

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is the leading cause of disability in young and middle-aged people in developed areas of the world (*MS Coalition 2017*). MS is characterized by repeated episodes of inflammation within the brain and spinal cord, resulting in injury to the myelin sheaths that surround and insulate nerves, and subsequently the nerve cell axons (*Goodin et al 2002*). 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 80 to 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 10% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
 - Progressive relapsing MS (PRMS) patients have a continuous decline in function while experiencing occasional attacks. Only 5% of MS patients have PRMS (*Goodin et al 2002, Sanvito et al 2011, National MS Society 2014a*).
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the prior category of PRMS can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity (*Lublin et al 2014*).
- An estimated 2.3 million people worldwide have been diagnosed with MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is reported more frequently in women than in men (*National MS Society 2014b*).
- Diagnosis of MS requires evidence of damage in at least 2 separate areas of the CNS, evidence of damage that occurred at 2 separate time points at least 1 month apart, and that other possible diagnoses have been ruled out. The clinically isolated syndrome (CIS) includes 1 attack and objective evidence of 1 lesion (*Polman et al 2011*). Following CIS, the course of MS is variable. The inclusion of CIS in the spectrum of MS phenotypes with prospective follow-up of most such patients determining their subsequent disease phenotype was also recommended in the recent revision of the MS clinical course descriptions (*Lublin et al 2014*).
- Disease-modifying therapies (DMTs) delay the development from CIS to clinically definite MS (CDMS) (*Miller et al 2012*). Evaluation includes an extensive patient history, neurological examination, laboratory tests to rule out other possible causes, MRI to evaluate for new disease and signs of more chronic damage, and lumbar puncture.
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that leads to damage to the myelin and slows or blocks transmission of nerve impulses. An exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits (*Frohman et al 2007*).
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of DMTs to reduce the frequency and severity of relapses and delay disease and disability progression (*Goodin et al 2002*). The 2002 American Academy of Neurology and the 2008 National MS Society guidelines recommend the use of interferon beta (IFN β) products or glatiramer acetate as first-line therapy in all patients with clinically definite RRMS and in select patients with CIS (*Goodin et al 2002, Miller et al 2008*). The MS Coalition, the American Academy of Neurology, and the Association of British Neurologists guidelines support access to the available DMTs for patients with MS. There are currently no recent universal algorithms to determine the order of product selection. It is suggested that the most appropriate agent may be selected on an individual basis and monitored for clinical response and tolerability (*Corboy et al 2015, Goodin et al 2002, MS Coalition 2017, Scolding et al 2015*).
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) [listed as a potassium channel blocker].

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ampyra (dalfampridine)	-
Aubagio (teriflunomide)	-
Avonex (interferon β-1a)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✓
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	-
Lemtrada (alemtuzumab)	-
mitoxantrone*	✓
Ocrevus (ocrelizumab)	!
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-
Zinbryta (daclizumab)	-

†Glatopa by Sandoz is the FDA-approved generic for the Copaxone (glatiramer acetate) 20 mg once daily dosage form.

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

(Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Ampyra (dalfampridine)‡	✓	-	-	-	-	-
Aubagio (teriflunomide)	-	✓	-	-	-	-
Avonex (IM interferon β-1a)	-	✓	✓	✓	✓	-
Betaseron/Extavia (interferon β-1b)	-	✓	-	✓	✓	-
Copaxone/Glatopa (glatiramer acetate)	-	✓	-	-	-	-
Gilenya (fingolimod)	-	✓	✓	✓	-	-
Lemtrada (alemtuzumab)	-	(3 rd line)*	-	-	-	-
mitoxantrone	-	(2 nd line)	✓ (neurologic disability)	✓	-	✓ §
Ocrevus (ocrelizumab)	!	✓	-	-	-	✓ ¶
Plegridy (peginterferon β-1a)	-	✓	-	-	-	-
Rebif (interferon β-1a)	-	✓	✓	✓	-	-
Tecfidera (dimethyl fumarate)	-	✓	-	-	-	-
Tysabri (natalizumab)	-	✓ †	-	-	-	-
Zinbryta (daclizumab)	-	(3 rd line)*	-	-	-	-

Data as of June 15, 2017 NA/JD

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IM=intramuscular; SC=subcutaneous

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

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

†Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML) (a rare, but often fatal demyelinating disease of the central nervous system caused by the John Cunningham virus [JCV]). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α .

§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.

¶Ocrevus is approved for PPMS.

(Prescribing information: Ampyra 2016, Aubagio 2016, Avonex 2016, Betaseron 2016, Copaxone 2016, Extavia 2016, Gilenya 2016, Glatopa 2016, Lemtrada 2016, mitoxantrone 2017, Novantrone 2012, Ocrevus 2017, Plegridy 2016, Rebif 2015, Tecfidera 2017, Tysabri 2016, Zinbryta 2017)

- 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 biologic response modifiers in reducing the frequency of relapses and delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on magnetic resonance imaging (MRI), and disability progression for the interferons and glatiramer acetate were published in the 1990's (*Jacobs et al 1996, Johnson et al, 1995, The 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 subcutaneous [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*). The results of 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 higher dose Rebif (IFN β -1a SC 3 times weekly or every other day) or glatiramer acetate (*Khan et al 2001a, Khan et al 2001b, Barbero et al 2006, Durelli et al 2002, Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008*).
- In a meta-analysis of 5 randomized studies comparing interferons with glatiramer acetate, there were no significant differences between interferons 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 interferons than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; P=0.002).
 - While 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 interferons 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).
- 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 secondary progressive MS 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 interferon NAb (*Govindappa et al 2015*). NAb development was most frequent with interferon β -1b, followed by interferon β -1a SC, and lowest with interferon 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 annualized relapse rate (ARR) for the combination therapy (IFN β -1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) ($P=0.27$). The ARR was 0.12 for the combination therapy, 0.16 for IFN β -1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFN β -1a, reducing the risk of exacerbation by 31% ($P=0.027$), and IFN β -1a + glatiramer acetate performed significantly better than IFN β -1a, reducing the risk of exacerbation by 25% ($P=0.022$). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume (*Lublin et al 2013*).
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively (*Coyle 2008, Portaccio et al 2008*). According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another first-line therapy is safe and effective (*Caon et al 2006, Zwibel 2006, Carra et al 2008*). Patients switching to glatiramer acetate after experiencing inadequate response to IFN β -1a therapy experienced 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*).
- Glatiramer acetate 20 mg daily and 40 mg 3 times weekly have not been directly compared. 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, multi-center, randomized, placebo-controlled trial. Eligible adult patients had RRMS with baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β -1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
 - At week 48, ARRs were significantly lower in the peginterferon β -1a every 2 week group (ARR=0.256; $P=0.0007$) and peginterferon β -1a every 4 week group (ARR=0.288; $P=0.0114$) compared to placebo (ARR=0.397).
 - There were also significant differences between the peginterferon β -1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 ($P=0.0003$ and $P=0.02$, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period was significantly lower in the peginterferon β -1a groups (both 6.8%; $P=0.0383$ for every 2 weeks group; $P=0.038$ for every 4 weeks group) compared to placebo (10.5%).
 - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β -1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; $P<0.0001$). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β -1a every 2 weeks compared to placebo ($P<0.0001$).
 - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β -1a groups compared to placebo (*Calabresi et al 2014b*).
 - NAb to interferon β -1a were identified in <1% of all groups after 1 year (peginterferon β -1a every 2 weeks, 4 patients; peginterferon β -1a every 4 weeks, 2 patients; placebo, 2 patients) (*Calabresi et al 2014b*). Preliminary data on NAb development to peginterferon β -1a over 2 years showed <1% for all groups (*White et al 2014*).
- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β -1a (the “placebo-switch group”). Peginterferon β -1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower

in the peginterferon β -1a every 2 weeks group (ARR 0.221; $P=0.0001$ vs placebo-switch group; $P=0.0209$ vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β -1a every 4 week group (ARR 0.291). The peginterferon β -1a every 4 week group (ARR 0.291; $P=NS$ vs placebo-switch group) was not significantly different than the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β -1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weight hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β -1a every 2 weeks group compared to the placebo-switch group (*Calabresi et al 2014b, Kieseier et al 2014*).

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) 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 IM IFN β -1a were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IM IFN β -1a. Patients switched from IFN β -1a to fingolimod experienced fewer adverse events compared to treatment with IFN β -1a 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 2014a*). Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio were evaluated in two Phase 3, randomized, double-blind, placebo-controlled trials – the TEMSO trial (O'Connor et al, 2011) and the TOWER trial (*Confavreux et al 2014*). In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
- The percentage of patients with confirmed disability progression was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; $P=0.03$) (*O'Connor et al 2011*).
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan (*O'Connor et al 2006*).
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability (*Confavreux et al 2014*).
- Teriflunomide and Rebif were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif (*Vermersch et al 2014*).

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two phase 3 studies: DEFINE and CONFIRM (*Gold et al 2012, Fox et al 2012, Xu et al 2015*). DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in patients with RRMS. There were 1237 patients enrolled, and the trial duration was 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl

fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression (*Gold et al 2012*).

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

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years (*Polman et al 2006, Pucci et al 2011, Rudick et al 2006*). The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo (*Polman et al 2006*). In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFN β -1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab and 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 randomized, Phase 3, open-label trials in patients with relapsing forms of MS – CARE-MS 1 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 intravenously for 3 consecutive days at the initiation of treatment and at month 12.
 - The CARE-MS 1 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 interferon beta 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 1 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%).
 - In the CARE-MS II trial, alemtuzumab significantly reduced 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 1 and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year (*Garnock-Jones 2014*).

Zinbryta (daclizumab)

- The efficacy and safety of daclizumab were studied in 2 pivotal trials: SELECT and DECIDE. The primary outcome measure in both studies was the ARR.
 - SELECT was a 52-week, Phase 2, double-blind, placebo-controlled, multicenter, RCT (N=621) that compared low and high doses of daclizumab to placebo (*Gold et al 2013*). The 52-week extension study (entitled SELECTION)

assessed the safety and immunogenicity of extended treatment with daclizumab (*Giovannoni et al 2014*). The SELECTED study enrolled 90% of patients who completed SELECTION and assessed the long-term safety and efficacy of daclizumab (*Gold et al 2016*). At 52 weeks, daclizumab demonstrated a statistically significant effect on the ARR compared to placebo (0.211 vs 0.458; 54% relative reduction in ARR, $P < 0.0001$) (*Gold et al 2013*). Reductions in MS disease activity achieved during the first year of monotherapy with daclizumab were sustained, while the risk of adverse events and immunogenicity did not appear to increase during the second year of treatment (*Giovannoni et al 2014*). The adverse event incidence did not increase with extension of therapy into a third year in SELECTED; the safety profile was similar to that previously observed.

- DECIDE was a 144-week, Phase 3, double-blind, active-control, multicenter, RCT (N=1841) that compared daclizumab 150 mg monthly to Avonex (IFN β -1a) 30 mcg weekly (*Kappos et al 2015*). Daclizumab had a statistically significant effect on the ARR compared to Avonex (0.216 vs 0.393; 45% relative reduction in ARR, $P < 0.0001$).

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO (*Hauser et al 2017[a]*, *Montalban et al 2017*).
 - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multi-center, 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 beta-1a; 44 mcg administered by SC injection 3 times per week) in 1656 patients with RMS (*Hauser et al 2017*, *ClinicalTrials.gov Web site*, *Ocrevus Formulary Submission Dossier 2017*).
 - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
 - Ocrelizumab achieved statistically significant reductions in the ARR vs. Rebif across both trials (primary endpoint).
 - OPERA I (0.16 vs. 0.29; 46% lower rate with ocrelizumab; $P < 0.001$)
 - OPERA II (0.16 vs. 0.29; 47% lower rate; $P < 0.001$)
 - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs. Rebif (9.1% vs. 13.6%; hazard ratio [HR]=0.60, 95% CI: 0.45 to 0.81; $P < 0.001$). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs. 10.5%; HR=0.60, 95% CI: 0.43 to 0.84; $P = 0.003$. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs. 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; $P = 0.02$).
 - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs. Rebif (secondary endpoint).
 - OPERA I: 0.02 vs. 0.29 (rate ratio=0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; $P < 0.001$)
 - OPERA II: 0.02 vs. 0.42 (rate ratio=0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; $P < 0.001$)
 - The most common adverse events (AEs) were infusion-related reactions and infections.
 - No opportunistic infections, including PML were reported in any group over the duration of either trial.
 - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs. 0.2% (2/826) of Rebif-treated patients.
 - Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
 - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.
 - ORATORIO was an event-driven, Phase 3, double-blind, multi-center, 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*). DB 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 (BL), with nearly 50% fewer lesions in the placebo group (1.21 vs. 0.6) (*FDA Medical and Summary Reviews 2017*).
- The percentages of patients with 12-week confirmed disability progression (CDP; primary endpoint) were 32.9% with ocrelizumab vs. 39.3% with placebo (HR=0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; P=0.03).
- The percentages of patients with 24-week CDP (secondary endpoint) were 29.6% with ocrelizumab vs. 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; P=0.04).
- Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
 - The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
 - From BL 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 OL 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 timed 25-foot walk (T25FW) (*Goodman et al 2009, Jensen et al 2014, Ruck et al 2014*).
 - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months (*Ruck et al 2014*).

Clinically Isolated Syndrome (CIS)

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

- In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a clinically definite MS diagnosis by 45% compared to placebo in patients with CIS (P=0.005). In addition, the time for 25% of patients to convert to clinically definite MS 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 clinically definite MS 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 clinically definite MS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; P=0.0002) (Comi et al 2012).
- A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of clinically definite MS with IFN therapy compared to placebo (P<0.0001) (Clerico et al 2008). A 10-year, multicenter, randomized clinical trial 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).
- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining clinically definite MS compared to placebo (Miller et al 2014). Teriflunomide 14 mg reduced the risk of conversion to clinically definite MS 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 clinically definite MS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; P=0.0271).

Progressive MS

- The role of the MS biologic response modifiers in the treatment of primary or secondary progressive MS has not been determined; mitoxantrone is FDA-approved for treating some of these forms of MS, 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, secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis (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, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data including cohort data for mitoxantrone. Evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia (Marriott et al 2010).
- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS, and due to being off-label, these uses are not included in Table 2. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with primary progressive MS (Wolinsky et al 2007).
- 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 ($I^2=57%$) (La Mantia et al 2013).

Decisions to discontinue DMTs in MS

- Patient with RRMS eventually progress to secondary progressive MS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for progressive MS. 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 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. Low strength evidence from 1 study reported that IFN use did not change disability progression in patients with RRMS. Most patients discontinue MS therapy after 2 or 3 years. Several observational studies have been published on the risks of relapse and rebound of disease activity following the interruption or discontinuation of natalizumab. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy.

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 daclizumab (46%) and 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 pegIFN β , dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab (*Fogarty et al 2016*).
- RCTs (n=39) evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS (*Tramacere et al 2015*). Drugs included were IFN β -1b, IFN β -1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegIFN 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: Lemtrada, mitoxantrone, Tysabri, and Gilenya were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N=17,897):
 - Lemtrada: 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
 - Tysabri: RR=0.56, 95% CI: 0.43 to 0.73; high quality evidence
 - Gilenya: RR=0.63, 95% CI: 0.53 to 0.74; low quality evidence
 - Tecfidera: RR=0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
 - Zinbryta: RR=0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
 - Copaxone: RR=0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
 - Relapses over 24 months vs placebo (26 studies; N=16,800):
 - Lemtrada: 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
 - Tysabri: RR=0.56, 95% CI: 0.47 to 0.66; high quality evidence
 - Gilenya: 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
 - Lemtrada: RR=0.35, 95% CI: 0.26 to 0.48; low quality evidence
 - Tysabri: 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 AEs compared to placebo over 12 months were reported for Aubagio (RR=2.24, 95% CI: 1.5 to 3.34); Plegridy (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 Gilenya (RR=8.26, 95% CI: 3.25 to 20.97).
 - Over 24 months, only Gilenya had a significantly higher proportion of participants who withdrew due to any AE (RR vs placebo=1.69, 95% CI: 1.32 to 2.17).
 - mitoxantrone: RR=9.82, 95% CI: 0.54 to 168.84
 - Tysabri: RR=1.53, 95% CI: 0.93 to 2.53
 - Lemtrada: 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, Tysabri 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, Tysabri 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.
 - Tysabri 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, intravenous 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 Tysabri and Lemtrada, 50% for Gilenya or Tecfidera, and 30% for SC IFNs, Copaxone, or Aubagio.
 - 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 Gilenya (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for Tecfidera (0.76, 95% CI: 0.62 to 0.93) compared with Copaxone.
 - Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, Tysabri, Gilenya, Aubagio, and Tecfidera; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for Tysabri to 0.74 (95% CI: 0.57 to 0.96) for Aubagio. Between-treatment differences were less apparent for risk of sustained disability progression.
 - Among active comparisons, the risk of sustained disability progression was statistically lower for Lemtrada (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 Lemtrada compared with Rebif, and more favorable for all 3 of Gilenya, Betaseron, and Rebif compared with Avonex. Compared with Copaxone, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
 - The incidence of serious AEs 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 Lemtrada.

CLINICAL GUIDELINES

- National treatment guidelines from the American Academy of Neurology (AAN) (published in 2002 and reaffirmed in 2008) stated that on the basis of several consistent Class I studies (ie, prospective RCTs with masked outcome assessments in representative populations), IFN β has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with MS or with CIS who are at high risk of developing MS (*Goodin et al 2002*). Treatment of MS with IFN β produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression. As a result, it is appropriate to consider IFN β for treatment in any patient who is at high risk for developing clinically definite MS (CDMS), or who already has either RRMS or SPMS and is still experiencing relapses. On the basis of Class I evidence, glatiramer acetate has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with RRMS. Treatment with glatiramer acetate produces a beneficial effect on MRI measures of disease severity, such as T2 disease burden, and possibly also slows sustained disability progression in patients with RRMS. As a result, it is appropriate to consider glatiramer acetate for treatment in any patient who has RRMS.
- In a 2008 Disease Management Consensus Statement, the National Clinical Advisory Board of the National Multiple Sclerosis Society stated the following: (*Miller et al 2008*)

- Initiation of treatment with an IFN β medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS.
- Treatment with mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with SPMS who are worsening, whether or not relapses are occurring.
- 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*).
- With an increasing number of options for the treatment of RRMS, the place in therapy for an individual agent is not straightforward. Treatment decisions will likely be based a consideration of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences. The 2015 AAN position statement supports access to all DMT for patients with MS. In addition, step therapy should be driven by evidence-based clinical and safety information and not just based on costs. Highly individualized treatment decisions are necessary for patients with MS according to the AAN (*Corboy et al 2015*).
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation (*Scolding et al 2015*). Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including pegIFN), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- In March 2017, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS. Major recommendations included the following:
 - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing or primary progressive MS, regardless of the person's age; for individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded; and for individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.
 - 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
 - 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.
 - 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:
 - 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.
 - 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.

SAFETY SUMMARY

- Warnings for IFN β include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, and risk of severe hepatic injury. IFN β (Avonex, Rebif, Betaseron, Extavia, and Plegridy) is associated with influenza-like symptoms including injection site reactions, musculoskeletal pain, fatigue, and headache. All IFN β products carry a warning for thrombotic microangiopathy

including thrombotic thrombocytopenia 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, systemic reaction of flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria immediately following injection. Injection site reactions including lipodystrophy 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.
- Fingolimod was approved with a risk evaluation and mitigation strategies program (REMS) to inform healthcare providers about the serious risks including bradyarrhythmia, atrioventricular block, infections, macular edema, respiratory effects, hepatic effects, fetal risk, increased blood pressure, basal cell carcinoma, immune system effects following discontinuation, and hypersensitivity reactions. 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 may take up to 2 months so monitoring for infections should continue during this time. Do not start fingolimod in patients with active acute or chronic infection until the infection is resolved. Establish immunity to varicella zoster virus prior to therapy initiation. Cases of PML have occurred in the postmarketing setting in patients who were treated with fingolimod for at least 2 years. A warning for PML has been added to the fingolimod labeling; at the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed.
- Teriflunomide is contraindicated in patients with severe hepatic impairment; patients who are pregnant, of childbearing potential, or that are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryo lethality that occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include risk of leukopenia, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels over 2 weeks. 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).
- Dimethyl fumarate has no contraindications, except in patients with hypersensitivity to dimethyl fumarate or any excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury reported in the post-marketing setting. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following dimethyl fumarate therapy. Common adverse events (incidence $\geq 10\%$ and $\geq 2\%$ 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 temporary dose reduction to 120 mg twice daily may reduce flushing.
- 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 to natalizumab. Other warnings with natalizumab include hypersensitivity reactions, increased risk of Herpes encephalitis and meningitis, increased risk of infections, and hepatotoxicity. The most common adverse reactions (incidence $\geq 10\%$) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea (not otherwise specified), and rash.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure (CHF), 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.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, and the possibility of an increased risk of malignancies.

Alemtuzumab is only available through a restricted distribution and REMS program which requires the member, provider, pharmacy and infusion facility to be certified by the REMS program. Approximately one-third of patients who receive alemtuzumab develop 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.

- Daclizumab is contraindicated in patients with pre-existing hepatic disease or hepatic impairment, including serum ALT or aspartate aminotransferase (AST) at least 2 times the upper limit of normal (ULN); history of autoimmune hepatitis or other autoimmune condition involving the liver; and history of hypersensitivity to daclizumab or any other components of the formulation – use in such patients may result in anaphylaxis or life-threatening multi-organ hypersensitivity. Daclizumab carries boxed warnings for hepatic injury including autoimmune hepatitis and other immune-mediated disorders including skin reactions, lymphadenopathy, non-infectious colitis, and others. Daclizumab is available only through a restricted distribution program called the daclizumab REMS Program.
 - Daclizumab can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. In clinical trials, 1 patient died due to autoimmune hepatitis. Liver injury, including autoimmune hepatitis, can occur at any time during treatment with daclizumab, with cases reported up to 4 months after the last dose of daclizumab. Serum transaminases (ALT and AST) and total bilirubin levels should be tested prior to starting treatment with daclizumab, monthly and before the next dose of daclizumab, and then for 6 months after the last dose of daclizumab. Treatment discontinuation or interruption may be required based on elevations in liver function tests.
 - Overall, serious immune-mediated conditions were observed in 5% of patients treated with daclizumab. If a patient develops a serious immune-mediated disorder, treatment with daclizumab may need to be stopped, and the patient should be referred to a specialist to ensure comprehensive diagnostic evaluation and appropriate treatment. Some patients required systemic corticosteroids or other immunosuppressant treatment for autoimmune hepatitis or other immune-mediated disorders and continued this treatment after the last dose of daclizumab.
 - Other warnings and precautions include acute hypersensitivity, infections, and depression and suicide.
 - The most common adverse events ($\geq 5\%$ and $\geq 2\%$ higher than comparator) with daclizumab use were nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, and lymphadenopathy compared with Avonex; and upper respiratory tract infection, depression, rash, pharyngitis, and increased ALT compared with placebo.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
 - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study (Kappos et al [2011]) was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs. 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) (Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017).
 - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs. in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
 - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with RMS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared (FDA approval letter 2017).
 - No cases of PML have been reported to date in any studies of ocrelizumab (Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017).
 - In patients with RMS, the most common adverse reactions with ocrelizumab (incidence $\geq 10\%$ and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse

reactions (incidence $\geq 10\%$ and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.

- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment ($\text{CrCl} \leq 50$ mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine can 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 adverse reactions in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence $\geq 2\%$ and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	<p>May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve.</p> <p>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 Ampyra should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment ($\text{CrCl} \leq 50$ mL/min).</p> <p>Based on animal data, dalfampridine may cause fetal harm.</p>
Aubagio (teriflunomide)	Tablets	Oral	Once daily	<p>May be taken with or without food.</p> <p>No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment.</p> <p>Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<p>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.</p> <p>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.</p>
Avonex (interferon β -1a)	Injection	IM	<p>Once weekly</p> <p><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.</p>	<p>Following initial administration by a trained healthcare provider, Avonex may be self-administered.</p> <p>Rotate injection sites to minimize the likelihood of injection site reactions.</p> <p>Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use.</p> <p>Use caution in patients with hepatic dysfunction.</p>
Betaseron (interferon β -1b)	Injection	SC	<p>Every other day</p> <p><u>Titration:</u> Generally, start at 0.0625 mg (0.25 mL) every other day,</p>	<p>Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered.</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			and increase over a 6-week period to 0.25 mg (1 mL) every other day.	<p>Rotate injection sites to minimize the likelihood of injection site reactions.</p> <p>Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.</p>
Copaxone, Glatopa (glatiramer acetate)	Injection	SC	<p>20 mg <u>once daily</u> OR 40 mg <u>3 times per week</u> at least 48 hours apart</p> <p><u>Note:</u> The 2 strengths are not interchangeable.</p>	<p>Following initial administration by a trained healthcare provider, Glatiramer acetate may be self-administered.</p> <p>Areas for SC self-injection include arms, abdomen, hips, and thighs.</p>
Extavia (interferon β -1b)	Injection	SC	<p>Every other day</p> <p><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.</p>	<p>Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered.</p> <p>Rotate injection sites to minimize the likelihood of injection site reactions.</p> <p>Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.</p>
Gilenya (fingolimod) [†]	Capsules	Oral	<p>Once daily</p> <p><u>Note:</u> 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>May be taken with or without food.</p> <p><u>First dose monitoring:</u> 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 <45 bpm, atrioventricular (AV) block, or if lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first dose</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<p>monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes.</p> <p>Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment.</p> <p>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.</p>
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 12 months after the first treatment course</p> <p><u>Important monitoring:</u> Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); and a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter).</p> <p>Conduct baseline and yearly</p>	<p>Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion.</p> <p>Pre-medicate with corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course.</p> <p>Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of two months after completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later.</p> <p>Patients should complete any necessary immunizations at least</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
mitoxantrone	Injection	IV	<p>skin exams to monitor for melanoma.</p> <p>Every 3 months</p> <p>Note: 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 congestive heart failure develop at any time during treatment with mitoxantrone.</p> <p>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.</p> <p>Liver function tests should be monitored prior to each course of therapy.</p>	<p>6 weeks prior to treatment with alemtuzumab.</p> <p>For MS-related indications: 12 mg/m² given as a short IV infusion over 5 to 15 minutes</p> <p>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.</p> <p>Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm³.</p> <p>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.</p> <p>Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.</p>
Ocrevus (ocrelizumab)	Injection	IV	<p>Every 6 months (24 weeks)</p> <p>Titration: 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> <p>Hepatitis B virus screening is required before the first dose.</p>	<p>Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details.</p> <p>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.</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<p>Administer all necessary immunizations according to immunization guidelines at least 6 weeks prior to initiation of ocrelizumab.</p> <p>Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.</p>
Plegridy (peginterferon β -1a)	Injection	SC	<p>Every 14 days</p> <p><u>Titration:</u> Start with 63 micrograms on day 1, 94 micrograms on day 15, and 125 micrograms (full dose) on day 29</p>	<p>Following initial administration by a trained healthcare provider, Plegridy may be self-administered.</p> <p>Patients should be advised to rotate injection sites; the usual sites are the abdomen, back of the upper arm, and thigh.</p> <p>Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms.</p> <p>Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.</p>
Rebif (interferon β -1a)	Injection	SC	<p>Three times per week at least 48 hours apart</p> <p><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</p>	<p>Following initial administration by a trained healthcare provider, Rebif may be self-administered.</p> <p>Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis.</p> <p>Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved.</p> <p>Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Tecfidera (dimethyl fumarate)	Capsules	Oral	<p>Twice daily</p> <p><u>Titration:</u> 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>	<p>treatment days.</p> <p>May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food.</p> <p>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.</p> <p>Obtain a complete blood cell count including lymphocyte count before initiation of therapy.</p> <p>Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with dimethyl fumarate.</p>
Tysabri (natalizumab) [†]	Injection	IV	Once a month (every 4 weeks)	<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> <p>Patients should be observed during the infusion and for 1 hour after the infusion is complete.</p>
Zinbryta (daclizumab) [†]	Injection	SC	Once a month (every 4 weeks)	<p>Following initial administration by a trained healthcare provider, daclizumab may be self-administered.</p> <p>Sites for injection include the thigh, abdomen, and back of the upper arm.</p> <p>Prior to initiating daclizumab, obtain and evaluate the following: serum transaminases (ALT and AST) and total bilirubin levels. Initiation of daclizumab is contraindicated in patients with</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<p>pre-existing hepatic disease or hepatic impairment including an ALT or AST at least 2 times the upper limit of normal.</p> <p>Avoid initiating daclizumab in patients with tuberculosis or other severe active infection; daclizumab is contraindicated in patients with pre-existing hepatic disease (ie, Hepatitis B or C).</p> <p>Test transaminase levels and total bilirubin monthly and assess before the next dose of daclizumab and follow transaminase levels and total bilirubin monthly for 6 months after the last dose of daclizumab. The interruption or discontinuation of daclizumab therapy is recommended for the management of certain liver test abnormalities; see the package insert for more details.</p>

*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 RRMS 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 RRMS begin DMTs (*MS Coalition 2017*).
- IFN β products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFN β or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period following treatment initiation with IFN β or Copaxone (glatiramer acetate) (*MS Coalition 2017*). Head-to-head clinical trials have found IFN β and glatiramer acetate to be comparable in terms of efficacy. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with the low dose IM IFN β -1a compared to the 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 including Plegridy. With IFN β , use caution in patients with depression or other mood disorders. Peginterferon β -1a every 2 weeks has demonstrated efficacy in reducing the ARR in relapsing forms of MS compared to placebo. Potential advantages of Plegridy are less frequent administration every 2 weeks and possibly the reduced risk of neutralizing antibody development. Adverse effect profile is similar among the interferons.
- 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. Generic glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial biologic response modifier therapy with glatiramer acetate or IFN β , primarily due to intolerable adverse effects or perceived 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 biologic response modifiers should be made accessible, and the choice of initial treatment should be based on patient-specific factors (Corboy et al 2015, MS Coalition 2017, Scolding et al 2015). 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 to another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different biologic response modifier (Coyle 2008, Portaccio et al 2008).

- There are now 3 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence to their drug regimen (Sanvito et al 2011). The available oral drugs each have different mechanisms of action and tolerability profiles. The oral products have not been compared to one another in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
- Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression (Kappos et al 2010). In a trial comparing fingolimod to 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.
 - In the postmarketing setting, third degree atrioventricular (AV) block and AV block with junctional escape have been observed. Isolated delayed events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. The relationship of these events to fingolimod is uncertain.
- 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.
- 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) (O'Connor et al, 2011). Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Tysabri (natalizumab) has demonstrated very high efficacy vs. placebo and although PML is a major safety concern, the overall incidence of PML has remained low (0.4%). The FDA's update to the labeled indication of Tysabri, with removal of the statement that it is recommended for patients who have had an inadequate response to, or are unable to tolerate an alternate MS therapy, suggests that natalizumab can be considered a first-line agent in RMS, as long as the benefit of higher efficacy is sufficient to offset the risk. Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a second highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The convenient 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).
- Zinbryta (daclizumab) is another option for patients with relapsing forms of MS who are not candidates for natalizumab and/or alemtuzumab. Daclizumab demonstrated statistically significant effects on ARR vs. Avonex and vs placebo, which place it near to or just ahead of the orals, but below the natalizumab level of efficacy. While daclizumab carries boxed warnings for hepatic injury and other immune-mediated disorders (ie, cutaneous reactions), there have been as yet no reported cases of PML.
- 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).

- The approval of Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of RMS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is, therefore, reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of $\geq 20\%$ are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.

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Publication Date: July 3, 2017