

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 2019*). Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes in the CNS. 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 2020[a]*).
- A 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 multiple 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 2020[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 (*Frohmman 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*). 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 (*Montalban et al 2018, Rae-Grant et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) (*Armoiry et al 2018, Miller et al 2012*). 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 (*MS Coalition 2019, Rae-Grant et al 2018, 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*).
- 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*). In April 2020, the FDA approved another agent in this class, Bafiertam (monomethyl fumarate). This drug is considered a “bioequivalent alternative” to dimethyl fumarate since dimethyl fumarate is a prodrug, and monomethyl fumarate is its active ingredient. Since the drug is already in its active form, it is administered at a lower dose than dimethyl fumarate, and it is thought that it may lead to fewer GI adverse effects (*Bafiertam prescribing information 2020*).
- 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)	-
Bafiertam (monomethyl fumarate)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✓
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	✓ *
Kesimpta (ofatumumab)§	-
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)	-
Zeposia (ozanimod)	-

*Generics have received FDA-approval; however, settlement agreements will delay launch.

†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate).

‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.

§Ofatumumab was originally approved as an IV formulation for treatment of chronic lymphocytic leukemia as a different product (Arzerra). Only clinical data for ofatumumab use in MS are included in this review.

|| Cladribine injection is indicated for the treatment of active hairy-cell leukemia. This oncology indication is not related to the treatment of MS and will not be discussed in this review.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

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 in adults	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease in adults	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
Ampyra (dalfampridine)	✓ *	-	-	-	-
Aubagio (teriflunomide)	-	✓	-	-	-
Avonex (interferon β-1a)	-	✓	-	-	-
Bafiertam (monomethyl fumarate)	-	✓	-	-	-
Betaseron/Extavia (interferon β-1b)	-	✓	-	-	-
Copaxone (glatiramer acetate)	-	✓	-	-	-
Gilenya (fingolimod)	-	✓ †	-	-	-
Kesimpta (ofatumumab)		✓			
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)	-	✓	-	-	-
Zeposia (ozanimod)	-	✓	-	-	-

*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. Lemtrada is not recommended for use in patients with CIS because of its safety profile.

§ 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

Data as of November 27, 2020 RR-U/MG-U/KMR/AKS

Page 3 of 37

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

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 2019, Aubagio 2020, Avonex 2020, Bafiertam 2020, Betaseron 2020, Copaxone 2020, Extavia 2020, Gilenya 2019, Glatopa 2020, Kesimpta 2020, Lemtrada 2020, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Ocrevus 2020, Plegridy 2021, Rebif 2020, Tecfidera 2020, Tysabri 2020, Vumerity 2020, Zeposia 2020)

- 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 DMTs in reducing the frequency of relapses, lesions on MRI scans, and possibly delaying disability progression.

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 [IFN β] Multiple Sclerosis Study Group 1993, The IFN β 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 (IFN β -1a SC), and Betaseron (IFN β -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 (IFN β -1a 30 mcg IM once weekly) may be less efficacious while being more tolerable compared to Rebif (IFN β -1a SC 3 times weekly) or Betaseron (IFN β -1b every other day) or glatiramer acetate (*Barbero et al 2006, Durelli et al 2002, Khan et al 2001[a, 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 controlled trials (RCTs) 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 SC every 2 weeks.
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFN β -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 (IFN β -1a) 30 mcg IM once weekly to be comparable to the other IFN β 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 (IFN β -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 IFN β -1a and IFN β -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 (IFN β -1a IM) over 3 years. The ARR for the combination therapy (IFN β -1a IM + 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 IFN β -1a IM, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFN β -1a IM, reducing the risk of exacerbation by 31% ($p = 0.027$), and IFN β -1a IM + glatiramer acetate performed significantly better than IFN β -1a IM, 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, Carra et al 2008, Zwibel 2006*). Patients switching to glatiramer acetate after experiencing an inadequate response to IFN β -1a therapy had a reduction in relapse rates and disability progression. Likewise, switching to IFN β -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 IFN β -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, placebo-controlled, RCT. 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 naive.
 - 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 2014[b]*). NAb to IFN β -1a were identified in $< 1\%$ of all groups after 1 year (peginterferon β -1a SC every 2 weeks, 4 patients; peginterferon β -1a SC every 4 weeks, 2 patients; placebo, 2 patients) (*Calabresi et al 2014[b]*). 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 SC 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 SC every 4 week group (ARR 0.291). The peginterferon β -1a SC every 4 week group (ARR 0.291; $p = \text{NS}$ 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 SC 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 SC every 2 weeks group compared to the placebo-switch group (*Calabresi et al 2014[b]*, *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 SC. 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 were 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).
- Bioequivalency was demonstrated for Plegridy administered by IM and SC injection in an unpublished, open-label, crossover, single-dose, Phase 1 study of 136 healthy volunteers; this study was the basis for the FDA-approval of the IM route of administration for Plegridy (*Zhao et al 2020*). Injection site reactions were reported less frequently after IM dosing (14.4%) than after SC dosing (32.1%).

ORAL AGENTS

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio (teriflunomide) were evaluated in two Phase 3, double-blind, placebo-controlled, RCTs – 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) at 12 weeks 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, double-blind, RCT. 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 at 12 weeks (*Confavreux et al 2014*).
- Teriflunomide and Rebif (IFN β -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*).

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter RCT 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 enrollment 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:
 - ARR 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 group had a lower risk of 3-month CDP vs placebo (hazard ratio [HR], 0.67; 95% CI, 0.48 to 0.93; $p = 0.02$). Lesions on MRI were significantly lower in the cladribine 3.5 mg/kg group vs placebo ($p < 0.001$ for all comparisons).

Oral Sphingosine-1-phosphate (S1P) receptor modulators

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, RCTs in adults against placebo and against Avonex (IFN β -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 IFN β -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 IFN β -1a IM were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IFN β -1a IM. Patients switched from IFN β -1a IM to fingolimod experienced fewer adverse events compared to treatment with IFN β -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) (Khatiri *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* 2014[a]). 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 IFN β -1a IM 30 mcg weekly for up to 2 years. Fingolimod significantly reduced ARR compared to IFN β -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 on MRI. However, serious adverse events occurred more frequently with fingolimod than IFN β -1a IM (16.8% vs 6.5%, respectively).

Mayzent (siponimod)

- The Phase 3 EXPAND trial was a double-blind, parallel-group, placebo-controlled, time-to-event RCT in patients with SPMS who had evidence of disability progression in the previous 2 years (Kappos *et al* 2018). A total of 1651 patients were randomized to treatment with either siponimod 2 mg ($n = 1105$) or placebo ($n = 546$). 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; $p = 0.013$).
 - 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.

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were compared to Avonex (IFN β -1a IM) in two multicenter, Phase 3, double-blind, double-dummy RCTs in patients with relapsing forms of MS— SUNBEAM and RADIANCE (Comi *et al* 2019, Cohen *et al* 2019). In the studies, which were conducted over a minimum of 12 months, patients were randomized 1:1:1 to oral ozanimod 0.5 mg daily, oral ozanimod 1 mg daily, or Avonex (IFN β -1a) 30 mcg IM once weekly. All patients received an initial 7-day dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Prophylactic administration of acetaminophen or ibuprofen was recommended 1 hour before each IFN or placebo injection and every 6 hours for 24 hours after the injection. Patients in both trials ($n = 1346$ for SUNBEAM and $n = 1320$ for RADIANCE) had an EDSS score of ≤ 5 , and a history of at least 1 relapse within 12 months prior to screening or 1 relapse within 24 months in addition to at least 1 Gd-enhancing lesion within 12 months prior to screening. The primary endpoint in both trials was the ARR.

- In the SUNBEAM, the ARR was 0.18 (95% CI, 0.14 to 0.24) for ozanimod 1 mg, 0.24 (95% CI, 0.19 to 0.31) for ozanimod 0.5 mg, and 0.35 (95% CI, 0.28 to 0.44) for IFN β -1a IM. Significant reductions in ARR were observed compared to IFN β -1a IM with both ozanimod 1 mg (rate ratio, 0.52; 95% CI, 0.41 to 0.66; $p < 0.0001$) and ozanimod 0.5 mg (rate ratio, 0.69; 95% CI, 0.55 to 0.86; $p = 0.0013$).
- In the RADIANCE trial, adjusted ARRs were found to be 0.17 (95% CI, 0.14 to 0.21) for ozanimod 1 mg, 0.22 (95% CI, 0.18 to 0.26) for ozanimod 0.5 mg, and 0.28 (95% CI, 0.23 to 0.32) for IFN β -1a IM. The rate ratios were significant when comparing ozanimod 1 mg (rate ratio, 0.62; 95% CI, 0.51 to 0.77; $p < 0.0001$) and ozanimod 0.5 mg (rate ratio, 0.79; 95% CI, 0.65 to 0.96; $p = 0.0167$) to IFN β -1a IM.
- Clinically significant evidence of bradycardia, second-, or third-degree heart block was not noted after administration of the first dose in either trial.

Oral Fumarates

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM (Fox *et al* 2012, Gold *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 1237 patients with RRMS over 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 at 12 weeks (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 confirmed disability progression at 12 weeks. 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).

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 2020).
- 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). 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.

Bafiertam (monomethyl fumarate)

- The efficacy of monomethyl fumarate, the active moiety of dimethyl fumarate, is based on bioavailability studies in healthy patients comparing oral dimethyl fumarate delayed-release capsules to monomethyl fumarate delayed-release capsules. Analyses compared the blood levels of monomethyl fumarate to establish bioequivalency and support the FDA approval (Bafiertam Prescribing Information 2020).

High Efficacy Infusibles and Injectables

Tysabri (natalizumab)

Data as of November 27, 2020 RR-U/MG-U/KMR/AKS

Page 8 of 37

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- 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 IFN β -1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab plus IFN β -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 (IFN β -1a SC) in two Phase 3, open-label RCTs 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 (IFN β -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 IFN β 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 IFN β -1a SC (p < 0.0001). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFN β -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 IFN β -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 IFN β -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 IFN β -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 of the extension study (*Garnock-Jones 2014*).
- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFN β -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). The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Kesimpta (ofatumumab)

- The two Phase 3, double-blind, double-dummy, active-controlled, multicenter, RCTs, the ASCLEPIOS I and II trials, included 1882 patients with relapsing MS who were treated with ofatumumab 20 mg SC every 4 weeks or teriflunomide 14 mg daily for up to 30 months. Approximately 40% of the patients in each group had no prior exposure to DMTs. Ofatumumab significantly reduced the ARR, the primary endpoint, compared with teriflunomide.
 - ASCLEPIOS I: ARR: 0.11 vs 0.22; difference, -0.11; 95% CI, -0.16 to -0.06; p < 0.001; RR, 0.49; 95% CI, 0.37 to 0.65; p < 0.001.
 - ASCLEPIOS II: ARR: 0.10 vs 0.25; difference, -0.15; 95% CI, -0.20 to -0.09; p < 0.001; RR, 0.42; 95% CI, 0.31 to 0.56; p < 0.001.

- o Pooled data demonstrated that the percentage of patients with confirmed disability worsening at 3 months was 10.9% vs 15.0% for ofatumumab vs teriflunomide, respectively (HR, 0.66; 95% CI, 0.50 to 0.86; $p = 0.002$). For the confirmed disability worsening at 6 months, the percentage was also lower in the ofatumumab group (8.1% vs 12.0%; HR, 0.68; 95% CI, 0.50 to 0.92; $p = 0.01$). There was no significant difference between the groups for disability improvement.
- o For the MRI endpoints, the ofatumumab group had significantly fewer mean number of Gd-enhancing lesions and mean number of new or enlarging lesions per year on T2-weighted MRI (all $p < 0.001$). Brain volume loss did not differ significantly between groups in either trial (*Hauser et al 2020[a]*).

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO (*Hauser et al 2017, Montalban et al 2017*).
 - o 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 (IFN β -1a 44 mcg SC 3 times weekly) 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%).
 - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif (IFN β -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%; 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.
 - o 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.
 - As of February 2018, the overall crude incidence rate of malignancies among patients from OPERA I and II who received ocrelizumab in the double-blind period or open-label extension was 0.40 per 100 patient-years of exposure to ocrelizumab. The incidence rate as of the data cutoff of May 2015 after the completion of the DB period was 0.28 for the ocrelizumab group and 0.14 for the IFN β -1a SC group (*Hauser et al 2020[b]*).
 - As of January 2019, the age- and sex-standardized incidence rate of all malignancies in the ocrelizumab all-exposure (all Phase 2 and 3 studies, plus 4 other trials) (0.22 per 100 patient-years; 95% CI, 0.16 to 0.33),

remained stable over time, with confidence intervals overlapping and within epidemiological references from the Surveillance, Epidemiology, and End Results [SEER] Program of the National Cancer Institute, which reports data on cancer incidence in approximately 28% of the general U.S. population (0.31 per 100 patient-years) (Genentech 2020[a])

- Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with IFN β -1a SC or placebo), the labeling of ocrelizumab recommends that patients follow standard breast cancer screening guidelines (Genentech 2020[b]). In an analysis of the all-exposure ocrelizumab population from the trials through January 2019, the incidence rate of female breast cancer using age at event onset methodology was 0.15 (95% CI, 0.08 to 0.27) per 100 patient-years compared to 0.14 per 100 patient-years (95% CI, 0.14 to 0.14) based on SEER (Genentech 2020[a]).
- 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).
 - For the primary endpoint, the percentages of patients with 12-week confirmed disability progression were 32.9% with ocrelizumab vs 39.3% with placebo (HR, 0.76, 95% CI, 0.59 to 0.98; $p = 0.03$).
 - The percentages of patients with 24-week CDP, a secondary endpoint, were 29.6% with ocrelizumab vs 35.7% with placebo (HR, 0.75, 95% CI, 0.58 to 0.98; $p = 0.04$).
 - Additional secondary endpoints included changes in the T25FW, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
 - The proportion of patients with 20% worsening of the T25FW 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.

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 (Miravalle 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)

- IFNs, 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 double-blind, placebo-controlled, RCTs 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, RCT with IFN β -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 IFN β -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 IFN β -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 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 AAN 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. 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 IFN β compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFN β demonstrated no benefit. The risk ratio for sustained progression with IFN β was 0.98 (95% CI, 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I² = 57%) (*La Mantia et al 2013*).

Timing of DMT initiation

- The best initial treatment strategy is uncertain, but 2 main concepts include safety focused (IFNs or glatiramer) and efficacy (ie, natalizumab, ocrelizumab, ofatumumab) approaches (*Olek & Mowry 2020b*). Retrospective observational studies have supported the earlier initiation of high efficacy DMT to reduce the risk of disability progression; however, evidence from RCTs is needed to determine the appropriate stage of MS in which to use a high efficacy DMT (*He et al 2020*).
- A 2017 systematic review evaluated the effect of high efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS (*Merkel et al 2017*). 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 IFN β -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*).

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 ARR (~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 IFN β 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 IFN β products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFN β , dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab (*Fogarty et al 2016*).
- A total of 39 RCTs 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 IFN β -1b, IFN β -1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFN β -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 β -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, dimethyl fumarate 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 12 mg (RR, 0.40, 95% CI, 0.27 to 0.60; very low quality evidence) was 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 12 mg (mean difference = -0.6; 95% CI, -1.02 to -0.24) was 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).
- A 2020 network meta-analysis of 34 RCTs compared ofatumumab with other DMTs for RRMS (*Samjoo et al 2020*). For the outcome of ARR, rate ratios were significantly improved with ofatumumab compared with teriflunomide, IFN β -1a SC

and IM, IFN β -1b, glatiramer acetate, dimethyl fumarate, and fingolimod; no differences were detected in comparisons with cladribine, ocrelizumab, natalizumab, or alemtuzumab. Values for SUCRA indicated alemtuzumab was most likely to be most effective (96%), followed by ofatumumab (91%), natalizumab (88%), and ocrelizumab (85%).

CLINICAL GUIDELINES

- 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*). 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)
 - 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)
- 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 Gd-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or Gd-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)
- 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.
- 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 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 peginterferon), 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.
 - 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 IFN β products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab (*Freedman et al 2013*).

SAFETY SUMMARY

Interferons and glatiramer acetate

- Warnings for IFN β 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. IFN β products (Avonex, Rebif, Betaseron, Extavia, and Plegridy) are associated with influenza-like symptoms including musculoskeletal pain, fatigue, and headache. All IFN β products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFN β 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 ($\geq 10\%$ 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 ($\geq 10\%$ and ≥ 1.5 times higher than placebo) were injection site reactions.

Oral agents

- Fingolimod is contraindicated in patients with a variety of cardiac issues and those with a hypersensitivity to the product. Because of a risk for bradyarrhythmia and atrioventricular (AV) blocks, patients should be monitored during Gilenya treatment initiation. In controlled clinical trials, first-degree AV block after the first dose occurred in 4.7% of patients receiving Gilenya and 1.6% of patients on placebo.
 - 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 $\geq 10\%$ 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. Vaccination against human papilloma virus (HPV) should be considered before initiating treatment with fingolimod; HPV infections including papilloma, dysplasia, warts, and HPV-related cancer have been reported in post marketing reports. Safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, and lymphoma in patients treated with fingolimod. 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. Relapses of MS with tumefactive demyelinating lesions on imaging have been observed both during therapy with fingolimod and after discontinuation in post marketing reports. If a severe MS relapse occurs during or after discontinuation of treatment with fingolimod, tumefactive MS should be considered, and imaging evaluation and initiation of appropriate treatment may be necessary.

- Siponimod is contraindicated in patients with a cytochrome P450C9*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. Mayzent may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta-blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate. 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.
- Ozanimod is 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. It is also contraindicated in patients with Mobitz type II second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker. Use is also contraindicated in patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor. Warnings and precautions for ozanimod 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 3 months after stopping ozanimod due to fetal risk. The most common adverse events (incidence > 10%) are upper respiratory tract infections and hepatic transaminase elevations. Zeposia (ozanimod) does not have a recommendation for first-dose cardiac observation like fingolimod and siponimod.
- Dimethyl fumarate, diroximel fumarate, and monomethyl 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. Serious cases of herpes zoster and other opportunistic viral (eg, herpes simplex virus, West Nile virus, cytomegalovirus), fungal (eg, Candida and Aspergillus), and bacterial (eg, Nocardia, Listeria monocytogenes, *Mycobacterium tuberculosis*) infections have been reported in patients treated with dimethyl fumarate, and may occur at any time during treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate. Patients with signs/symptoms of any of these infections should undergo diagnostic evaluation and receive appropriate treatment; treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate may need to be withheld until the infection has resolved. 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.
- 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/embryoletality 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, **drug reaction with**

eosinophilia and systemic symptoms, 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 ($\geq 10\%$ and $\geq 2\%$ greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).

- 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.

High Efficacy Infusibles and Injectables

- 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 $\geq 10\%$ 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), thrombocytopenia, and hepatotoxicity.
- 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 IFN β -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 IFN β -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, decreased immunoglobulin levels, 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.

- No cases of PML were reported in the controlled Phase 2 or 3 studies or in the OLE of these studies. Outside of clinical trials, as of January 31, 2020, there have been 9 confirmed cases of PML in patients treated with ocrelizumab for MS. Of the 9 cases, 8 patients had been switched from natalizumab (n = 7) or fingolimod (n = 1). In 1 additional case, the patient had no prior exposure to DMTs but had contributing factors for PML including advanced age (78 years) and preexisting grade 1 lymphopenia which progressed to grade 2 during treatment (Genentech 2020[c], Hauser et al 2020[b], Ng et al 2020).
- 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.
- Live or live-attenuated vaccines should not be administered until B-cell count recovery is confirmed (as measured by CD19+ B-cells) in infants born from mothers who were exposed to ocrelizumab during pregnancy.
- Ofatumumab is contraindicated in patients with active hepatitis B virus infection. The prescribing information contains warnings and precautions regarding the risk of infection, injection-related reactions, reduction in immunoglobulins, and fetal risk. The most common adverse events (incidence > 10%) include upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- 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/m². Monitoring of cardiac function is required prior to all mitoxantrone doses.

Symptomatic therapy

- 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.

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablet	Oral	Twice daily	<ul style="list-style-type: none"> • 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 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)	Tablet	Oral	Once daily	<ul style="list-style-type: none"> • May be taken with or without food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<ul style="list-style-type: none"> 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 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. Transaminase and bilirubin levels should be obtained within 6 months before initiation; transaminase levels should be monitored for at least 6 months after initiation.
Avonex (interferon β -1a)	Injection; pen, prefilled syringe	IM	Once weekly <u>Titration:</u> 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.	<ul style="list-style-type: none"> 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Bafiertam (monomethyl fumarate)	Capsule (delayed-release)	Oral	Twice daily <u>Titration:</u> 95 mg twice daily for 7 days (initiation), then 190 mg twice daily (maintenance) Temporary dose reductions to 95 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	<ul style="list-style-type: none"> • May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. • 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 monomethyl fumarate; studies did not show that the presence of food had an impact on the incidence of flushing with monomethyl fumarate. • Obtain a complete blood cell count including lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Betaseron (interferon β -1b)	Injection	SC	Every other day <u>Titration:</u> 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.	<ul style="list-style-type: none"> • 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 <u>once daily</u> OR 40 mg <u>3 times per week</u> at least 48 hours apart <u>Note:</u> The 2 strengths are not interchangeable.	<ul style="list-style-type: none"> • 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 <u>Titration:</u> 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.	<ul style="list-style-type: none"> • 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.
Gilenya (fingolimod)	Capsule	Oral	Once daily Approved for adults and pediatric patients 10 years of age or older. For pediatric patients \leq 40 kg, a lower dose is recommended.	<ul style="list-style-type: none"> • May be taken with or without food. <u>First dose monitoring:</u> <ul style="list-style-type: none"> • 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 heart rate [HR] < 45 bpm in adults, < 55 bpm in pediatric patients \geq 12 years of age, or < 60 bpm

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			<p>Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).</p>	<p>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.</p> <ul style="list-style-type: none"> • 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. • Fingolimod exposure is doubled in patients with severe hepatic impairment so patients 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. • Fingolimod may cause fetal harm when administered to a pregnant woman. Before initiation of treatment with fingolimod, females of reproductive potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception during treatment and for 2 months after treatment to allow the compound to be eliminated from the body. In females planning to become pregnant, fingolimod should be stopped 2 months before planned conception.
Kesimpta (ofatumumab)	Injection	SC	20 mg at weeks 0, 1, and 2 followed by subsequent dosing of 20 mg once monthly starting at week 4	<ul style="list-style-type: none"> • Prior to initiation, perform hepatitis B virus screening and tests for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, immunology experts should be consulted.
Lemtrada (alemtuzumab) [†]	Injection	IV	<p>2 treatment courses <u>First course:</u> 12 mg/day on 5 consecutive days <u>Second course:</u> 12 mg/day on 3 consecutive days</p>	<ul style="list-style-type: none"> • Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. • Infused over 4 hours for both treatment courses; patients should be observed for

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			<p>months after the first treatment course</p> <p><u>Subsequent course:</u> 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.</p>	<p>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.</p> <ul style="list-style-type: none"> 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 > 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab. <p><u>Important monitoring:</u></p> <ul style="list-style-type: none"> Complete blood count with differential, serum creatinine, and urinalysis (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) 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	<p>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:</p> <ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			<ul style="list-style-type: none"> Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle. 	
Mayzent (siponimod)	Tablet	Oral	<p>Once daily</p> <p>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).</p>	<ul style="list-style-type: none"> 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	<p>Every 3 months</p> <p>For MS-related indications: 12 mg/m² given as a short IV infusion over 5 to 15 minutes</p> <p><u>Note:</u> Left ventricular ejection fraction (LVEF) should be 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.</p>	<ul style="list-style-type: none"> 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/m². Mitoxantrone generally should not be administered to MS patients with neutrophil counts < 1500 cells/mm³. 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. 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
Ocrevus (ocrelizumab)	Injection	IV	<p>Every 6 months (24 weeks)</p> <p><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</p>	<ul style="list-style-type: none"> 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. Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<p>reactions depend on the severity. See package insert for more details.</p> <ul style="list-style-type: none"> • Administer all necessary immunizations according to immunization guidelines at least 2 (non-live vaccines) to 4 (live or live-attenuated vaccines) weeks prior to initiation of ocrelizumab. • Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab. • Hepatitis B virus screening is required before the first dose. • Prior to initiation, quantitative serum immunoglobulin levels should be performed. For patients with low serum immunoglobulins, immunology experts should be consulted.
Plegridy (peginterferon β -1a)	Injection; pen, prefilled syringe for SC use; prefilled syringe for IM use	SC, IM	Every 14 days <u>Titration:</u> Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	<ul style="list-style-type: none"> • Following initial administration by a trained healthcare provider, Plegridy may be self-administered. • Patients should be advised to rotate injection sites. The usual sites for SC administration are the abdomen, back of the upper arm, and thigh; IM injections should be administered in the 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 <u>Titration:</u> 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	<ul style="list-style-type: none"> • 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)	Capsule (delayed-release)	Oral	Twice daily <u>Titration:</u>	<ul style="list-style-type: none"> • 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
			<p>120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance)</p> <p>Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.</p>	<ul style="list-style-type: none"> 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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Tysabri (natalizumab) [†]	Injection	IV	<p>Once a month (every 4 weeks)</p> <p>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.</p>	<ul style="list-style-type: none"> Patients should be observed during the infusion and for 1 hour after the infusion is complete.
Vumerity (diroximel fumarate)	Capsule (delayed-release)	Oral	<p>Twice daily</p> <p><u>Titration:</u> 231 mg twice daily for 7 days (initiation), then 462 mg twice daily (maintenance)</p> <p>Temporary dose reductions to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.</p>	<ul style="list-style-type: none"> 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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Zeposia (ozanimod)	Capsule	Oral	<p>Once daily</p> <p>Titration: 0.23 mg once daily on days 1 to 4, then 0.46 mg once daily on days 5 to 7, then 0.92 mg once daily on day 8 and thereafter.</p>	<ul style="list-style-type: none"> May be taken with or without food. Capsules should be swallowed whole. Obtain a complete blood count (including lymphocyte count), transaminase and bilirubin levels, electrocardiogram, and ophthalmic assessment before initiation of therapy. If a dose is missed during the first 2 weeks of treatment, treatment should be restarted using the titration regimen; if a dose is missed after 2 weeks of

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<p>treatment, continue treatment as planned.</p> <ul style="list-style-type: none"> • Use in patients with hepatic impairment is not recommended.

*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*).
- IFN β products have been shown to decrease MRI lesion activity, prevent relapses, and delay disability progression. In general, patients treated with IFN β 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 IFN β 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 IFN β -1a compared to higher dose SC IFN β -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 IFN β products. With IFN β , use caution in patients with depression or other mood disorders.
 - 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.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFN β , primarily due to intolerable adverse effects or inadequate efficacy (*Coyle 2008, Portaccio et al 2008*). Clinical trials have shown that patients switching from IFN β 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 (*MS Coalition 2019, Scolding et al 2015, Montalban et al 2018, Rae-Grant 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, Rae-Grant et al 2018*).
- There are now 8 available oral agents. 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. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
 - Gilenya (fingolimod) is a S1P 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 IFN β -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 IFN β -1a (*Chitnis et al 2018*).
 - Mayzent (siponimod) is a S1P receptor modulator, similar to fingolimod. 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.

- Zeposia (ozanimod), the third S1P receptor modulator, has to significantly decrease ARR compared to IFN β -1a; however, unlike other drugs in this class, it does not require first dose cardiac monitoring (*Comi et al 2019, Cohen et al 2019*).
- 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 an oral fumarate that is rapidly converted to monomethyl fumarate, 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 2019*).
- Bafiertam (monomethyl fumarate) was approved by the FDA in April 2020 and is considered to be a “bioequivalent alternative” to dimethyl fumarate (*Bafiertam prescribing information 2020*).
- 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 liver enzymes, alopecia, diarrhea, influenza, nausea, and paresthesia.
- 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, Mavenclad had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Mavenclad carries a boxed warning for risk of malignancies and teratogenicity. Lymphopenia is the most common adverse effect.
- Tysabri (natalizumab) is a recombinant monoclonal antibody indicated for the treatment of relapsing forms of MS and is also approved for use in the treatment of moderately to severely active CD in patients with an inadequate response to or who are unable to tolerate conventional CD therapies and TNF inhibitors.
 - In a 2011 systematic review of trials evaluating natalizumab for RRMS, pooled efficacy data from 2 RCTs (AFFIRM and SENTINEL) showed that natalizumab significantly reduced the risk for having a relapse during 2 years of treatment. In addition, natalizumab significantly reduced the risk for experiencing 12-week CDP at 2 years (*Pucci et al 2011*). Natalizumab has been associated with an increased risk of PML; however, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Kesimpta (ofatumumab) is the first self-administered CD20-directed cytolytic antibody indicated for relapsing forms of MS. Ofatumumab has demonstrated superiority to teriflunomide in patients with relapsing forms of MS for the outcome of ARR (*Hauser et al 2020[a]*). Ofatumumab is self-administered monthly by SC injection after an initial loading regimen. Key warnings include the risk for infections, including PML and HBV reactivation. Injection-related reactions, possible reduction in immunoglobulins, and fetal risk (B cell depletion in infants born to mothers treated with ofatumumab during pregnancy) are other warnings. The most common AEs (incidence > 10%) were upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- 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.
- 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*).

- 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 quality of life in MS patients, 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 $\geq 20\%$ are meaningful to people with MS. 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*).

REFERENCES

- Alsup JC for the PRISMS (Prevention of Relapses and Disability by Interferon β -1a Subcutaneously in Multiple Sclerosis) Study Group. Interferon β -1a in MS: results following development of neutralizing antibodies in PRISMS. *Neurology*. 2005;65:48-55.
- Ampyra [package insert], Ardsley, NY: Acorda Therapeutics, Inc., December 2019.
- Armoiry X, Kan A, Melendez-Torres GJ, et al. Short- and long-term clinical outcomes of use of beta-interferon or glatiramer acetate for people with clinically isolated syndrome: a systematic review of randomised controlled trials and network meta-analysis. *J Neurol*. 2018;265(5):999-1009.
- Aubagio [package insert], Cambridge, MA: Genzyme; November 2020.
- Avonex [package insert], Cambridge, MA: Biogen Idec.; March 2020.
- Bafiertam [package insert], High Point, NC: Banner Life Sciences LLC; April 2020.
- Barbero P, Bergui M, Versino E. Every-other-day interferon beta-1b vs once-weekly interferon β -1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. *Mult Scler*. 2006;12:72-76.
- Betaseron [package insert], Whippany, NJ: Bayer Healthcare Pharmaceuticals; October 2020.
- Butler M, Forte ML, Schwehr N, et al. Decisional dilemmas in discontinuing prolonged disease-modifying treatment for multiple sclerosis. Comparative Effectiveness Review No. 150. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-1.) AHRQ Publication No. 15-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2015. <https://effectivehealthcare.ahrq.gov/products/multiple-sclerosis/research/>. Accessed November 27, 2020.
- Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFN β -1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology*. 2009;72(23):1976-1983.
- CADTH. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis. 2013. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0060853/?report>. Accessed November 27, 2020.
- Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. *Lancet Neurol*. 2014[b];13:657-665.
- Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014[a];13(6):545-556.
- Caon C, Din M, Ching W, et al. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2006;13:471-474.
- Carra A, Onaha P, Luetic G. Therapeutic outcome three years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. *Eur J Neurol*. 2008;15:386-393.
- Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379(11):1017-1027.
- Clerico M, Faggiano F, Palace J, et al. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. *Cochrane Database Syst Rev*. 2008; (2):CD005278.
- Clinical Pharmacology Web site. <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed November 27, 2020.
- ClinicalTrials.gov Web site. <http://clinicaltrials.gov/>. Accessed November 27, 2020.
- Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362:402-415.
- Cohen JA, Coles AJ, Arnold DL, et al for the CARE-MS 1 investigators. Alemtuzumab versus interferon beta-1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomized controlled phase 3 trials. *Lancet*. 2012;380:1819-1828.
- Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomized, 24-month, phase 3 trial. *Lancet Neurol*. 2019;18(11):1021-1033. doi: 10.1016/S1474-4422(19)30238-8
- Cohen JA, Khatri B, Barkhof F, et al for the TRANSFORMS (TRial Assessing injectable interferon vS FTY720 Oral in RRMS) Study Group. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomized TRANSFORMS study. *J Neurol Neurosurg Psychiatry*. 2015;0:1-8.
- Coles AJ, Twyman CL, Arnold DL, et al for the CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomized controlled phase 3 trial. *Lancet*. 2012;380:1829-1839.

- Comi G, Cohen JA, Arnold DL, et al for the FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. *Ann Neurol*. 2011;69(1):75-82.
- Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomized, minimum 12-month, phase 3 trial. *Lancet Neurol*. 2019;18(11):1009-1020. doi: 10.1016/S1474-4422(19)30239-X
- Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9700):1503-1511.
- Comi G, Martinelli V, Rodegher M, et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. *Mult Scler*. 2012;19(8):1074-1083.
- Confavreux C, O'Connor P, Comi G, et al for the TOWER trial group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:247-256.
- Copaxone [package insert]. Overland Park, KS: Teva Neuroscience Inc.; January 2020.
- Coyle PK. Switching algorithms: from one immunomodulatory agent to another. *J Neurol*. 2008; 255(Suppl 1):44-50.
- Disease-modifying therapies for relapsing-remitting and primary-progressive multiple sclerosis: effectiveness and value (Final evidence report; March 6, 2017). Prepared for the California Technology Assessment Forum by the Institute for Clinical and Economic Review (ICER). ICER Web site. https://icer-review.org/wp-content/uploads/2016/08/CTAF_MS_Final_Report_030617.pdf. Accessed November 27, 2020.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed November 27, 2020.
- Durelli L, Verdun E, Barbero P. Every-other-day interferon beta-1b vs once-weekly interferon β -1a for multiple sclerosis: results of a 2-year prospective randomized multicentre study (INCOMIN). *Lancet*. 2002;359:1453-1460.
- Edan G, Kappos L, Montalban X, et al for the BENEFIT Study Group. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. *J Neurol Neurosurg Psychiatry*. 2014;85:1183-1189.
- Extavia [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; October 2020.
- FDA Center for Drug Evaluation and Research. Ocrevus (ocrelizumab) Medical Review. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761053Orig1s000TOC.cfm. Accessed November 27, 2020.
- FDA Center for Drug Evaluation and Research. Ocrevus (ocrelizumab) Summary Review. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761053Orig1s000TOC.cfm. Accessed November 27, 2020.
- Filippini G, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2013, Issue 6. Art. No.: CD008933.
- Flechter S, Vardi J, Rabey JM. Comparison of glatiramer acetate (Copaxone®) and interferon β -1b (Betaseron®) in multiple sclerosis patients: an open-label 2-year follow-up. *J Neurol Sci*. 2002;197:51-55.
- Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. *Mult Scler Relat Disord*. 2016;9:23-30.
- Fox RJ, Miller DH, Phillips T, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367:1087-1097.
- Freedman MS, Hughes B, Mikol DD, et al. Efficacy of disease-modifying therapies in relapsing-remitting multiple sclerosis: a systematic comparison. *Eur Neurol*. 2008;60(1):1-11.
- Freedman MS, Selchen D, Arnold DL, et al for the Canadian Multiple Sclerosis Working Group. Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations. *Can J Neurol Sci*. 2013;40:307-323.
- Frohman EM, Shah A, Eggenberger E, et al. Corticosteroids for multiple sclerosis: I. Application for treating exacerbations. *Neurotherapeutics*. 2007;4(4):618-626.
- Garnock-Jones KP. Alemtuzumab: a review of its use in patients with relapsing MS. *Drugs*. 2014;74:489-504.
- Genentech. Ocrevus (ocrelizumab) Over 6 years of safety experience in clinical trials. Ocrevus Web site. <https://www.ocrevus.com/hcp/rms/safety.html>. 2020[b]. Accessed November 20, 2020.
- Genentech. Ocrevus and Malignancies. Ocrevus Web site. <https://www.ocrelizumabinformo.com/content/dam/gene/ocrelizumabinformo/pdfs/Malignancies.pdf>. 2020[a]. Accessed November 20, 2020.
- Genentech. Ocrevus information: Progressive Multifocal Leukoencephalopathy. Ocrevus Web site. <https://www.ocrelizumabinformo.com/content/dam/gene/ocrelizumabinformo/pdfs/progressive-multifocal-leukoencephalopathy.pdf>. 2020[c]. Accessed November 20, 2020.
- Gilenya [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2019.
- Giovannoni G, Comi G, Cook S, et al for the CLARITY Study Group. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010; 362:416-426.
- Giovannoni G. Cladribine to treat relapsing forms of multiple sclerosis. *Neurotherapeutics*. 2017;14(4): 874-887.
- Glatopa [package insert], Princeton, NJ: Sandoz Inc.; July 2020.
- Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367:1098-1107.
- Goodin DS, Frohman EM, Hurwitz B. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2007;68(13):977-984.
- Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: A randomized cohort study 21 years after the start of the pivotal IFN β -1b trial. *Neurology*. 2012;78:1315-1322.
- Goodman AD, Brown TR, Krupp LB et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. *Lancet*. 2009;373:732-738.
- Govindappa K, Sathish J, Park K, et al. Development of interferon beta-neutralizing antibodies in multiple sclerosis – a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2015;71:1287-1298.

- Hamidi V, Couto E, Ringerike T, Klemp M. A multiple treatment comparison of eleven disease-modifying drugs used for multiple sclerosis. *J Clin Med Res.* 2018;10(2):88-105.
- Hartung HP, Gonsette R, König N, et al for the Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomized, multicenter trial. *Lancet.* 2002;360(9350):2018-2025.
- Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med.* 2020[a];383(6):546-557. doi: 10.1056/NEJMoa1917246
- Hauser SL, Bar-Or A, Comi G, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med.* 2017;376(3):221-234.
- Hauser SL, Kappos L, Arnold DK, et al. Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. *Neurology.* 2020[b];95:e1854-e1867. doi: 10.1212/WNL.0000000000010376.
- He A, Merkel B, Brown JW, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol.* 2020;19:307-316.
- Jacobs LD, Cookfair DL, Rudick RA, et al for The Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon β -1a for disease progression in relapsing multiple sclerosis. *Ann Neurol.* 1996;39:285-294.
- Jensen HB, Ravnborg M, Dalgas U, et al. 4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review. *Ther Adv Neurol Disord.* 2014;7(2):97-113.
- Johnson KP, Brooks BR, Cohen JA, et al for the Copolymer 1 Multiple Sclerosis Study Group. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology.* 1995;45:1268-1276.
- Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol.* 2018;17(5):405-415.
- Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. *Lancet.* 2018;391(10127):1263-1273.
- Kappos L, Freedman MS, Polman CH, et al for the BENEFIT Study Group. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT Study. *Lancet.* 2007;370:389-397.
- Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet.* 2011;378(9805):1779-1787.
- Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010;362(5):387-401.
- Kappos L, Traboulsee A, Constantinescu C. Long-term subcutaneous interferon β -1a therapy in patients with relapsing-remitting MS. *Neurology.* 2006;67:944-953.
- Kesimpta [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2020.
- Khan O, Rieckmann P, Boyko A, et al for the GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol.* 2013;73:705-713.
- Khan OA, Tselis AC, Kamholz JA, et al. A prospective, open-label treatment trial to compare the effects of IFN β -1a (Avonex), IFN β -1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. *Mult Scler.* 2001[b];7:349-353.
- Khan OA, Tselis AC, Kamholz JA. A prospective, open-label treatment trial to compare the effect of IFN β -1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol.* 2001[a];8:141-148.
- Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon β -1a in relapsing-remitting multiple sclerosis: a randomized extension of the TRANSFORMS study. *Lancet Neurol.* 2011;10(6):520-529.
- Kieseier BC, Arnold DL, Balcer LJ et al. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. *Mult Scler.* 2015;21(8):1025-1035.
- Kinkel RP, Dontchev M, Kollman C, et al for the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance Investigators. Association between immediate initiation of intramuscular interferon β -1a at the time of a clinically isolated syndrome and long-term outcomes: a 10-year follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. *Arch Neurol.* 2012;69(2):183-190.
- Krapp H, Morrissey SP, Zenker O, et al for the MIMS Study Group. Effect of mitoxantrone on MRI in progressive MS: results of the MIMS trials. *Neurology.* 2005;65(5):690-695.
- La Mantia L, Di Pietrantonj C, Rovaris M, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev.* 2016;11:CD009333.
- La Mantia L, Vacchi L, Rovaris M, et al. Interferon β for Secondary Progressive Multiple Sclerosis: A Systematic Review. *J Neurol Neurosurg Psychiatry.* 2013; 84(4):420-426.
- Lemtrada [package insert], Cambridge, MA: Genzyme Corporation; September 2020.
- Limmroth V, Malessa R, Zettl UK. Quality assessments in multiple sclerosis therapy (QUASIMS). *J Neurol.* 2007;254:67-77.
- Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol.* 2013;73:327-340.
- Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014;83(3):278-286.
- Lucchetta RC, Tonin FS, Borba HHL, et al. Disease-modifying therapies for relapsing-remitting multiple sclerosis: a network meta-analysis. *CNS Drugs.* 2018;32(9):813-826. doi: 10.1007/s40263-018-0541-5.
- Marriott JJ, Miyasaki JM, Gronseth G, et al for Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2010;74(18):1463-1470.
- Mavenclad [package insert], Rockland, MA: EMD Serono, Inc.; April 2019.
- Mayzent [package insert], East Hanover, NJ: Novartis; March 2019.
- McGinley MP, Moss BP, Cohen JA. Safety of monoclonal antibodies for the treatment of multiple sclerosis. *Expert Opin Drug Saf.* 2017;16(1):89-100.

- Melendez-Torres GJ, Amoiry X, Court R, et al. Comparative effectiveness of beta-interferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages. *BMC Neurol.* 2018;18(1):162. doi: 10.1186/s12883-018-1162-9.
- Merkel B, Butzkueven H, Traboulsee AL, Havrdova E, Kalincik T. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: A systematic review. *Autoimmun Rev.* 2017;16(6):658-665.
- Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous acetate in patients with relapsing multiple sclerosis (the Rebif vs Glatiramer acetate in Relapsing MS Disease [REGARD] study): a multicenter, randomized, parallel, open-label trial. *Lancet Neurol.* 2008;7:903-914.
- Miller AE, Wolinsky JS, Kappos L, et al for the TOPIC Study Group. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2014;13:977-986.
- Miller DH, Chard DT, Ciccarelli O. Clinically Isolated Syndromes. *Lancet Neurol.* 2012;11(2):157-169.
- Minagara A, Murray TJ. Efficacy and tolerability of intramuscular interferon β -1a compared to subcutaneous interferon β -1a in relapsing MS: results from PROOF. *Curr Med Res Opin.* 2008; 24(4):1049-1055.
- Miravalle AA. Guidelines and best practices for appropriate use of dalfampridine in managed care populations. *Am J Manag Care.* 2011;17:S154-S160.
- Mitoxantrone [package insert], Lake Forest, IL: Hospira Inc.; May 2018.
- Montalban X, Gold R, Thompson AJ, et al.ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler.* 2018;24(2):96-120.
- Montalban X, Hauser SL, Kappos L, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med.* 2017;376(3):209-220.
- MS Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. Updated September 2019. http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed November 27, 2020.
- Multiple Sclerosis Association of America. Bafiertam oral capsules approved by the FDA for relapsing forms of MS. Updated May 15, 2020. <https://mymsaa.org/news/bafiertam-oral-capsules-approved-by-the-fda-for-relapsing-forms-of-ms/> Accessed November 27, 2020.
- Naismith RT, Wolinsky JS, Wundes A, et al for the EVOLVE-MS-1 study group. Diroximel fumarate (DRF) in patients with relapsing-remitting multiple sclerosis: interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study. *Multiple Sclerosis J.* 2020;26(13):1729-1739. doi: 10.1177/1352458519881761
- National Institutes of Health. Multiple sclerosis. Updated November 2019. <https://www.nccih.nih.gov/health/multiple-sclerosis>. Accessed November 27, 2020.
- National Multiple Sclerosis Society, 2020[a]. Types of MS. <https://www.nationalmssociety.org/What-is-MS/Types-of-MS>. Accessed November 27, 2020.
- National Multiple Sclerosis Society, 2020[b]. Who Gets MS? <http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS>. Accessed November 27, 2020.
- Newsome SD, Scott TF, Arnold DL, et al. Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN. *Ther Adv Neurol Disord.* 2018;11:1756286418791143. doi: 10.1177/1756286418791143.
- Ng HS, Luzon Rosenbult C, Tremlett H. Safety profile of ocrelizumab for the treatment of multiple sclerosis: a systematic review. *Expert Opin Drug Safety.* 2020;19(9):1069-1094.
- O'Connor P, Wolinsky JS, Confavreux C, et al for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* 2011;365:1293-1303.
- O'Connor PW, Li D, Freedman MS, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology.* 2006;66:894-900.
- O'Connor P, Filippi M, Arnason B, et al. 250 mcg or 500 mcg interferon beta-1b vs 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomized, multicentre study. *Lancet Neurol.* 2009;8(10):889-897.
- Ocrevus [dossier], South San Francisco, CA: Genentech, Inc.; 2017.
- Ocrevus [package insert], South San Francisco, CA: Genentech, Inc.; November 2020.
- Olek MJ, Mowry E. Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults. UpToDate Web site. www.uptodate.com. Updated October 21, 2020. Accessed November 17, 2020.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed November 27, 2020.
- Otallah S, Banwell B. Pediatric multiple sclerosis: an update. *Curr Neurol Neurosci Rep.* 2018;18(11):76. doi: 10.1007/s11910-018-0886-7.
- Palte MJ, Wehr A, Tawa M, et al. Improving the gastrointestinal tolerability of fumaric acid esters: early findings on gastrointestinal events with diroxime fumarate in patients with relapsing-remitting multiple sclerosis from the phase 3, open-label EVOLVE-MS-1 study. *Adv Ther.* 2019;36(11):3154-3165. doi: 10.1007/s12325-019-01085-3.
- Panitch H, Goodin D, Francis G. Benefits of high-dose, high-frequency interferon β -1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. *J Neurol Sci.* 2005;239:67-74.
- Panitch H, Goodin D, Francis G. Randomized, comparative study of interferon β -1a treatment regimens in MS: the EVIDENCE trial. *Neurology.* 2002;59:1496-1506.
- Plegridy [package insert], Cambridge, MA: Biogen Inc.; January 2021.
- Polman CH, O'Connor PW, Havrdova, et al for the AFFIRM Study Investigators. Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med.* 2006; 354:899-910.
- Portaccio E, Zipoli V, Siracusa G, et al. Long-term adherence to interferon β therapy in relapsing-remitting multiple sclerosis. *Eur Neurol.* 2008;59:131-135.
- PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon β -1a in relapsing/remitting multiple sclerosis. *Lancet.* 1998;352:1498-1504.
- Pucci E, Giuliani G, Solari A, et al. Natalizumab for relapsing remitting multiple sclerosis (Review). *Cochrane Database Syst Rev.* 2011;(10):CD007621.

- Rae-Grant A, Day GS, Marrie RA et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(17):777-788.
- Rebif [package insert], Rockland, MA: EMD Serono; **May 2020**.
- Rio J, Tintore M, Nos C, et al. Interferon beta in relapsing-remitting multiple sclerosis: an eight years' experience in a specialist multiple sclerosis centre. *J Neurol*. 2005;252:795-800.
- Rizvi SA, Agius MA. Current approved options for treating patients with multiple sclerosis. *Neurology*. 2004;63(12 Suppl 6):S8-14.
- Ruck T, Bittner S, Simon OJ et al. Long-term effects of dalfampridine in patients with multiple sclerosis. *J Neurol Sci*. 2014;337(1-2):18-24.
- Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus Interferon β -1a for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354:911-923.
- Samjoo IA, Worthington E, Drudge C et al. Comparison of ofatumumab and other disease-modifying therapies for relapsing multiple sclerosis: a network meta-analysis. *J Comp Eff Res*. 2020; doi: 10.2217/cer-2020-0122.
- Sanvito L, Constantinescu CS, Gran B. Novel therapeutic approaches to autoimmune demyelinating disorders. *Curr Pharm Des*. 2011;17(29):3191-3201.
- Schwid SR, Panitch HS. Full results of the evidence of interferon dose-response European North American comparative efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly vs high dose, high-frequency interferon β -1a for relapsing multiple sclerosis. *Clin Ther*. 2007;29(9):2031-2048.
- Schwid SR, Thorpe J, Sharief M. Enhanced benefit of increasing interferon β -1a dose and frequency in relapsing multiple sclerosis. The EVIDENCE study. *Arch Neurol*. 2005;62:785-792.
- Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: Revised (2015) Guidelines for prescribing disease-modifying treatments in multiple sclerosis. <http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139>. Accessed **November 27**, 2020.
- Selmaj K, Wundes A, Ziemssen T, et al, on behalf of the EVOLVE-MS-2 study group. Diroximel fumarate demonstrates improved gastrointestinal tolerability profile compared to dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: Results from the randomized, double-blind, phase 3 EVOLVE-MS-2 study. Presented at: European Charcot Foundation - 2019 Annual Symposium. November 21 to November 23. Baveno, Italy. P50.
- Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. *Ther Adv Neurol Disord*. 2016;9(1):44-52.
- Sorensen PS, Deisenhammer F, Duda P, et al for the EFNS Task Force on Anti-IFN-beta Antibodies in Multiple Sclerosis. Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. *Eur J Neurol*. 2005;12(11):817-827.
- Tecfidera [package insert], Cambridge, MA: Biogen Inc.; February 2020.
- The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. *Neurology*. 1995;45:1277-1285.
- The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting - multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:655-661.
- Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi: 10.1016/S1474-4422(17)30470-2.
- Traboulsee A, Sabbagh AL, Bennett R, et al. Reduction in magnetic resonance imaging T2 burden of disease in patients with relapsing-remitting multiple sclerosis: analysis of 48-week data from the EVIDENCE (evidence of interferon dose-response: European North American comparative efficacy) study. *BMC Neurol*. 2008;8:11.
- Tramacere I, DelGiovane C, Salanti G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2015, Issue 9. Art. No.: CD011381.
- Trojano M, Liguori M, Paolicelli D. Interferon beta in relapsing-remitting multiple sclerosis: an independent post marketing study in southern Italy. *Mult Scler*. 2003;9:451-457.
- Trojano M, Pellegrini F, Fuiani A. New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann Neurol*. 2007;61:300-306.
- Tysabri [package insert], Cambridge, MA: Biogen Inc.; June 2020.
- Vermersch P, Czlonkowska A, Grimaldi LME, et al for the TENERE Trial Group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial. *Mult Sclerosis Journal*. 2014;20(6):705-716.
- Vumerity [package insert]. Cambridge, MA: Biogen Inc.; March 2020.
- White JT, Kieseier BC, Newsome SD, et al. Immunogenicity with peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis: 2-year data from the randomized phase 3, multicenter ADVANCE study in relapsing-remitting multiple sclerosis (EP4152). *Eur J Neurol*. 2014;21(Suppl 1):104-387 [abstract].
- Wingerchuk DM, and Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. *Mayo Clin Proc*. 2014;89(2):225-240.
- Wolinsky JS, Narayana PA, O'Connor P. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol*. 2007;61:14-24.
- Xu M, Lu X, Fang J, et al. The efficacy and safety of teriflunomide based therapy in patients with relapsing multiple sclerosis: A meta-analysis of randomized controlled trials. *J Clin Neurosci*. 2016;33:28-31.
- Xu Z, Zhang F, Sun F, et al. Dimethyl fumarate for multiple sclerosis. *Cochrane Database Syst Rev*. 2015, Issue 4. Art. No.: CD011076.
- Zeposia [package insert], Summit, NJ: Celgene Corporation; **September 2020**.
- Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, Yang X. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2017;11:CD010968.
- Zhao Y, Chen K, Ramia N, et al. A phase 1, open-label, crossover study to evaluate the bioequivalence of intramuscular and subcutaneous peginterferon beta-1a in healthy volunteers. Presented at: Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) 2020, Feb 27th - Feb 29th, 2020; West Palm Beach, FL, USA. https://biogen-inscite.veevavault.com/ui/approved_viewer?token=5266-a8eb514d-a24b-4a43-933c-0a519ac36f74&dns=biogen-inscite.veevavault.com



- Zwibel HL. Glatiramer acetate in treatment-naïve and prior interferon b-1b-treated multiple sclerosis patients. *Acta Neurol Scand.* 2006;113:378-386.

Publication Date: December 16, 2020; Last Revision Date: February 5, 2021