRMS, the place in therapy for an individual agent is not straightforward. Treatment decisions will likely be based on a consideration of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences. The 2015 AAN position statement supports access to all DMT for patients with MS. In addition, step therapy should be driven by evidence-based clinical and safety information and not just based on costs. Highly individualized treatment decisions are necessary for patients with MS according to the AAN *(Corboy et al 2015)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including pegIFN), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- In September 2019, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS *(MS Coalition 2019)*. Major recommendations included the following:
    - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing MS, regardless of the person's age. Relapsing MS includes CIS, RRMS, and active SPMS with clinical relapses or inflammatory activity on MRI.
    - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly diagnosed individuals with highly active MS.
    - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents.
    - Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
        - Suboptimal treatment response as determined by the individual and his or her treating clinician
        - Intolerable side effects
        - Inadequate adherence to the treatment regimen
        - Availability of a more appropriate treatment option
        - The healthcare provider and patient determine that the benefits no longer outweigh the risks.
    - Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
    - When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
    - The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the patient and his/her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data.
    - Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
        - MS clinical phenotypes may respond differently to different DMTs.
        - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
        - Potential contraindications limit options for some individuals.
        - Risk tolerance varies among people with MS and their treating clinicians.
        - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.

- Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
- Pregnancy and breastfeeding limit the available options.

- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.
- Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.
- Treatment should not be withheld during determination of coverage by payors as this puts the patient at risk for recurrent disease activity.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, anaphylaxis, congestive heart failure (CHF), potential development of autoimmune disorders (eg, lupus erythematosus), and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) is associated with influenza-like symptoms including musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.
- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, post-injection reaction of flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, or urticaria immediately following the injection. Injection site reactions including lipoatrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions.
- Fingolimod was originally approved with a risk evaluation and mitigation strategies program (REMS) to inform healthcare providers about serious risks including bradyarrhythmia, atrioventricular (AV) block, infections, macular edema, respiratory effects, hepatic effects, fetal risk, increased blood pressure, basal cell carcinoma, immune system effects following discontinuation, and hypersensitivity reactions; however, the FDA lifted the REMS requirements in November 2016. Fingolimod is contraindicated in patients with a variety of cardiac issues and those with a hypersensitivity to the product. Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination of the drug may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with an active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Recent safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, and lymphoma in patients treated with fingolimod. This recent labeling change also notes that clinically significant hepatic injury has occurred in patients treated with fingolimod in the postmarketing setting; hepatic function should be monitored prior to, during, and until 2 months after medication discontinuation. Cases of PML have occurred in the postmarketing setting, primarily in patients who were treated with fingolimod for at least 2 years. At the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Additionally, severe increases in disability after discontinuation of fingolimod have been described in post marketing reports.
- Teriflunomide is contraindicated in patients with severe hepatic impairment; pregnancy, those with a history of hypersensitivity to the medication, women of childbearing potential who are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include bone marrow effects, immunosuppression leading to potential infections, malignancy risk, interstitial lung disease, peripheral neuropathy, severe skin reactions, and elevated blood

pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels more rapidly. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).

- Dimethyl fumarate and diroximel fumarate are contraindicated in patients with hypersensitivity to the products or any of their excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or a temporary dose reduction may reduce flushing. Diroximel fumarate should not be coadministered with dimethyl fumarate.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program, which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10% in MS) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include hypersensitivity reactions, increased risk of herpes encephalitis and meningitis, increased risk of infections (including opportunistic infections), and hepatotoxicity.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure, potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia, autoimmune hepatitis, and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies (ie, thyroid cancer, melanoma, and lymphoproliferative disorders/lymphoma). Alemtuzumab is only available through a restricted distribution and REMS program, which requires the member, provider, pharmacy, and infusion facility to be certified. Approximately one-third of patients who received alemtuzumab in clinical trials developed thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients. Other safety concerns within the product labeling include a warning that patients administered alemtuzumab are at risk for serious infections, including those caused by *Listeria monocytogenes,* the potential development of pneumonitis, and PML. Patients that are prescribed alemtuzumab should be counseled to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should also undergo tuberculosis screening according to local guidelines. With regard to PML, alemtuzumab should be withheld, and appropriate diagnostic evaluations performed, at the initial occurrence of suggestive signs or symptoms.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator

groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with relapsing MS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (*Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017*).
  - In patients with relapsing MS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine may cause seizures; permanently discontinue this medication in patients who have a seizure while on treatment. Dalfampridine can also cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as an adverse reaction in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree AV block or sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Women of childbearing potential should use effective contraception during and for 10 days after stopping siponimod due to fetal risk. The most common adverse events (incidence > 10%) are headache, hypertension, and transaminase increases.
- Cladribine is contraindicated in patients with current malignancy, HIV infection, active chronic infection such as hepatitis or tuberculosis, hypersensitivity to cladribine, and in pregnant women. There is a boxed warning for potential malignancy and risk of teratogenicity. The warnings and precautions are lymphopenia, active infection, hematologic toxicity, liver injury, and graft vs host disease with blood transfusion. The most common adverse events (incidence > 20%) are upper respiratory tract infection, headache, and lymphopenia.

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				dalfampridine should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). There are no adequate and well-controlled studies of dalfampridine in pregnant women; use during pregnancy only if the benefit justifies the potential fetal risk.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female partners should use effective

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection; pen, prefilled syringe	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. Use caution in patients with hepatic dysfunction.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	Following initial administration by a trained healthcare provider, glatiramer acetate may be self-administered. Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration:	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsules	Oral	Once daily Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	May be taken with or without food. Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤40 kg, a lower dose is recommended. First dose monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. Monitor until resolution if HR < 45 bpm in adults, < 55 bpm in pediatric patients ≥ 12 years of age, or < 60 bpm in pediatric patients 10 or 11 years of age, new onset second degree or higher AV block, or if the lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with continuous ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with a known risk of torsades de pointes or drugs that slow heart rate or AV conduction.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course Subsequent course: 12 mg/day for 3 consecutive days may be administered, as needed, at least 12 months after the last dose of any prior treatment courses. Important monitoring: Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter); serum transaminases and total bilirubin (prior to treatment initiation and periodically thereafter)	Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of 2 months after completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Measure the urine protein to creatinine ratio prior to treatment initiation Conduct baseline and yearly skin exams to monitor for melanoma.	
Mavenclad (cladribine)	Tablet	Oral	Cumulative dosage of 3.5 mg/kg divided into 2 yearly treatment courses of 1.75 mg/kg per treatment course. Each treatment course is divided into 2 treatment cycles: • First course/first cycle: start anytime • First course/second cycle: administer 23 to 27 days after the last dose of first course/first cycle. • Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle. • Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle.	The use of Mavenclad in patients weighing less than 40 kg has not been investigated. Mavenclad is contraindicated in pregnant women and in female/males of reproductive potential that do not plan to use effective contraception. Follow standard cancer screening guidelines because of the risk of malignancies. Administer all immunizations according to guidelines prior to treatment initiation. Obtain a complete blood count with differential including lymphocyte count. Lymphocytes must be within normal limits before treatment initiation and at least 800 cells/microliter before starting the second treatment course.
Mayzent (siponimod)	Tablets	Oral	Once daily Initiate treatment with a 5-day titration; a starter pack should be used for patients who will be titrated to the maintenance dosage starting on Day 6 (refer to prescribing information for titration regimen).	Mayzent can cause fetal harm when administered to pregnant women. Dosage should be titrated based on patient's CYP2C9 genotype. Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block, or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
mitoxantrone	Injection	IV	Every 3 months Note: Left ventricular ejection fraction (LVEF) should be	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of CHF develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop. Liver function tests should be monitored prior to each course of therapy.	Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥ 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3. Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) <u>Titration</u>: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months Hepatitis B virus screening is required before the first dose.	Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details. Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. Administer all necessary immunizations according to immunization guidelines at least 6 weeks prior to initiation of ocrelizumab.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection; pen, prefilled syringe	SC	Every 14 days Titration: Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	Following initial administration by a trained healthcare provider, Plegridy may be self-administered. Patients should be advised to rotate injection sites; the usual sites are the abdomen, back of the upper arm, and thigh. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a); Rebif Rebidose	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	Following initial administration by a trained healthcare provider, Rebif may be self-administered. Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration:	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with dimethyl fumarate.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks)	Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection. Patients should be observed during the infusion and for 1 hour after the infusion is complete.
Vumerity (diroximel fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration: 231 mg twice daily for 7 days (initiation), then 462 mg twice daily (maintenance) Temporary dose reductions to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	Must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. Avoid administration with a high-fat, high-calorie meal/snack. Avoid co-administration with alcohol. The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to diroximel fumarate. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				bilirubin levels prior to treatment with diroximel fumarate.

*See the current prescribing information for full details
†Currently available through a restricted distribution program as part of a REMS requirement.

CONCLUSION

- DMTs for MS have shown benefits in patients with relapsing MS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite relapsing MS begin DMTs *(MS Coalition 2019)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2019)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy on relapse rate. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with low dose IM IFNβ-1a compared to higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products including Plegridy (peginterferon β-1a). With IFNβ, use caution in patients with depression or other mood disorders. Plegridy (peginterferon β-1a) every 2 weeks has demonstrated efficacy in reducing the ARR in relapsing forms of MS compared to placebo. Potential advantages of Plegridy are less frequent administration and possibly a reduced risk of NAb development. The adverse effect profile is similar among the IFNs.
- The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression. Glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(Corboy et al 2015, MS Coalition 2017, Scolding et al 2015, Montalban et al 2018)*. The premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure with another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008)*.
- There are now 6 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved in 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. Mavenclad (cladribine), Mayzent (siponimod), and Vumerity (diroximel fumarate) were all approved in 2019. Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and/or tolerability profiles. The efficacy of the oral products has not been directly compared in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Mayzent (siponimod) is a sphingosine 1-phosphate receptor modulator, similar to fingolimod, indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.
  - Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, both Mavenclad 3.5 mg/kg and 5.25 mg/kg treatment groups had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Lymphopenia is the most common adverse effect.

- Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
  - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate of new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Vumerity (diroximel fumarate) is the most recently approved oral agent for MS and is rapidly converted to MMF, which is also the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved GI tolerability as compared to dimethyl fumarate (*Naismith et al 2019*; *Selmaj et al 2109*).
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) as compared to placebo *(O'Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.

- Tysabri (natalizumab) has demonstrated very high efficacy vs placebo, and although PML is a major safety concern, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.
  - Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of relapsing MS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.

- Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS (*MS Coalition 2019*).
- Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents (*MS Coalition 2019*).

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