



Multiple Sclerosis Agents Therapeutic Class Review (TCR)

April 7, 2020

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
alemtuzumab (Lemtrada®) ¹	Genzyme	<ul style="list-style-type: none"> Relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults Due to its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of multiple sclerosis (MS) Due to its safety profile, alemtuzumab is not recommended for patients with clinically isolated syndrome (CIS)
cladribine (Mavenclad®) ²	EMD Serono	<ul style="list-style-type: none"> Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease, in adults Due to its safety profile, the use of cladribine should generally be reserved for patients who have had an inadequate response to or are unable to tolerate an alternate drug indicated to treat MS Due to its safety profile, cladribine is not recommended for patients with CIS
dalfampridine (Ampyra®) ³	generic, Acorda	<ul style="list-style-type: none"> Improve walking in patients with MS, demonstrated by an increase in walking speed
dimethyl fumarate (Tecfidera®) ⁴	Biogen-Idec	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
diroximel fumarate (Vumerity™) ⁵	Biogen-Idec	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
fingolimod (Gilenya®) ⁶	Novartis	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older
glatiramer acetate (Copaxone®) ⁷	generic*, Teva Neurosciences	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
interferon β-1 ^a IM (Avonex®) ⁸	Biogen-Idec	<ul style="list-style-type: none"> Relapsing forms of multiple sclerosis, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
interferon β-1a SC (Rebif®) ⁹	EMD Serono	
interferon β-1a SC (pegylated) (Plegridy®) ¹⁰	Biogen-Idec	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
interferon β-1b (Betaseron®) ¹¹	Bayer	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
interferon β-1b (Extavia®) ¹²	Novartis	

* Sandoz' Glatopa™ is available as a branded generic of Copaxone; it was approved via an Abbreviated New Drug Application (ANDA).¹³

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
natalizumab (Tysabri®) ¹⁴	Biogen-Idec	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults[†] Inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn’s disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies, including other biologic agents
ocrelizumab (Ocrevus®) ¹⁵	Genentech	<ul style="list-style-type: none"> Relapsing MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults Primary progressive MS (PPMS), in adults
siponimod (Mayzent®) ¹⁶	Novartis	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
teriflunomide (Aubagio®) ¹⁷	Sanofi-Aventis	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults

[†] Natalizumab (Tysabri) increases the risk of progressive multifocal leukoencephalopathy (PML); a risk and benefit assessment should be completed prior to initiation and during treatment.

On March 2, 2018, Abbvie/Biogen announced a voluntary global withdrawal of the interleukin-2 blocking antibody, daclizumab (Zinbryta®), following 7 reports of serious inflammatory encephalitis and meningoencephalitis.¹⁸ Daclizumab is no longer included in this review.

OVERVIEW

Multiple sclerosis (MS) is a complex human autoimmune-type inflammatory disease of the central nervous system (CNS).^{19,20,21} Although the etiology is predominantly unknown, MS is characterized pathologically by demyelination and subsequent axonal degeneration. The nerve degeneration associated with MS can result in a wide variety of symptoms, including sensory disturbances in the limbs (e.g., numbness, paresthesias, burning, pain), optic nerve dysfunction, ataxia, fatigue, and bladder, bowel, and sexual dysfunction. Severe cases may result in partial or complete paralysis. MS results in significant physical disability in over 30% of patients within 20 to 25 years of onset. Cognitive dysfunction occurs in an estimated 40% to 70% of MS patients, but no correlation exists with the degree of physical disability. It is estimated that nearly 1 million people are living with MS in the United States (US).^{22,23} Multiple sclerosis occurs most commonly in Caucasians, with rare cases in African-Americans and Asian-Americans. Like other presumed autoimmune diseases, MS is more common in females and clinical symptoms often first manifest during young adulthood. The prevalence of MS varies widely with location; the highest prevalence is reported at higher latitudes in northern regions of Europe and North America.

At onset of the disease, MS can be categorized as either relapsing-remitting MS (observed in 85% to 90% of patients) or primary progressive MS (observed in 10% of patients). Relapses or “attacks” typically present subacutely, with symptoms developing over hours to several days, persisting for several days or weeks, and then gradually dissipating. The attacks are likely caused by the migration of activated, myelin-reactive T cells into the CNS, resulting in acute inflammation with associated edema. The use of high-dose corticosteroids to quickly relieve MS symptoms suggests that acute edema and its subsequent resolution underlie the clinical relapse and remission, respectively.²⁴ Detailed guidelines on

the diagnosis of MS are available.^{25,26,27} The clinical course of MS, therefore, falls into 1 of the following categories, with the potential to progress from less severe to more serious types and cannot be predicted with certainty:^{28,29,30}

- **Clinically isolated syndromes (CIS):** the first episode of neurologic symptoms due to inflammation or demyelination lasting at least 24 hours. Patients with magnetic resonance imaging (MRI)-detected brain lesions consistent with MS are at high risk of developing MS.
- **Relapsing-remitting MS (RRMS):** Clearly defined, self-limited attacks of neurologic dysfunction, followed by periods of remission without disease progression. Most patients experience a recovery of function that is often, but not always, complete.
- **Primary progressive MS (PPMS):** Nearly continuous worsening of disease not interrupted by distinct relapses; some individuals have occasional plateaus and temporary minor improvements.
- **Secondary progressive MS (SPMS):** Relapsing-remitting disease course at onset, followed by progression with or without occasional relapses, minor remissions, and plateaus; most patients eventually convert to progressive MS.

The term radiologically isolated syndrome (RIS) has also been used, although it is not considered a clinical course.³¹ RIS is sometimes used to classify those who have MRI abnormalities consistent with MS, and not explained by another disease state, but who do not have neurologic abnormalities.

Interferons are a family of naturally occurring proteins produced by cells in response to viral infection. Three major groups have been identified: interferon alpha, beta, and gamma. Interferon alpha and beta are grouped as Type I and interferon gamma is Type II. Interferon beta (IFN β) and glatiramer are immunoregulatory agents that have been shown to reduce the relapse rate and possibly slow disease progression in MS. Treatment with these medications has been shown to reduce the frequency and severity of relapses in persons with RRMS by approximately one-third, improve brain lesion activity on MRI, and possibly modify disease progression.³²

Ocrelizumab marks the first medication approved for the treatment of PPMS and is also approved for relapsing MS. Multiple treatment strategies that are not FDA approved for PPMS have been used historically, but few provide significant benefit on disease progression; thus, treatment of PPMS is often primarily symptomatic.³³

In 2018, the Guideline Development, Dissemination, and Implementation Subcommittee of the AAN developed and published practice guidelines for disease-modifying therapies (DMT) for adults with MS.³⁴ The multidisciplinary panel developed several recommendations using findings from a systematic review, a modified Delphi process, consensus, and patient engagement. The guidelines discuss patient counseling, including patient readiness, medication adherence, and treatment-related adverse effects; therapy initiation; and treatment selection, switching, and discontinuation. Notably, the guidelines clarify that prescribers should counsel patients with MS that treatments are intended to reduce relapses and new MRI lesion activity; they are not intended for symptom improvement (Level B). Regarding treatment initiation, AAN states that clinicians should offer DMT to people with relapsing forms of MS with recent clinical relapses or MRI activity (Level B). In addition, after discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS in those amenable to DMT (Level B). AAN further states that clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS

(Level B). Clinicians may recommend azathioprine or cladribine for people with relapsing forms of MS who do not have access to approved DMTs (Level C), but they should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks (Level B). Similarly, natalizumab treatment should only be initiated in people with MS with positive anti-JCV antibody indexes above 0.9 when there is a reasonable chance of benefit compared with the risk of progressive multifocal leukoencephalopathy (PML) (Level C). For PPMS, clinicians should offer ocrelizumab to those who are likely to benefit unless the risks outweigh the benefit (Level B). In addition, the recommendations emphasize a discussion regarding the importance of adherence in order to provide full efficacy (Level B). Siponimod and diroximel fumarate were approved after the publication of these guidelines, and cladribine was not approved for the treatment of MS at the time of publication.

Regarding treatment switching, clinicians should evaluate disease activity, adherence, adverse effects, and pharmacology when switching DMTs in people with breakthrough disease activity during DMT use (Level B).³⁵ A change to non-injectable or less frequently injected treatments or a change due to adverse effects impacting adherence may be considered based on patient feedback (both Level B). Furthermore, a switch (or dosage adjustment) may be warranted due to laboratory abnormalities, pregnancy, PML risk, malignancy, serious infections, and in those with select antibodies (all Level B). Clinicians should then advocate that patients with stable MS (e.g., no relapses, no disability progression, stable imaging) continue their current treatment unless the patient and prescriber decide that a trial off therapy is warranted (Level B); however, discontinuation may be advised in patients with SPMS who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (Expanded Disability Status Scale [EDSS] ≥ 7) for ≥ 2 years (Level C).

The International Pediatric MS Study Group provided insight on the treatment of MS and other demyelinating disorders in pediatric patients in a series of publications in 2016; although, these were published prior to the FDA approval of fingolimod for relapsing forms of MS in pediatric patients ≥ 10 years of age.^{36,37} The group states that DMT use in pediatric MS remains off-label in the majority of countries. Nonetheless, they recommend that clinicians treat children with MS in order to prevent relapses, prevent new lesions, and delay disability, which is of particular concern in pediatrics since they have a higher relapse rate and more significant inflammation on MRI. They state that IFN β and glatiramer should be considered standard of care in this population and treatment should be started early. Although the clinician should counsel families regarding realistic expectations, a treatment switch may be warranted if there is inadequate or suboptimal response. Clinical trials may be available and useful for those who require escalating or emerging treatments.

Neutralizing antibodies (Nabs) may occur with IFN β and may also disappear even with continued treatment. A report of the Therapeutics and Technology Assessment Subcommittee of the AAN assessed the clinical effect of these Nabs on efficacy of IFN β agents and found that Nabs are probably associated with a reduction in clinical and radiographic effectiveness of these agents.³⁸ The subcommittee further found that the rate of Nab production is probably less with IFN β -1a treatment than with IFN β -1b treatment, but the extent of the difference was difficult to determine. In addition, the intramuscular formulation of IFN β -1a (Avonex) appeared less immunogenic than the subcutaneous formulations of either IFN β -1a (Rebif) or IFN β -1b (Betaseron, Extavia). Moreover, there was insufficient evidence regarding the utility of Nab testing to recommend in whom testing should occur and how the results should be applied.

In 2019, the AAN issued guidelines regarding vaccinations in patients with MS.³⁹ The AAN recommends clinicians discuss immunization options with patients to develop an optimal strategy for each patient, taking into account all vaccine standards and local recommendations, patient risks and benefits, contraindications, and patient preferences. Notably, they recommend that prescribers should assess and address vaccination status at least 4 to 6 weeks prior to initiating immune-suppressing MS therapy, as advised by each agent’s prescribing information (Level B), and further state that clinicians should address vaccination status as soon as possible following diagnosis, regardless of the initial therapeutic plan, to prevent future treatment delays (Level C). They also recommend that all patients receive an annual influenza vaccine, unless contraindicated (Level B). The AAN recommends against the use of live attenuated vaccines in patients receiving immune-suppressing MS therapy or in those who have recently discontinued one of these agents; however, the use of these vaccines may be recommended if the risk of infection is high and alternatives are unavailable (Level C). Prescribers should also screen for select infections, including hepatitis, tuberculosis, and varicella zoster, as described in product labeling of individual products or regardless of this recommendation in endemic or high-risk areas (Level A), treating discovered latent infections (Level B), prior to initiating therapy. Vaccination should be delayed in patients experiencing a relapse until clinical resolution or no longer active (Level B).

The use of natalizumab (Tysabri) in the treatment of Crohn’s disease is not addressed in this therapeutic class review.

PHARMACOLOGY^{40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55}

As suggested by their name, the immunomodulators’ mechanism of action impacts the immunologic pathophysiology of MS. IFN β binds to cell surface-specific receptors, initiating a cascade of signaling pathways that end with the secretion of antiviral, antiproliferative, and immunomodulatory gene products. While IFN β has no direct effects in the CNS, it rapidly (within 2 weeks) blocks blood-brain barrier leakage and resolves gadolinium (Gd)-enhanced MRI activity.

Two subspecies of IFN β are indicated for use in MS: IFN β -1a (Avonex, Plegridy, Rebif) and IFN β -1b (Betaseron, Extavia). While both subspecies have similar biological effects, the extent of activity varies between the 2. Plegridy is a pegylated formulation of IFN β -1a. Two IFN β -1a products (Avonex, Rebif) are equipotent and the potency of the pegylated formulation (Plegridy) has not been compared to the other formulations. A study utilized *in vitro* stimulation of peripheral blood with each of the 2 IFN β products (Betaseron, Extavia) resulting in a dose-dependent increase in antiviral protein that was roughly equivalent for each agent on an International Unit (IU) basis.⁵⁶ This study and other published data indicate that 30 mcg IFN β -1a is equivalent to approximately 220 to 280 mcg IFN β -1b.⁵⁷

Alemtuzumab (Lemtrada) is a CD52 directed cytolytic monoclonal antibody. Although the exact mechanism of action of alemtuzumab for MS is unknown, it is presumed to involve binding to CD52, a cell surface antigen present on T and B lymphocytes. Following cell surface binding to T and B lymphocytes, alemtuzumab results in antibody-dependent cellular cytotoxicity and complement mediated lysis.

Cladribine (Mavenclad) is a purine antimetabolite that is thought to have cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes; however, its therapeutic effect in patients with MS has not been fully elucidated.

Although the mechanism of action of dalfampridine (Ampyra) has not been fully elucidated, in animal studies, dalfampridine has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels. Dalfampridine is a broad-spectrum potassium channel blocker.

Dimethyl fumarate (Tecfidera) and **diroximel fumarate (Vumerity)** share monomethyl fumarate (MMF) as a metabolite. These have been shown to activate the Nuclear factor-like (Nrf2) pathway in animal and human studies which may be the mechanism by which it achieves its therapeutic effect, but the exact mechanism is unknown. The Nrf2 pathway is involved in the cellular response to oxidative stress.

Fingolimod (Gilenya), once converted to the active metabolite, binds to sphingosine 1-phosphate receptors 1, 3, 4, and 5. **Siponimod (Mayzent) binds to sphingosine 1-phosphate (S1P) receptors 1 and 5.** This inhibits lymphocyte egress from lymph nodes, reducing their number in the peripheral blood.⁵⁸ While the exact mechanism of action for fingolimod **and siponimod** are unknown, it may involve the reduction of lymphocyte migration into the CNS.

Glatiramer (Copaxone), a synthetic molecule, is thought to inhibit the activation of myelin basic protein-reactive T cells and may also induce antigen-specific suppressor T cells (T cells with activity characterized by anti-inflammatory effects).^{59,60,61} Glatiramer produces a less rapid resolution of Gd-enhanced MRI activity, but glatiramer acetate-specific T cells are believed to have access to the CNS, where they exert anti-inflammatory and possibly neuroprotective effects.⁶²

Natalizumab (Tysabri) inhibits α 4-mediated adhesion of leukocytes (excluding neutrophils) to their counter-receptors by binding to the α 4-subunit of α 4 β 1 and α 4 β 7 integrins that are expressed on the leukocytes cell surface. These receptors include vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Ultimately, this prevents leukocytes from transmigrating across endothelium, such as the blood brain barrier. However, the exact mechanism of natalizumab in MS is unknown.

Ocrelizumab (Ocrevus) is a recombinant humanized CD20 monoclonal antibody. The precise mechanism in the treatment of MS is unknown; however, it targets and binds to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. This results in antibody-dependent cellular cytotoxicity and complement-mediated lysis.

Teriflunomide (Aubagio), the active metabolite of leflunomide, is an immunomodulator with anti-inflammatory properties that inhibits dihydro-orotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis. Although the mechanism of action of teriflunomide is not completely known, it may reduce the number of activated lymphocytes in the CNS.

PHARMACOKINETICS^{63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78}

It is suggested that intramuscular (IM) administration of IFN β -1a causes a greater area under the concentration-time curve for IFN β activity in the serum compared to subcutaneous (SC) administration.⁷⁹ Yet, several studies demonstrated no difference in biologic effects between the different routes of administration.^{80,81,82} The majority of evidence suggests that the route of IFN β administration is of no clinical importance

Drug	Tmax (hrs)	Half-life (hrs)	Peak Activity* (hrs)	Duration of Activity*
alemtuzumab injection (Lemtrada)	nd	2 weeks	nd	nd
cladribine (Mavenclad)	0.5-1.5	1 day	nd	nd
dalfampridine oral (Ampyra)	3-4	5.2-6.5	nd	nd
dimethyl fumarate oral (Tecfidera)	2-2.5	1	nd	1 day
diroximel fumarate oral (Vumerity)	2.5-3	1	nd	nd
fingolimod oral (Gilenya)	12-16	6-9 days	nd	nd
glatiramer SC injection (Copaxone)	nd	nd	nd	nd
IFN β -1a IM injection (Avonex)	6-36	8-54	48	at least 4 days
IFN β -1a SC injection (Rebif)	16	69	12-48	up to 4 days
IFN β -1a SC (pegylated) injection (Plegridy)	1-1.5 days	78	nd	nd
IFN β -1b SC injection (Betaseron)	1-8	0.13-4.3	40-124	7 days
IFN β -1b SC injection (Extavia)	1-8	0.13-4.3	40-124	7 days
natalizumab (Tysabri)	nd	7-15 days	nd	nd
ocrelizumab (Ocrevus)	nd	26 days	nd	nd
siponimod (Mayzent)	3-8	30	nd	nd
teriflunomide oral (Aubagio)	nd	18-19 days	nd	nd

*Activity was measured by the levels of biological response markers (e.g., 2', 5'-OAS activity, neopterin and beta 2-microglobulin), which are induced by IFN β -1a.

nd = no data

Tmax = time to peak serum concentration

CONTRAINDICATIONS/WARNINGS^{83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98}

alemtuzumab (Lemtrada)

Alemtuzumab is contraindicated in patients who are infected with human immunodeficiency virus (HIV) because it causes prolonged reductions of CD4+ lymphocyte.

Alemtuzumab carries boxed warnings for autoimmunity, infusion reactions, **stroke**, and malignancies.

Alemtuzumab can result in the formation of autoantibodies and increase the risk of serious autoimmune-mediated conditions. Immune thrombocytopenia (ITP), glomerular nephropathies, autoimmune thyroid disorders, **autoimmune hepatitis, vitiligo**, pneumonitis, and autoimmune cytopenias (e.g., neutropenia, hemolytic anemia, and pancytopenia) occurred in alemtuzumab-treated patients in clinical studies. **Cases of glomerular nephropathies and anti-glomerular basement membrane (anti-GBM) disease have been reported with alemtuzumab, some requiring dialysis or renal transplantation. If symptoms occur, urgent evaluation and treatment is required as these can be life-threatening.** Thyroid disorders have included Graves' disease, hyperthyroidism, hypothyroidism, autoimmune thyroiditis, and goiter. **Guillain-Barré also has been reported in postmarketing cases.** Patients should be monitored for these adverse effects. Monitor complete blood counts (CBC) with differential, serum creatinine levels **(and urine protein to creatinine ratio)**, serum transaminases and **total bilirubin**, and urinalysis with urine cell counts before and during treatment. **Appropriate**

monitoring is recommended until 48 months following the last infusion, as detailed in the product labeling. Further monitoring in select patients may be required.

Alemtuzumab also causes cytokine release syndrome resulting in infusion reactions, some of which may be serious and life threatening. Patients should be premedicated with a corticosteroid and monitored during treatment. Cases of alveolar hemorrhage and myocardial ischemia have also been reported within 48 hours of treatment. In addition case of neutropenia have been noted within 2 months of alemtuzumab infusion. Postmarketing cases of serious and life-threatening stroke (ischemic and hemorrhagic) have been reported within 3 days of alemtuzumab administration (most within 1 day). In addition, postmarketing cases of cervicocephalic (e.g., vertebral, carotid) arterial dissection involving multiple arteries have been reported within 3 days of alemtuzumab administration. Patients should be instructed to seek immediate medical attention if they experience symptoms related to stroke or cervicocephalic arterial dissection. In November 2018, the FDA issued a Drug Safety Communication regarding these cases, and the labeling has been updated accordingly.⁹⁹ Physicians should alert patients that this reactions may occur within 48 hours of infusion.

Alemtuzumab may increase the risk of malignancies including thyroid cancer, melanoma, lymphoproliferative disorders, and lymphoma. Patients and healthcare providers should monitor for signs and symptoms of malignancies. Caution should also be exercised when initiating alemtuzumab in patients with pre-existing or ongoing malignancies.

Alemtuzumab may increase the risk of acute acalculous cholecystitis. In controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with interferon beta-1a. The timing of onset ranged from < 24 hours to 2 months following alemtuzumab infusion. If this condition is suspected, the patient should be evaluated and treated promptly.

Infections were more common in alemtuzumab-treated patients compared to patients treated with interferon beta-1a in clinical trials; these included nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, herpetic infections, influenza, and bronchitis. Serious infections occurred in the alemtuzumab-treated patients, including appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection. Cases of opportunistic infections, including aspergillosis, coccidioidomycosis, histoplasmosis, *Pneumocystis jirovecii* pneumonia, nocardiosis, and cytomegalovirus infections, have been reported. Tuberculosis (TB) screening, according to local guidelines, should be completed prior to initiating therapy. Do not administer live viral vaccines following a course of alemtuzumab and consider delaying alemtuzumab administration in patients with active infection until the infection is fully controlled. In addition, cases of *Listeria monocytogenes* infections, including fatal cases, have been reported with alemtuzumab. These have occurred as early as 3 days following treatment initiation and for up to 8 months following discontinuation. Patients should avoid potential sources of *Listeria monocytogenes* and properly heat foods that may have *Listeria monocytogenes* (e.g., select dairy products, meats).

One postmarketing case of progressive multifocal leukoencephalopathy (PML) has been reported in a patient with MS treated with alemtuzumab, which was diagnosed 2 months after the second course of alemtuzumab and the patient subsequently developed immune reconstitution inflammatory syndrome (IRIS). The patient was not taking any other concomitant immunosuppressive medications and had not received treatment for MS for over 1 year. PML is a rare and serious brain infection caused by the John

Cunningham virus (JCV) and can be fatal. The JCV is a common virus that is harmless in most people but can cause PML in some patients who have weakened immune systems. Risk factors for PML development include presence of anti-JCV antibodies, prior use of immunosuppressants, and duration of therapy. Healthcare providers should monitor for any signs or symptoms of PML, taking into consideration that patients at a higher risk may need more frequent monitoring; any signs or symptoms of PML warrant immediate withholding of the possible offending agent and a diagnostic workup. MRI findings consistent with PML may be apparent before clinical signs or symptoms; any suspicious findings should lead to further investigation to allow for an early diagnosis of PML. Following discontinuation of another MS medication associated with PML, lower mortality and morbidity have been reported with other medications associated with PML in patients who were initially asymptomatic versus symptomatic patients. It is unknown if this difference is due to early detection and discontinuation or due to disease differences.

cladribine (Mavenclad)

Cladribine carries several contraindications, most of which are related to its warnings. In addition, it is contraindicated in patients with known hypersensitivity to cladribine.

Cladribine also is contraindicated in patients with current malignancy and carries a boxed warning for increased risk of malignancy compared to placebo; the benefits and risks of cladribine use should be evaluated prior to initiating therapy. In clinical studies, the incidence of malignancy was higher in cladribine-treated patients compared placebo-treated patients (0.27 versus 0.13 per 100 patient-years, respectively). These included cases of metastatic pancreatic carcinoma, malignant melanoma, and ovarian cancer. Notably, the incidence was higher in patients who received additional cladribine treatment within 2 years after the first 2 treatment courses (0.91 events per 100 patient-years). Therefore, after the completion of 2 treatment courses, do not administer additional cladribine treatment during the next 2 years.

Cladribine is contraindicated in women who are breastfeeding (within 10 days following the last dose) or pregnant and women and men of reproductive potential who do not plan to use effective contraception during the course of therapy and for ≥ 6 months following the last dose in each treatment course. The labeling has a boxed warning for increased risk of teratogenicity; pregnancy should be excluded prior to initiating cladribine.

Cladribine is contraindicated in patients with HIV or other active chronic infections (e.g., hepatitis, TB). Patients treated with cladribine are at an increased risk of infection, including herpes zoster, pyelonephritis, and fungal infections. Exclude diagnoses of hepatitis, HIV, and active TB prior to starting therapy. Delay treatment until acute infections are fully controlled. Treatment with cladribine in patients on immunosuppressive therapy is not recommended. No cases of PML were reported in clinical studies; however, PML has been reported with the use of intravenous cladribine in the oncology setting. An MRI should be obtained at baseline and within 3 months of starting the first treatment course of cladribine to evaluate for PML; withhold cladribine for any sign suggestive of PML and perform appropriate diagnostic tests.

Cladribine causes a dose-dependent reduction in lymphocyte count. The lymphocyte nadir typically occurred 2 to 3 months after the start of each treatment course. Median time to recovery was about 28 weeks. Serious cases of thrombocytopenia, neutropenia, and pancytopenia have also been reported

with cladribine. A CBC with differential should be obtained before, during, and after treatment; the lymphocyte count should be ≥ 800 cells/mL prior to start of therapy. A CBC with differential should also be obtained prior to the second course of therapy and 2 and 6 months after the start of each treatment course. If the lymphocyte count is < 200 cells/mL, interrupt cladribine and monitor lymphocyte count monthly until month 6. Thereafter, monitor lymphocyte count periodically as clinically indicated. In addition, administer herpes prophylaxis antiviral medication if lymphocyte count is < 200 cells/mL.

Vaccinations should be administered prior to therapy. Live or live-attenuated vaccines should be given 4 to 6 weeks prior to therapy.

Rarely, transfusion-associated graft-versus-host disease has been observed in patients treated with cladribine for non-MS treatment indications; irradiation of cellular blood components is recommended.

A higher incidence of liver injury has been reported with cladribine compared to placebo. Onset was as early as a few weeks to several months after starting therapy, and resolution was seen upon treatment discontinuation. Perform liver function tests prior to the first and second treatment courses. Interrupt therapy if signs of liver toxicity are demonstrated.

In clinical trials, a single case of life-threatening acute cardiac failure was reported with cladribine to treat MS, and cases of cardiac failure have been reported with parenteral use of cladribine for non-MS conditions.

dalfampridine (Ampyra)

Dalfampridine is contraindicated in patients with a history of seizures and in patients with moderate to severe renal impairment (creatinine clearance [CrCl] < 50 mL/minute) as dalfampridine is eliminated through the kidneys as unchanged drug. Dalfampridine is also contraindicated in patients with a history of hypersensitivity to dalfampridine or 4-aminopyridine, as cases of anaphylaxis have occurred.

Dalfampridine should not be administered concurrently with other forms of 4-aminopyridine (e.g., compounded formulations of the drug) since the active ingredient is the same. Urinary tract infections were reported more frequently in patients receiving dalfampridine (12%) compared to patients receiving placebo (8%). Dalfampridine can cause anaphylaxis and severe allergic reactions including respiratory compromise, urticaria, and angioedema; patients should discontinue dalfampridine immediately and seek medical attention if anaphylaxis occurs.

dimethyl fumarate (Tecfidera) and diroximel fumarate (Vumerity)

Dimethyl fumarate and diroximel fumarate can cause anaphylaxis and angioedema following the first dose and at any point during treatment. Prescribers should discuss this with patients, instructing them to seek medical attention should symptoms or signs of anaphylaxis or angioedema occur.

Dimethyl fumarate and diroximel fumarate may decrease lymphocyte counts. In clinical trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment and increased after stopping the agent, but the lymphocyte count did not return to baseline. A CBC, including lymphocyte count, should be obtained prior to initiating therapy with either agent, 6 months after treatment initiation, and again every 6 to 12 months thereafter. Therapy interruption should be

considered in patients with lymphocyte counts $< 0.5 \times 10^9/L$ that persist for more than 6 months. Treatment may need to be withheld. Monitoring should continue until the lymphocyte count has recovered, even if therapy has been withheld or discontinued.

Dimethyl fumarate and diroximel fumarate may cause flushing (e.g., redness, itching, burning sensation). In clinical trials, 40% of patients experienced flushing which generally began soon after initiation. The majority of patients experience flushing of mild to moderate severity.

Cases of liver injury have been reported with dimethyl fumarate with an onset ranging from a few days to several months following initiation; thus, this risk is also possible with dimethyl diroximel fumarate. Signs and symptoms of liver injury, including elevated serum aminotransferases and total bilirubin, have occurred. Abnormalities resolved upon treatment discontinuation; however, some cases resulted in hospitalization. Serum aminotransferase, alkaline phosphatase, and total bilirubin should be monitored prior to treatment and during treatment when clinically indicated. Discontinue these agents if liver injury is suspected.

Cases of PML have been reported with dimethyl fumarate; thus, this risk is also possible with dimethyl diroximel fumarate, as these agents share an active metabolite.¹⁰⁰ Monitor for any signs or symptoms of PML, taking into consideration that patients at a higher risk may need more frequent monitoring (e.g., lymphopenia); any signs or symptoms of PML warrant immediate withholding of the possible offending agent and a diagnostic workup. MRI findings consistent with PML may be apparent before clinical signs or symptoms; any suspicious findings should lead to further investigation to allow for an early diagnosis of PML. Lower mortality and morbidity have been reported with other medications associated with PML in patients who were initially asymptomatic versus symptomatic patients. It is unknown if this difference is due to early detection and discontinuation or due to disease differences.

Cases of herpes zoster and other serious opportunistic infections have been reported with dimethyl fumarate, and may be reported at any time during treatment; thus, this risk is also possible with diroximel fumarate. Serious infections may occur in patients with reduced and normal lymphocyte counts. Patients should be monitored for these infections and prescribers should consider withholding treatment until the infection has resolved.

fingolimod (Gilenya)

Fingolimod is contraindicated in patients who have had a hypersensitivity reaction (e.g., rash, urticaria, angioedema) to any component of the medication.

The FDA evaluated a report of a patient who died after the first dose of fingolimod plus clinical trial and post-market data including reports of patients who died of cardiovascular events or unknown causes.¹⁰¹ Although fingolimod was not definitively related to any of the deaths, the FDA remains concerned about cardiovascular effects of fingolimod after the first dose. Due to the risk of death from cardiac complications, fingolimod is contraindicated in patients who have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure during the previous 6 months, or with cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs. It is also contraindicated in patients who have a history or the presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless the patient has a functioning

pacemaker, in patients who have a baseline QTc interval \geq 500 msec, or patients who are receiving treatment with a Class Ia or Class III anti-arrhythmic drug.

The first dose of fingolimod can cause a decrease in heart rate and/or atrioventricular (AV) conduction. After the first dose, the heart rate decrease starts within 1 hour. The maximal decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8 to 10 hours post dose. A second period of decreased heart rate occurs within 24 hours after the first dose. In some patients, the heart rate decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Patients who experience bradycardia are generally asymptomatic, but some patients experience hypotension, orthostasis, fatigue, palpitations, and chest pain that usually resolve within the first 24 hours of treatment. With the first dose of fingolimod, patients are to be observed for signs and symptoms of bradycardia and heart block for 6 hours, with an electrocardiogram (ECG) at the beginning and end of the observation period and hourly checks of pulse and blood pressure obtained. Patients who develop a reduced heart rate (adults $<$ 45 beats per minute [bpm], $<$ 55 bpm in pediatric patients \geq 12 years of age, or $<$ 60 bpm in pediatric patients 10 or 11 years of age), significant bradycardia, or a new onset second degree or higher AV block should be monitored until resolution. Patients with the lowest post-dose heart rate at the end of the observation period should be monitored until the heart rate increases. Patients experiencing symptomatic bradycardia should begin continuous ECG monitoring until the symptoms resolve. If pharmacological intervention is required to treat bradycardia, continuous ECG monitoring should be performed overnight in a medical facility, and first-dose monitoring procedures should be repeated for the second dose. Patients at higher risk of symptomatic bradycardia or heart block because of a coexisting medical condition, including patients with a low heart rate, history of syncope, sick sinus syndrome, second degree or higher conduction block, ischemic heart disease, or congestive heart failure or who are on certain concomitant medications, including beta-blockers and calcium channel blockers, should be observed overnight with continuous ECG monitoring. In addition, patients with prolonged QTc interval at baseline or during the observation period, or taking drugs with known risk of torsades de pointes, should be observed overnight with continuous ECG monitoring. If a patient requires pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of fingolimod. If fingolimod therapy is discontinued for more than 2 weeks, the same precautions as for initial dosing apply upon restarting fingolimod therapy.^{102,103} In addition, within the first 2 weeks of treatment, first dose procedures are recommended after interruption of 1 day or more within the first 2 weeks of treatment and an interruption of $>$ 7 days during weeks 3 and 4 of treatment.

Cases of PML have also been reported with fingolimod, the majority of which occurred in patients treated for at least 2 years.¹⁰⁴ Providers should monitor for any signs or symptoms of PML, taking into consideration that patients at a higher risk may need more frequent monitoring; any signs or symptoms of PML warrant immediate withholding of the possible offending agent and a diagnostic workup. MRI findings consistent with PML may be apparent before clinical signs or symptoms; any suspicious findings should lead to further investigation to allow for an early diagnosis of PML. Lower mortality and morbidity have been reported with other medications associated with PML in patients who were initially asymptomatic versus symptomatic patients. It is unknown if this difference is due to early detection and discontinuation or due to disease differences.

Fingolimod may increase the risk of infections, including herpetic and cryptococcal infections and fatal or life-threatening infections, due to its dose-dependent effects on lymphocytes; lymphocyte suppression may continue for 2 months after discontinuation. In addition, obtain CBC at baseline and monitor periodically during therapy. Patients with active or chronic infections should not take fingolimod. Patients should be evaluated for antibodies to varicella zoster virus (VZV) prior to initiation; if vaccination for VZV is needed, it should occur 1 month prior to initiation of fingolimod. Human papilloma virus (HPV) infections have also been reported in patients treated with fingolimod. Vaccination against HPV should be considered prior to fingolimod initiation. In addition, cancer screening including a Papanicolaou (Pap) test is recommended. A recent CBC results should be available prior to initiating therapy (e.g. within 6 months or after discontinuation of prior therapy). Pediatric patients, if possible, should complete all guideline-recommended immunizations prior to initiating fingolimod. A serious infection may warrant treatment suspension and a subsequent risk and benefit evaluation prior to initiation. Concomitant use with other potentially immunosuppressive agents would be expected to increase the risk of immunosuppression.

Fingolimod can cause macular edema. An appropriate ophthalmologic evaluation should be performed at baseline and 3 to 4 months after fingolimod initiation and if the patient reports visual disturbances during therapy. Patients with a history of uveitis or diabetes mellitus are at increased risk of macular edema and should have regular follow-up assessments. Data from clinical trials suggest the risk may be dose-dependent and is most likely to occur within the first 6 months of treatment.

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in adults receiving fingolimod. Symptoms included a sudden onset of severe headache, altered mental status, visual disturbances, and seizure, which are usually reversible but can result in an ischemic stroke or cerebral hemorrhage. A delay in diagnosis and/or treatment may lead to permanent neurological sequelae; thus, if PRES is suspected, fingolimod should be discontinued immediately.

Significant liver injury, acute liver failure requiring transplant, hepatocellular and/or cholestatic hepatitis, elevated liver transaminases, and total bilirubin have occurred in patients treated with fingolimod. Baseline serum transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and total bilirubin levels should be obtained prior to starting fingolimod (within 6 months) and periodically until 2 months after treatment discontinuation. If significant liver injury is confirmed, fingolimod therapy must be discontinued; levels typically return to normal 2 months after discontinuing therapy. Patients with preexisting liver disease may be at an increased risk for liver injury. Additional monitoring is warranted if clinically indicated. Due to its prolonged elimination, effective contraception should be used up to 2 months after discontinuing fingolimod therapy to reduce the risk of fetal harm.

Other adverse events with fingolimod include a decrease in pulmonary function tests, including dose-dependent reductions in forced expiratory volume over 1 second (FEV₁) and diffusion lung capacity for carbon monoxide (DLCO). Changes in FEV₁ appear to be reversible upon discontinuation; the reversibility of DLCO decreases after treatment discontinuation is unknown. Consequently, obtain spirometry and diffusion lung capacity for carbon monoxide (DLCO) if clinically indicated. Blood pressure may increase during fingolimod therapy; monitor blood pressure during fingolimod therapy.

Malignancies, including cutaneous malignancies (basal cell carcinoma, squamous cell carcinoma, melanoma, and Merkel cell carcinoma) and lymphoma (both T-cell and B-cell types and CNS lymphoma) have also been associated with fingolimod use; evaluate suspicious skin lesions promptly.

In addition, fingolimod may cause fetal harm based on the results of animal studies. Females of reproductive potential should use effective contraception during fingolimod use and for 2 months following fingolimod discontinuation. Pregnancy status should be verified prior to initiating fingolimod treatment. Fingolimod should be stopped 2 months prior to planned contraception.

Fingolimod also carries a warning regarding a risk of severe increase in disability and multiple lesions on MRI after treatment discontinuation. These generally occur within 12 weeks after stopping fingolimod, although cases of up to 24 weeks following discontinuation have been reported. The FDA issued a safety announcement in November 2018 regarding the risks of disease progression when treatment is stopped as well, and the labeling has been updated accordingly to include this risk.¹⁰⁵

Relapses with tumefactive demyelinating lesions on imaging have occurred during fingolimod treatment and following fingolimod discontinuation. These cases have generally occurred within the first 9 months following treatment initiation and within the first 4 months following discontinuation; however, this may occur at any time during treatment.

glatiramer acetate (Copaxone)

Glatiramer is contraindicated in patients with a hypersensitivity to glatiramer acetate, mannitol, or any other excipient.

Warnings associated with glatiramer include post-injection reaction, chest pain, lipoatrophy and skin necrosis, and effects on the immune system. A post-injection reaction, which can be immediate, consisting of various symptoms, including flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and/or urticaria, may occur within seconds to minutes following injection; most patients experienced symptoms within 1 hour. Generally, this occurs many months following treatment initiation, but it can occur earlier. Most often, symptoms are transient, but, rarely, may require emergency management. The cause of this syndrome (whether nonimmunologic or immunologic mediated) is unknown. In addition, a greater percentage of patients in clinical trials experienced chest pain with glatiramer compared to placebo. Some cases were related to a post-injection reaction. Pain was generally transient, but a temporal relationship and the pathogenesis is unknown. Localized lipoatrophy and, rarely, injection site skin necrosis have been reported with glatiramer at the injection site. Lipoatrophy also can occur at various times throughout treatment and is thought to be permanent.

Since it can modify the immune response, glatiramer may interfere with immune functions. There is no evidence of this, but a systematic evaluation has not been completed.

IFN β -1a (Avonex, Plegridy, Rebif) and IFN β -1b (Betaseron, Extavia)

All interferon products are contraindicated in patients with hypersensitivity to natural or recombinant interferon beta or any component of the formulation. Except for IFN β -1a SC (Plegridy) and IFN β -1a IM (Avonex) prefilled syringes, IFN β -1a (Avonex, Rebif), and IFN β -1b (Betaseron, Extavia) are contraindicated in patients with hypersensitivity to albumin. Pegylated IFN β -1a SC (Plegridy) and

prefilled syringes of IFN β -1a IM (Avonex) do not contain albumin. IFN β -1a IM (Avonex), pegylated IFN β -1a SC (Plegridy), and IFN β -1b (Betaseron) have also been associated with rare reports of anaphylaxis.

IFN β products should be used with caution in patients with depression. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving these compounds.

Additionally, decreased peripheral blood cell counts, including rare pancytopenia and thrombocytopenia, have been reported during IFN β -1a IM and pegylated IFN β -1a SC (Plegridy) use. Pegylated IFN β -1a SC therapy has also been associated with an increased incidence of congestive heart failure and seizures. Autoimmune disorders of multiple target organs, including idiopathic thrombocytopenia, hyper and hypothyroidism, and autoimmune hepatitis, have also been reported with use of pegylated IFN β -1a SC.

IFN β -1a products can cause severe liver damage. Events have occurred in the presence of other drugs also associated with hepatic injury. IFN β -1b carries a similar, but weaker, warning. Monitoring of liver function at regular intervals is recommended for patients receiving these drugs.

Cases of drug-induced lupus erythematosus have been reported with some interferon IFN β products, such as Betaseron and Extavia. Discontinue treatment if patient develops new signs and symptoms associated with lupus.

Injection site necrosis has been reported in 4% of patients in controlled clinical trials for IFN β -1b. It typically occurred within the first 4 months of therapy, although post-marketing reports have documented injection site necrosis occurring over 1 year after initiation of therapy. It generally affects the subcutaneous layer of fat around the injection site. In some cases, patients experienced healing during continuation of therapy. Therapy should be held if the patient experiences multiple lesions, and may be resumed once the lesions have healed. Injection site reactions, including injection site necrosis, have also been reported with pegylated IFN β -1a SC (Plegridy) treatment.

All IFN β products carry a warning for thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Any IFN β should be discontinued should signs or symptoms of TMA occur.

The removable cap of the diluent pre-filled syringe for Extavia contains natural latex, which may cause allergic reactions in patients sensitive to latex.

natalizumab (Tysabri)

Hypersensitivity reactions, including serious systemic reactions like anaphylaxis have been reported with natalizumab. Natalizumab is contraindicated in patients with PML and in patients with a prior hypersensitivity reaction. Patients experiencing a hypersensitivity reaction should not be rechallenged with natalizumab.

Natalizumab carries a boxed warning for increased risk of PML. Providers should monitor for any signs or symptoms of PML, taking into consideration that patients at a higher risk may need more frequent monitoring; any signs or symptoms of PML warrant immediate withholding of the possible offending agent and a diagnostic workup. Details on timing for testing for anti-JCV antibodies following plasma

exchange or intravenous immunoglobulin are outlined in the prescribing information to limit false negative or false positive results. Limited retrospective data suggest that the risk of developing PML may be associated with relative levels of serum anti-JCV antibody compared to a calibrator (e.g., anti-JCV antibody index value). JCV granule cell neuropathy (JCV GCN) can occur with or without concomitant PML and has also been reported in patients treated with natalizumab. JCV GCN can cause cerebellar dysfunction (e.g., ataxia, incoordination, apraxia, visual disorders) and cerebellar atrophy. JCV GCN should be managed similarly to PML.

Like some other agents in this class, natalizumab increases the risk of developing encephalitis and meningitis caused by viruses such as herpes simplex and varicella zoster, and these conditions may be life-threatening. A higher risk of acute retinal necrosis (ARN), caused by the family of herpes viruses, has been reported with natalizumab. Patients should be referred for retinal screening for ARN if experiencing ocular symptoms, including decreased visual acuity, redness, or eye pain, and discontinuation of natalizumab may be appropriate. Immunosuppression from natalizumab may also increase the risk of other infections, including less common, opportunistic infections. Opportunistic infections have been observed in < 1% of those treated with natalizumab. There are no data on natalizumab use with vaccinations, including the risk of secondary transmission from live vaccines.

Antibodies to natalizumab may develop. Patients looking to restart natalizumab following a treatment interruption should be tested for antibodies.

Hepatotoxicity, including cases of acute liver failure requiring transplant, have occurred with natalizumab. Signs and symptoms of liver failure (e.g., jaundice) warrant natalizumab discontinuation and a full workup.

Natalizumab may interfere with certain laboratory tests, such as inducing increases in circulating lymphocytes, monocytes, eosinophils, basophils, and red blood cells. Levels typically return to normal approximately 16 weeks following the last dose of natalizumab. Transient decreases in hemoglobin levels have also been reported.

siponimod (Mayzent)

Siponimod is contraindicated in patients with cytochrome p450 (CYP) 2C9 *3/*3 genotype; patients who have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure in the last 6 months; and patients with Mobitz type II second-degree, third-degree atrioventricular [AV] block, or sick sinus syndrome (unless patient has a functioning pacemaker).

Siponimod causes a dose-dependent decrease in peripheral lymphocyte count to approximately 20% to 30% due to lymphoid tissue sequestration of lymphocytes, which may persist for up to 3 to 4 weeks. This is reversible; however, this may increase the risk of infections, including life-threatening and fatal infections. While the overall rate of infections was similar in clinical trials, a higher number of herpes zoster, herpes infection, bronchitis, sinusitis, upper respiratory infection, and fungal skin infections occurred with siponimod compared to placebo. Treatment initiation should be delayed in patients with severe active infection until resolution of symptoms. Likewise, treatment suspension should be considered if a patient develops a serious infection. Rare cases of cryptococcal infections have been reported with siponimod; suspected cryptococcal infections require prompt evaluation and treatment and siponimod treatment suspension. Cases of herpes viral infections, including a case leading to

varicella zoster virus (VSV) meningitis, have been reported with siponimod. No cases of PML have been reported with siponimod; however, PML has been reported with another S1P receptor modulator and with other MS pharmacologic treatments. Suspected cases of PML require prompt evaluation and treatment and siponimod treatment suspension. Antineoplastic agents, immune-modulators, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution. Antibody testing for VZV should be assessed in patients without a confirmed history of chickenpox or documented full course of VZV vaccination; a full course of VZV vaccination is recommended for any antibody-negative patients, and siponimod should be postponed for 4 weeks following completion of vaccination. Live attenuated vaccines should be avoided during siponimod treatment. In addition, vaccines may be less effective when administered during siponimod treatment; siponimod should be discontinued 1 week prior to and for 4 weeks following a planned vaccination.

Transient bradycardia and AV conduction delays can occur with siponimod. The heart rate decrease generally begins within an hour of the initial dose and reaches the maximum decrease at around 3 to 4 hours. The highest daily post-dose heart rate decrease generally occurs on day 1 with a decrease of approximately 5 to 6 beats per minute (bpm); post-dose decreases on subsequent days are less pronounced. The maximum decrease in heart rate is typically reached on days 5 or 6 and starts increasing to baseline thereafter following continued dosing, typically reaching placebo (baseline) levels about 10 days following initiation of treatment. In studies, most patients were asymptomatic and heart rate < 40 bpm were rarely observed. A similar pattern in transient AV conduction delays is seen with siponimod, which are generally asymptomatic and resolved within 24 hours. These most commonly manifested as first-degree AV block (prolonged PR interval on electrocardiogram [ECG]). Notably, siponimod was not studied in patients who had experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, or decompensated heart failure requiring hospitalization in the last 6 months; with New York Heart Association [NYHA] Class II through IV heart failure; cardiac conduction or rhythm disorders (e.g., left bundle branch block, sinus arrest or sinoatrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second degree AV-block or higher grade AV-block [unless patient has a functioning pacemaker]); QT prolongation (QTc > 500 msec); and arrhythmias requiring treatment with Class Ia or Class III antiarrhythmics. A cardiologist's advice should be sought in the following situations: patients with QTc > 500 msec; patients with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs; patients with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension; and patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block. Use of siponimod is not recommended in patients with a history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea (cardiologist consult recommended if treatment considered). A risk versus benefit assessment is recommended in patients with a history of recurrent syncope or symptomatic bradycardia (cardiologist consult recommended). Experience with siponimod in patients receiving concurrent medications that can decrease heart rate (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, ivabradine, digoxin). The resting heart rate should be > 50 bpm in patients taking beta-blockers, and a cardiologist consult is recommended if treatment will be initiated in patients using the other heart rate -reducing medications.

An increase in blood pressure of approximately 3 mmHg systolic and 1.2 mmHg diastolic was seen in trials with siponimod. This was first detected approximately 1 month following initiation and continued

during treatment. Blood pressure should be monitored, and clinically managed if appropriate, during treatment.

Macular edema occurred in a higher proportion of siponimod-treated patients compared to placebo (1.8% versus 0.2%, respectively). An ophthalmic evaluation of the fundus (including the macula) is recommended in all patients prior to initiation of siponimod and during therapy if vision changes occur. Patients with a history of uveitis or diabetes mellitus are at an increased risk of macular edema.

In trials of siponimod, dose-dependent reductions in FEV₁ were observed as early as 3 months following treatment initiation; data are insufficient to determine the reversibility of the decrease in FEV₁ after drug discontinuation. In 1 clinical study, some patients discontinued treatment due to decreases in pulmonary function testing. Spirometric evaluation of respiratory function should be performed if clinically indicated.

Elevations of transaminases may occur in patients treated with siponimod. In 1 clinical trial, elevations in transaminases and bilirubin occurred in 10.1% and 3.7% of siponimod-treated and placebo-treated patients, respectively. This difference was primarily driven by increases in ALT/AST/gamma-glutamyltransferase (GGT). Significant elevations (3 to 10 times the upper limit of normal [ULN]) in ALT and AST were also reported more with siponimod than placebo. The majority of elevations occurred within 6 months of treatment initiation. Patients who develop symptoms associated with hepatic dysfunction (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, jaundice, or dark urine) should have liver function assessed; siponimod should be discontinued if liver injury is confirmed. Caution should be used in patients with a history of significant liver disease.

Cases of posterior reversible encephalopathy syndrome (PRES) have occurred rarely in patients using another S1P receptor modulator. Symptoms are usually reversible, but this can evolve into ischemic stroke, cerebral hemorrhage, or permanent neurological sequelae. If a patient treated with siponimod develops unexpected neurological or psychiatric symptoms (e.g., cognitive deficits, behavioral changes, cortical visual disturbances), a symptom of increased intracranial pressure, or accelerated neurological deterioration, siponimod should be discontinued, a complete physical and neurological examination should occur, and a magnetic resonance imaging (MRI) scan should be considered.

Additive immunosuppressive effects may occur with other immunosuppressive or immune-modulating treatments, and the half-life and pharmacology of these agents should be considered. Treatment of siponimod following treatment with alemtuzumab is not recommended. Siponimod can generally be initiated immediately after discontinuation of beta interferon or glatiramer acetate. In addition, siponimod exposure generally occurs for up to 10 days following treatment. Lymphocyte counts generally return to normal in most patients within 10 days of treatment discontinuation; however, residual effects may persist for 3 to 4 weeks after the last dose. Additive effects with other agents affecting the immune system and appropriate caution should be considered during this period. Rarely, cases of severe exacerbation, including disease rebound, following discontinuation of a S1P receptor modulator have been reported. Patients should be monitored for increased disability following siponimod discontinuation.

Siponimod carries a warning for fetal harm. Effective contraception is recommended during treatment and for 10 days following siponimod discontinuation.

ocrelizumab (Ocrevus)

Ocrelizumab is contraindicated in patients with a history of life-threatening infusion reactions to ocrelizumab. While there were no cases of hepatitis B virus (HBV) reactivation in patients in clinical trials with ocrelizumab, reactivation has been reported with other anti-CD20 antibodies. An HBV screening prior to initiation is required. Ocrelizumab is contraindicated in patients with active HBV infection. Providers should consult with a liver disease expert prior to initiating therapy for patients who are negative for surface antigen (HbsAg) and positive for HB core antibody (HbcAb+) or who are carriers of HBV (HbsAg+).

Cases of PML have not been reported with ocrelizumab. However, cases of PML could occur as these have been reported with other anti-CD20 antibodies and other MS therapies.

Ocrelizumab carries a warning for infusion reactions including pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, pharyngeal or laryngeal edema, dyspnea, oropharyngeal pain, flushing, pyrexia, fatigue, headache, dizziness, nausea, hypotension, **anaphylaxis**, and tachycardia. Healthcare providers should administer pre-medication (e.g., methylprednisolone or equivalent corticosteroid and an antihistamine) prior to the infusion, and use of an antipyretic may also be considered. In clinical trials, infusion reactions occurred in 34% to 40% of patients who were premedicated (e.g., corticosteroid), and the incidence was highest with the first infusion. Healthcare providers should observe patients during the infusion and for at least 1 hour after infusion completion and inform patients that infusion reactions can occur up to 24 hours following the infusion. Healthcare providers should immediately and permanently stop ocrelizumab infusion in patients with life-threatening infusion reactions. Less severe reactions may be managed based on the severity of the reaction (e.g., temporarily discontinue or decrease the rate of infusion, administer symptomatic treatment).

In clinical trials, a higher proportion of patients treated with ocrelizumab experienced infections compared to patients treated with placebo or IFN β -1a (Rebif). Ocrelizumab increased the risk of both upper and lower respiratory tract infections, skin infections, and herpes-related infections; however, no increased risk in serious infections was found. The safety of immunization with live or live-attenuated vaccines following ocrelizumab use has not been evaluated, **and the effectiveness of non-live vaccines may be altered**. Administer all immunizations **at least 4 weeks prior to initiation of ocrelizumab for live or live-attenuated vaccines and at least 2 weeks prior to initiation of ocrelizumab for non-live vaccines**. Vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion upon discontinuation of ocrelizumab. **Do not administer live or live-attenuated vaccines before confirming B-cell count recovery in infants of mothers exposed to ocrelizumab during pregnancy. Non-live vaccines may be administered to these infants, but the risk of possible altered immune response should be considered.**

A higher rate of malignancies, including breast cancer, occurred in patients treated with ocrelizumab in clinical trials compared to the active comparator (IFN β -1a [Rebif]) or placebo. Patients should adhere to standard breast cancer screening guidelines.

teriflunomide (Aubagio)

Teriflunomide is contraindicated in patients with known hypersensitivity to teriflunomide, leflunomide, or any inactive ingredients. Teriflunomide may also cause anaphylaxis and severe allergic reactions, including serious skin reactions like Stevens-Johnson syndrome and toxic epidermal necrolysis. Cases of drug reaction with eosinophilia and systemic symptoms (DRESS) have also been reported with leflunomide; thus, teriflunomide also carries this warning.

Teriflunomide is contraindicated in patients with severe hepatic impairment. A similar risk of severe liver injury including fatal liver failure and dysfunction would be expected with teriflunomide as leflunomide. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases on teriflunomide. Baseline serum transaminase and total bilirubin levels should be obtained prior to starting teriflunomide (within 6 months) and monitored at least monthly for 6 months after treatment initiation. If drug-induced liver injury is suspected, discontinue teriflunomide and start an accelerated elimination procedure with cholestyramine or charcoal.

Teriflunomide is contraindicated in patients on current leflunomide therapy.

Teriflunomide may cause fetal harm when administered to pregnant women due to teratogenic and embryo lethal effects. Teriflunomide is contraindicated in women who are pregnant or women of child bearing potential not using reliable contraception during both treatment and an accelerated drug elimination procedure following treatment. Use should be discontinued if the patient becomes pregnant and an accelerated drug elimination procedure should occur.

Teriflunomide may decrease white blood cell count (WBC) and platelet count; a recent CBC should be obtained before initiating therapy. While not reported in clinical trials of teriflunomide, rare cases of pancytopenia and agranulocytosis have been reported with leflunomide; thus, a similar risk is anticipated for teriflunomide.

Cytomegalovirus hepatitis and cases of TB have been observed in clinical studies with teriflunomide. Due to the potential for immunosuppression, teriflunomide is not recommended in patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled, infections. Screen patients for TB prior to initiating teriflunomide. Discontinue treatment and start an accelerated elimination procedure if a serious infection develops.

Peripheral neuropathy, acute renal failure/hyperkalemia, interstitial lung disease, and elevated blood pressure are among other reported warnings.

Risk Evaluation and Mitigation Strategy (REMS) Programs¹⁰⁶

Agents within this review assigned REMS programs include alemtuzumab (Lemtrada) and natalizumab (Tysabri).

Due to the risk of autoimmunity, infusion reactions, **stroke**, and malignancy, alemtuzumab has a prescriber, patient, pharmacy, and healthcare facility program. Prescribers must be certified with the program and complete training. Patients must enroll in the program and comply with ongoing monitoring requirements. Pharmacies must be certified and only dispense to healthcare facilities authorized to receive alemtuzumab. Healthcare facilities must enroll in the program and verify that patients are enrolled before administering alemtuzumab.

Due to the risk of serious adverse effects, including an increased risk of PML, the REMS for natalizumab consists of prescriber, infusion site, and pharmacy certification; and patient enrollment following a full evaluation of the risks and benefits.

DRUG INTERACTIONS^{107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122}

Interactions between glatiramer (Copaxone) and other drugs have not been fully evaluated. No formal drug interaction studies have been conducted with IFN β -1a (Avonex, Rebif, Plegridy) or IFN β -1b (Betaseron, Extavia). Caution and/or additional monitoring of liver enzymes is required when using IFN β -1a with potentially hepatotoxic drugs. No formal drug interaction studies have been conducted with alemtuzumab (Lemtrada). No potential drug interactions with dimethyl fumarate or MMF were identified in *in vitro* CYP inhibition and induction studies, or in P-glycoprotein studies.

Caution should be used in patients previously treated with alemtuzumab (Campath[®]), for B-cell chronic lymphocytic leukemia (B-CLL), due to the drug containing the same active ingredient and possible additive and long lasting effects on the immune system.

Concurrent treatment with OCT2 inhibitors (e.g., cimetidine) may increase dalfampridine (Ampyra) exposure, potentially increasing the risk of seizures.

Coadministration of diroximel fumarate (Vumerity) and dimethyl fumarate (Tecfidera) is contraindicated as these agents share the same active metabolite. Concomitant use may cause severe gastrointestinal (GI) intolerance, immunosuppression, or hepatotoxicity. Alcohol should not be consumed simultaneously with diroximel fumarate. Administration with alcohol leads to decreased peak plasma monomethyl fumarate (MMF) concentrations, which is the active metabolite of diroximel fumarate.

Natalizumab (Tysabri) should not be used with other immunosuppressants. Likewise, cladribine (Mavenclad) should not be used with any immunomodulatory, immunosuppressive, or myelosuppressive drugs due to additive effects. Concurrent use of cladribine with IFN β may increase the risk of leukopenia, and concurrent use of cladribine with hepatotoxic drugs may lead to additive hematologic effects. Compounds that require intracellular phosphorylation to become active (e.g., antiviral and antiretroviral drugs [lamivudine, zalcitabine, ribavirin, stavudine, and zidovudine]) could interfere with the metabolism and activity of cladribine; avoid concurrent use. In addition, the effect of cladribine on systemic hormonal contraceptives is unknown; women should use an effective barrier method during and for ≥ 4 weeks after treatment. Co-administration of cladribine with potent breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) transporter inducers may lead to decreased cladribine exposure, and potent equilibrative nucleoside transporter 1 (ENT1), concentrative nucleoside transporter 3 (CNT3), and BCRP transporter inhibitors may impact the pharmacokinetics of cladribine.

Siponimod has not been studied with concomitant antineoplastic, immune-modulating, or immunosuppressive therapies. Vaccinations may be less effective and siponimod should be interrupted 1 week prior and 4 weeks after a planned vaccination; live vaccines should be avoided during treatment and for 4 weeks following siponimod discontinuation. Siponimod also has not been studied in patients using QT-prolongating drugs; due to potential additive effects, siponimod should generally not be initiated in patients using concomitant QT-prolongating agents or other agents that can

decrease heart rate. Caution should be used, as described above, in patients using beta-blockers. Concomitant use of siponimod with drugs that are moderate CYP2C9 and moderate or strong CYP3A4 inhibitors (as a single agent or multiple agents) is not recommended. Likewise, concomitant use of siponimod with drugs that are moderate CYP2C9 and strong CYP3A4 inducers (as a single agent or multiple agents) is not recommended. Use with moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended in patient with CYP2C9*1/*3 and*2/*3 genotypes. Caution should be used with moderate CYP2C9 inhibitors or inducers.

Patients taking class Ia or III antiarrhythmics, beta-blockers, and calcium channel blockers are at increased risk of developing bradycardia or heart blocks while on fingolimod (Gilenya). Co-administration of ketoconazole can increase fingolimod exposure by 70%; a higher risk of adverse effects is possible. Use of live attenuated vaccines during fingolimod treatment and for 2 months following discontinuation should be avoided. Pediatric patients, if possible, should be brought up to date with all immunizations according to current immunization guidelines prior to initiation of fingolimod.

Concomitant use of ocrelizumab (Ocrevus) with other immune-modulating or immunosuppressive therapy may increase the risk of immunosuppression. Additive immunosuppressive effects should be considered, particularly when co-administered with drugs with prolonged immune effects (e.g., daclizumab, fingolimod, natalizumab, teriflunomide, mitoxantrone).

Patients taking teriflunomide (Aubagio) and drugs metabolized by CYP2C8 should be monitored due to a possible increase in exposure to the CYP2C8 medication as a result of teriflunomide inhibiting the enzyme. Also, patients taking teriflunomide drugs metabolized by CYP1A2 and should be monitored due to a possible decrease in exposure to the CYP1A2 medication as a result of teriflunomide inducing the enzyme. Warfarin should be co-administered with teriflunomide with close international normalized ratio (INR) follow-up and monitoring due to a 25% decrease in peak INR when administered together. The type or dose of oral contraceptive should be considered when co-administered with teriflunomide due to an increase in contraceptive drug levels after repeated doses of teriflunomide.

ADVERSE EFFECTS^{123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138}

The most frequent adverse effects in patients receiving immunomodulators requiring clinical intervention were flu-like symptoms and depression.

Drug	Asthenia	Depression	Flu-like Symptoms	Injection Site Reaction	Increased Liver Enzymes	Leukopenia	Pain
alemtuzumab (Lemtrada)	5	0.6*	8	92	nr	nr	12
cladribine (Mavenclad)	nr	5 (3)	nr	n/a	reported	24 (2) (lymphopenia)	8 (6)
dalfampridine (Ampyra)	7 (4)	nr	nr	n/a	nr	nr	back: 5 (2)
dimethyl fumarate (Tecfidera)	nr	nr	nr	n/a	reported	reported	18 (10)
diroximel fumarate (Vumerity)	nr	nr	nr	n/a	reported	reported	reported
fingolimod (Gilenya)	2 (1)	nr	11 (8)	n/a	15 (4)	2 (<1)	10 (7-9)
glatiramer (Copaxone) 20 mg once daily	22 (21)	reported	14 (13) [†]	2-43 [‡] (0-20)	reported	<1	20 [§] (17)
glatiramer (Copaxone) 40 mg 3 times weekly	nr	nr	3 (2)	2-22 [‡] (0-2)	nr	nr	2 [§] (1)
IFNβ-1a IM (Avonex)	24 (18)	18-20 (13-14)	49 (29)	3-28 (6)	reported	reported	23 (21)
IFNβ-1a SC (Rebif)	reported	17-25 (25-28)	56-59 (51)	89-92 (39)	10-27 (4)	28-36 (14)	10-25 (10-20)
IFNβ-1a SC (pegylated) (Plegridy)	13 (8)	8 (8)	47 (13)	62 (7)	2 (1)	nr	5 (3)
IFNβ-1b (Betaseron)	53 (48)	34 (34)	57 (37)	78 (26)	4-12 (1-4)	18 (6)	42 (35)
IFNβ-1b (Extavia)	53 (48)	nr	57 (37)	78 (26)	4-12 (1-4)	18 (6)	42 (35)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

nr = not reported

n/a = not applicable

* Attempted suicide or had suicidal ideation

† Influenza

‡ Glatiramer 40 mg versus 20 mg package insert incidence of injection site erythema (22% versus 43%), pain (10% versus 40%), and pruritus (6% versus 27%)

§ For glatiramer 20 mg, 13% is chest pain; for glatiramer 40 mg, the 2% reflects chest pain

Adverse Effects (continued)

Drug	Asthenia	Depression	Flu-like Symptoms	Injection Site Reaction	Increased Liver Enzymes	Leukopenia	Pain
natalizumab (Tysabri)	nr	19 (16)	nr	24 (18)	5 (4)	nr	16 (14)
ocrelizumab (Ocrevus)	nr	8 (7)	nr	34-40 (10-26)	nr	nr	5-6 (4-5)
siponimod (Mayzent)	< 5	nr	nr	n/a	11 (3)	< 5 (lymphopenia)	6 (4)
teriflunomide (Aubagio)	nr	nr	9-12 (10)	n/a	12-14 (7)	1-2 (0.3)	upper abdominal: 5-6 (4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

nr = not reported

n/a = not applicable

|| Infusion-related reactions

Additional adverse effects reported with alemtuzumab (Lemtrada) ($\geq 10\%$ of patients and more than interferon beta-1a alone) were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Neutralizing antibodies have also been reported with alemtuzumab.

The most common adverse effects ($\geq 10\%$) reported with cladribine relative to placebo, respectively, in clinical trials and not reported above were upper respiratory tract infection (38%, 32%), headache (25%, 19%), and nausea (10%, 9%). Herpes meningoencephalitis was reported in 1 patient given a higher dose and longer duration of cladribine in combination with interferon beta-1a. In addition, cases of myelodysplastic syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with parenteral cladribine.

Urinary tract infections were reported more frequently with dalfampridine (12%) in clinical trials compared to placebo (8%).

Additional adverse effects reported with dimethyl fumarate (Tecfidera) ($> 2\%$ incidence) are flushing, abdominal pain, diarrhea, nausea, vomiting, pruritus, rash, albumin present in urine, erythema, dyspepsia, aspartate aminotransferase increase, and lymphopenia. Adverse effects of diroximel fumarate (Vumerity) in clinical studies are similar to those of dimethyl fumarate.

Cough, diarrhea, and headache (incidence $\geq 10\%$ and greater than placebo) have also been reported with fingolimod (Gilenya). Serious adverse events described for fingolimod include bradyarrhythmia and atrioventricular blocks, infections, macular edema, respiratory effects, cutaneous malignancies, and hepatic adverse effects. Adverse effects in a controlled pediatric trial were similar to those

experienced by adults in clinical trials. In the study, however, 5.6% of pediatric patients reported seizure compared to 0.9% of those treated with IFN β -1a.

In pre-marketing studies, approximately 16% of patients receiving glatiramer (Copaxone) versus 4% of patients receiving placebo experienced a transient, immediate post-injection reaction that included flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. Other adverse events associated with glatiramer included infection (30% versus 28% for placebo), skin rash (19% versus 11% for placebo), dyspnea (14% versus 4% for placebo), and nausea (15% versus 11% for placebo).

In a study of the drop-out rate in patients with RRMS under long-term treatment with the 3 available IFN β preparations, 122 patients were divided into 4 treatment groups: IFN β -1b 24 MIU SC (Betaseron) weekly; IFN β -1a 6 MIU IM (Avonex) weekly; IFN β -1a 18 MIU SC (Rebif) weekly; and 10 patients switching from IFN β -1b to IFN β -1a IM.¹³⁹ During the 5-year observation period, 39.9% of enrolled patients dropped out. Forty-eight percent in the IFN β -1b group withdrew at a median of 758 days, 26% in the IFN β -1a IM group withdrew at a median of 356 days, 38% in the IFN β -1b SC group withdrew at a median of 421 days, and 40% in those who switched from IFN β -1b to IFN β -1a IM withdrew at a median of 259 days. The differences among the groups were not significant on survival analysis. Patients receiving higher dose treatment (IFN β -1b and IFN β -1b SC groups) dropped out mainly due to clinical adverse events; conversely, patients receiving lower dose therapy (IFN β -1a IM group) dropped out mainly due to ineffectiveness. Patients who switched to a lower dose treatment (fourth group) had a dropout rate similar to that of the initial treatment groups. The remaining two-thirds of patients were still on treatment without problems at up to 5 years of follow-up. In this study, compliance appeared to be related to the dose of the drug.

The most common adverse effects (incidence \geq 10%) reported in clinical trials of natalizumab (Tysabri) for MS not described in the table above were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, abdominal discomfort, diarrhea, and rash. Hepatotoxicity, herpes infections, antibody formation, and hemolytic anemia have also been reported.

The most common adverse reactions reported with ocrelizumab (Ocrevus) in relapsing MS clinical trials were upper respiratory tract infections (40%) and infusion reactions (34%). Other notable adverse effects not described above included lower respiratory tract infections (8%) and herpes virus-associated infections (6%). The most common adverse reactions reported with ocrelizumab in PPMS clinical trials were upper respiratory tract infections (49%), infusion reactions (40%), skin infections (14%), decreased neutropenia (13%), and lower respiratory tract infections (10%). Other notable adverse effects not described above included cough (7%), diarrhea (6%), peripheral edema (6%), and herpes virus-associated infections (5%).

The most common adverse reactions (incidence \geq 5% and \geq 1% higher than placebo) reported in clinical trials with siponimod (versus placebo, respectively) not described above were headache (15% versus 14%), hypertension (13% versus 9%), falls (11% versus 10%), peripheral edema (8% versus 4%), nausea (7% versus 4%), dizziness (7% versus 5%), and diarrhea (6% versus 4%), bradycardia (6% versus 3%).

Additional frequent adverse effects associated with teriflunomide (Aubagio) (\geq 10% incidence or 2% greater than placebo) are alopecia, nausea, and paresthesia. Teriflunomide has also been associated

with the following serious adverse reactions: hepatotoxicity, bone marrow and immunosuppression, peripheral neuropathy, hyperkalemia, acute renal failure, and serious skin reactions.

SPECIAL POPULATIONS [140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155](#)

Pediatrics

Fingolimod (Gilenya) is approved in patients ≥ 10 years of age. No other drugs in this class review are indicated for use in pediatric patients.

Pregnancy

IFN β -1a SC (Rebif) is Pregnancy Category C. Previously, [alemtuzumab \(Lemtrada\)](#), [dalfampridine \(Ampyra\)](#), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), [IFN \$\beta\$ -1a IM \(Avonex\)](#), [IFN \$\beta\$ -1a SC \(Plegridy\)](#), IFN β -1b (Betaseron, [Extavia](#)), and natalizumab (Tysabri) were assigned Pregnancy Category C, but this has been replaced in their labeling with descriptive text in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). There are no adequate data on the developmental risk associated with the use of these agents in pregnant women, although limited data suggest fingolimod may cause fetal harm. Elimination of fingolimod takes approximately 2 months upon discontinuation. Therefore, women of childbearing potential should use effective contraception to avoid pregnancy during and for 2 months after stopping fingolimod therapy. Limited observational data with IFN β -1b (Betaseron, Extavia), [IFN \$\beta\$ -1a IM \(Avonex\)](#), and [IFN \$\beta\$ -1a SC \(Plegridy\)](#) in pregnant women have not generally indicated a drug-associated risk of major birth defects. [Previously, glatiramer \(Copaxone\) was assigned Pregnancy Category B, but this has been replaced in the labeling with descriptive text in compliance with the PLLR. Although limited animal studies have not found major adverse embryofetal adverse effects, available data are insufficient to support conclusions regarding glatiramer-associated risks for birth defects and miscarriage.](#)

[Based on data from animal studies and the mechanism of action, cladribine \(Mavenclad\) can cause embryofetal harm; therefore, it is contraindicated in pregnant women and in females and males of reproductive potential who do not plan on using effective contraception.](#)

[Human data for siponimod \(Mayzent\) and diroximel fumarate \(Vumerity\) in pregnancy are inadequate to advise of maternal or fetal risk; however, based on pharmacology and animal data, these agents can cause fetal harm.](#)

There are no data in pregnant women receiving ocrelizumab (Ocrevus) to inform of the drug-related risk. However, lymphocytopenia and transient peripheral B-cell depletion have been reported in infants whose mothers were exposed to other CD20 antibodies during pregnancy. [The duration and impact on vaccines of the B-cell decrease in infants following maternal exposure is unknown.](#) Ocrelizumab is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placenta. Women of childbearing potential should use contraception while on treatment with ocrelizumab and for 6 months following the last ocrelizumab infusion.

Teriflunomide (Aubagio) is contraindicated in pregnant women or women of child bearing potential not using reliable contraception. To minimize risk, female partners of men taking teriflunomide should also use reliable contraception. [If teriflunomide is discontinued, contraception use should continue](#)

until teriflunomide plasma concentration is < 0.02 mg/L. Although it is contraindicated, a pregnancy registry does exist for teriflunomide and pregnant women should be encouraged to enroll in order to monitor fetal outcomes. Human data from clinical trials and postmarketing reports have not demonstrated an increased risk of birth defects or miscarriage with teriflunomide exposure in the early first trimester following an accelerated elimination procedure.

Hepatic Impairment

No dosage adjustment of cladribine (Mavenclad) is recommended in patients with mild hepatic impairment; however, it is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh score > 6).

Blood levels of fingolimod (Gilenya), but not its active metabolite fingolimod-phosphate, are doubled in patients with severe hepatic impairment; however, no dosing adjustments are advised.

No significant pharmacokinetic difference was found in patients with mild hepatic impairment versus normal hepatic function in clinical trials of ocrelizumab (Ocrevus). Effects in patients with more severe impairment are unknown.

No dose adjustments of dimethyl fumarate (Tecfidera) or siponimod (Mayzent) are needed in patients with hepatic impairment.

No studies of diroximel fumarate (Vumerity) have been conducted in patients with hepatic impairment; however, hepatic impairment would not be expected to affect exposure so no dosage adjustment is recommended.

Dose adjustments of teriflunomide (Aubagio) are not necessary in patients with mild and moderate hepatic impairment. Teriflunomide is contraindicated in patients with severe hepatic impairment.

Pharmacokinetics of dalfampridine (Ampyra) and natalizumab (Tysabri) in patients with hepatic impairment have not been studied. Hepatic impairment is not expected to significantly affect dalfampridine pharmacokinetics or recommended dosing. Pharmacokinetics of interferon beta-1a (Rebif) in patients with hepatic impairment have not been established. Labeling for alemtuzumab (Lemtrada), glatiramer (Copaxone), and remaining interferon products (Avonex, Betaseron, Extavia, Plegridy) do not address use in patients with hepatic impairment.

Renal Impairment

Patients treated with alemtuzumab (Lemtrada) with severe renal impairment should be monitored for adverse reactions due to increased drug exposure.

Renal impairment may increase the concentration of cladribine (Mavenclad). No dosage adjustment is recommended in patients with mild renal impairment (CrCl, 60 to 89 mL/min). Cladribine is not recommended in those with moderate to severe renal impairment (CrCl < 60 mL/min).

The risk of seizures in patients with mild renal impairment taking dalfampridine (Ampyra) is unknown, but plasma levels of dalfampridine may approach those seen at a dose that may be associated with increased seizure risk. In patients with moderate to severe renal impairment (CrCl ≤ 50 mL/min), use of dalfampridine is contraindicated.

Renal impairment can increase exposure of diroximel fumarate's metabolite, 2-hydroxyethyl succinimide (HES). No dosage adjustment is necessary in patients with mild renal impairment; however, diroximel fumarate is not recommended in patients with moderate or severe renal impairment.

Blood levels of fingolimod (Gilenya) may be increased in patients with severe renal impairment, but no dosing adjustments are advised.

No significant pharmacokinetic difference was found in patients with mild renal impairment versus normal renal function in clinical trials of ocrelizumab (Ocrevus). Effects in patients with more severe impairment are unknown.

No dose adjustments of siponimod (Mayzent) are needed in patients with renal impairment. Siponimod has not been studied in patients with end-stage renal disease (ESRD) or on hemodialysis; however, hemodialysis is unexpected to affect siponimod concentration due to its high protein binding.

No dosage adjustments of dimethyl fumarate (Tecfidera) or teriflunomide (Aubagio) are necessary in patients with renal impairment.

The pharmacokinetics of glatiramer (Copaxone), interferon beta 1-a (Rebif), or natalizumab (Tysabri) in patients with impaired renal function have not been determined. Patients with severe renal impairment taking peginterferon beta-1a (Plegridy) should be monitored for adverse reactions. Labeling for remaining interferon products (Avonex, Betaseron, Extavia) do not address use in patients with renal impairment.

DOSAGES 156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171

Drug	Dosage	Comments	Availability
alemtuzumab (Lemtrada)	12 mg per day by intravenous (IV) infusion over 4 hours for 2 courses of therapy; course 1 is for 5 days and course 2 is for 3 days 1 year after the first course Additional courses may be completed as needed	Refrigerate; may be stored at room temperature (25°C) for up to 8 hours before administration Protect from light	Single use vial: 12 mg/1.2 mL solution
cladribine (Mavenclad)	3.5 mg/kg body weight orally, divided into 2 yearly treatment courses (1.75 mg/kg/treatment course); each treatment course is divided into 2 treatment cycles Administer the second cycle of each course 23 to 27 days after the last dose of the first cycle; Administer the second course at least 43 weeks after the last dose of the first course/second cycle Administer the total cycle dosage divided into a daily dose over 4 or 5 consecutive days as 1 or 2 tablets per day; do not exceed 2 tablets per day (see prescribing information for additional details)	Take tablets with water, without regard to food; swallow tablets whole and do not chew; separate timing of dose by 3 hours of administration of other oral medications Cladribine is a cytotoxic drug; proper handling and disposal should be followed; avoid prolonged tablet contact with skin Cladribine has not been studied in patients weighing < 40 kg Following 2 treatment courses, do not administer additional cladribine treatment during the next 2 years; the safety and efficacy of reinitiating cladribine > 2 years after completing 2 treatment courses has not been studied	10 mg tablets in packets of 4, 5, 6, 7, 8, 9, and 10 tablets
dalfampridine (Ampyra)	10 mg by mouth twice daily about 12 hours apart	--	Extended-release (ER) tablets: 10 mg
dimethyl fumarate (Tecfidera)	120 mg by mouth twice daily for 7 days and then 240 mg twice daily	Should not be crushed, chewed, or sprinkled on food; Can be taken with or without food; administration with food may reduce the incidence of flushing	Delayed-release capsules: 120 mg and 240 mg; 30 day starter pack
diroximefumarate (Vumerity)	231 mg orally twice daily for 7 days, then increase to the maintenance dose of 462 mg orally twice daily (maximum dose 924 mg/day)	Do not administer with a high-fat, high-calorie meal or snack; A temporary dose reduction to 231 mg orally twice daily may be considered for tolerability, but the recommended maintenance dose of 462 mg orally twice daily should be resumed within 4 weeks (consider discontinuation if unable to tolerate)	Delayed-release capsules: 231 mg in 30-day starter dose bottles and 30-day maintenance dose bottles

Dosages (continued)

Drug	Dosage	Comments	Availability
fingolimod (Gilenya)	Adults and pediatric patients ≥ 10 years weighing > 40 kg: 0.5 mg by mouth once daily; Pediatric patients ≥ 10 years and weighing ≤ 40 kg: 0.25 mg by mouth once daily	Doses higher than 0.5 mg are associated with a greater incidence of adverse reactions without additional benefit	Capsules: 0.25 mg, 0.5 mg capsules
glatiramer acetate (Copaxone*)	20 mg SC once daily 40 mg SC 3 times weekly (at least 48 hours apart)	Refrigerate; may be stored at room temperature for up to 1 month (refrigeration preferred)	Single-dose prefilled syringes: 20 mg/mL, 40 mg/mL 20 mg and 40 mg strengths are <i>not</i> interchangeable
IFNβ-1a (Avonex)	30 mcg IM once weekly	Refrigerate; may be stored at room temperature (25°C) for up to 7 days; Use immediately following reconstitution; however, may be refrigerated for up to 6 hours Protect from light	Powder for injection vial with diluent: 30 mcg
IFNβ-1a (Avonex prefilled syringe)		Refrigerate; allow to come to room temperature before use (~30 minutes); may be stored at room temperature (≤ 25°C) for up to 7 days Protect from light	Prefilled syringes: 30 mcg/0.5 mL
IFNβ-1a (Avonex pen)			Prefilled autoinjectors/pens: 30 mcg/0.5 mL
IFNβ-1a (Rebif)	4.4 mcg or 8.8 mcg SC 3 times weekly, titrated over 4 weeks up to 22 mcg or 44 mcg SC 3 times weekly	Refrigerate; may be stored at or below room temperature for up to 30 days away from heat and light	Prefilled syringes: 22 mcg/0.5 mL, 44 mcg/0.5 mL, titration pack
IFNβ-1a (Rebif Rebidoose®)			Prefilled autoinjector: 22 mcg/0.5 mL, 44 mcg/0.5 mL, titration pack
IFN β-1a SC (pegylated) (Plegridy)	125 mcg SC every 14 days, titrated over 4 weeks with a dose of 63 mcg at initiation and 94 mcg 2 weeks later	Refrigerate; may be stored at room temperature for up to 30 days; allow to come to room temperature before use (~30 minutes) Protect from light	Prefilled syringes: 125 mcg, starter pack (63 mcg and 94 mcg) Prefilled autoinjectors/pens: 125 mcg, starter pack (63 mcg and 94 mcg)
IFNβ-1b (Betaseron)	0.0625 mg SC every other day; increased over a 6-week period to 0.25 mg SC every other day	Store at room temperature prior to reconstitution; stable refrigerated for 3 hours after reconstitution	Powder for injection, vial with diluent: 0.3 mg May use with or without the Betaconnect™ autoinjector†
IFNβ-1b (Extavia)	0.0625 mg SC every other day; increased over a 6-week period to 0.25 mg SC every other day	Store at room temperature prior to reconstitution; stable refrigerated for 3 hours after reconstitution	Powder for injection vial with diluent: 0.3 mg

*Sandoz' Glatopa is a branded generic of Copaxone in both 20 mg/mL and 40 mg/mL strengths.

† The Betaconnect electronic autoinjector is approved for use with Betaseron.¹⁷² It is not supplied with Betaseron but is available through the Betaplus® patient support program. The FDA has also approved a myBETAapp and BETACONNECT software that can be used to connect the autoinjector to a mobile device or computer in order to share data with healthcare providers.

Dosages (continued)

Drug	Dosage	Comments	Availability
natalizumab (Tysabri)	300 mg IV infusion over 1 hour every 4 weeks	Observe for 1 hour following infusion completion; discontinue infusion if hypersensitivity occurs Prescribers must be enrolled in MS TOUCH® program Preparation procedures for dilution are described in the prescribing information	Single-use vial: 300 mg/15 mL
ocrelizumab (Ocrevus)	Initial dose: 300 mg as an IV infusion over at least 2.5 hours, followed 2 weeks later by a second 300 mg IV infusion Maintenance dose: 600 mg as an IV infusion over at least 3.5 hours every 6 months beginning 6 months after the first infusion	Observe for 1 hour following infusion completion; discontinue infusion if life-threatening or disabling hypersensitivity occurs Premedicate with a corticosteroid and antihistamine with or without an antipyretic prior to infusion as detailed in the prescribing information Preparation procedures for dilution and recommended infusion rate guidelines (including rates based on adverse effects/tolerability during infusion) are described in the prescribing information	Single-dose vial: 300 mg/10 mL
siponimod (Mayzent)	Dosing recommendations based on CYP2C9 which must be completed prior to initiation CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2: 2 mg orally once daily (beginning on day 6) following titration; can use starter pack for titration CYP2C9 Genotypes *1/*3 or *2/*3: 1 mg orally once daily (beginning on day 5); do not use starter pack for titration See titration table below for additional details and prescribing information for detailed pre-treatment and post-treatment monitoring	If 1 titration dose is missed for > 24 hours, treatment should be reinitiated with day 1 of the titration regimen Following titration period, if siponimod treatment is interrupted for ≥ 4 consecutive daily doses, reinitiate treatment with day 1 of the titration regimen; first dose monitoring, as recommended, should also occur Unopened containers should be stored in a refrigerator. Once opened, siponimod may be stored at room temperature for 1 week in the starter pack or 1 month in the bottle	Tablets: 0.25 mg, 2 mg, starter pack (twelve 0.25 mg tablets)
teriflunomide (Aubagio)	7 mg or 14 mg by mouth once daily	--	Tablets: 7 mg, 14 mg tablets

Following the second treatment course of alemtuzumab, additional treatment courses of 12 mg per day for 3 consecutive days may be administered as needed. Each additional subsequent course must occur ≥ 12 months following the last dose of the prior treatment course. Prior to initiation, a urine protein to creatinine ratio should be assessed. A CBC with differential, serum creatinine, urinalysis, and

thyroid function tests should be monitored during treatment (see labeling for details monitoring schedule).

A recent CBC is recommended before initiation of dimethyl fumarate therapy to identify patients with pre-existing low lymphocyte counts. Serum aminotransferases, alkaline phosphatase, and total bilirubin levels should also be obtained prior to treatment.

For dalfampridine, a Patient Service Hub has also been created as an initial contact between the patient and prescriber. The role of the Service Hub is to triage all patients receiving dalfampridine to a limited network of specialty pharmacies. The specialty pharmacy will dispense the medication and provide the patient with counseling and a medication guide. The specialty pharmacy will also be required to reinforce the recommended dosage of 10 mg twice daily. The pharmacist will contact the prescriber to verify any total daily doses exceeding 20 mg.

Significant first dose monitoring is needed for fingolimod. All patients must be observed for signs and symptoms of bradycardia for at least 6 hours after first dose with hourly pulse and blood pressure measurement. ECG must be obtained prior to dosing and at the end of the observation period. Prescribers should review results of a recent complete blood cell count (CBC) and obtain serum transaminases and total bilirubin levels within 6 months prior to initiation. See product labeling for additional details.

Several monitoring parameters should be considered when administering teriflunomide. Transaminase and bilirubin levels should be taken 6 months before starting therapy and monitored monthly for at least 6 months. A CBC should be taken 6 months before initiating therapy and further monitoring should occur based on signs and symptoms of infection. Before starting therapy, patients should be screened for TB and should have their blood pressure measured at initiation of therapy and periodically afterwards. Pregnancy should be excluded prior to initiation in women of reproductive potential.

Significant first dose monitoring of siponimod also is recommended in patients with sinus bradycardia (heart rate < 55 bpm), first- or second-degree (Mobitz type I) AV block, or a history of myocardial infarctions or heart failure as siponimod decreases heart rate. All patients must be observed for signs and symptoms of bradycardia for at least 6 hours after first dose with hourly pulse and blood pressure measurement. An ECG should be obtained at the end of the day 1 observation period. Monitoring should continue if select abnormalities are present after 6 hours, regardless of patient symptoms. Consultation with a cardiologist should occur to determine the most appropriate management and monitoring plan during treatment initiation in select patients with additional risk factors. See product labeling for additional details. Results of a recent CBC and liver function tests as well as a cardiac and ophthalmic evaluation should be assessed prior to initiation. A specific titration schedule for siponimod is required (see below).

Siponimod Titration Schedule

Genotype	Titration Dose (all oral doses)	
CYP2C9 Genotypes: *1/*1, *1/*2, or *2/*2	Titration Day	Titration Dose
	Day 1	0.25 mg
	Day 2	0.25 mg
	Day 3	0.5 mg (2 x 0.25 mg)
	Day 4	0.75 mg (3 x 0.25 mg)
	Day 5	1.25 mg (5 x 0.25 mg)
CYP2C9 Genotypes: *1/*3 or *2/*3	Titration Day	Titration Dose
	Day 1	0.25 mg
	Day 2	0.25 mg
	Day 3	0.5 mg (2 x 0.25 mg)
	Day 4	0.75 mg (3 x 0.25 mg)

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, other criteria included studies with clearly stated, predetermined outcome measure(s) of known or probable clinical importance, used data analysis techniques consistent with the study question, and included follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many of the trials with agents in this class were performed in an open-label or partially blinded manner; introduction of bias must be considered when evaluating study findings. Clinical trials of IFN β -1b (Betaseron) were used for IFN β -1b (Extavia) approval.¹⁷³

Diroximel fumarate (Vumerity) was approved via the 505(b)(2) pathway. Thus, at least a portion of the data supporting its approval may have been derived from another manufacturer. Bioavailability studies comparing dimethyl fumarate (Tecfidera) to diroximel fumarate in patients with relapsing forms of MS and healthy subjects were used to establish the efficacy of diroximel fumarate.¹⁷⁴

Relapsing MS

alemtuzumab (Lemtrada) versus IFN β -1a SC (Rebif)

The efficacy of alemtuzumab was demonstrated in 2 studies that evaluated alemtuzumab 12 mg in patients with relapsing-remitting multiple sclerosis (RRMS).^{175,176} Alemtuzumab was administered by

intravenous (IV) infusion once daily over a 5-day course, followed 1 year later by IV infusion once daily over a 3-day course in both trials. Both studies included patients who had experienced at least 2 relapses during the 2 years prior to trial entry and at least 1 relapse during the year prior to trial entry. Neurological examinations were performed every 12 weeks and at the time of suspected relapse. Magnetic resonance imaging (MRI) evaluations were performed annually.

The first study was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously 3 times a week) controlled study in patients with RRMS.¹⁷⁷ Patients entering the study had Expanded Disability Status Scale (EDSS) scores of 5 or less and had to have experienced at least 1 relapse while on interferon beta or glatiramer acetate therapy. Patients were randomized to receive alemtuzumab (n=426) or interferon beta-1a (n=202). The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression. Confirmed disability progression was defined as at least a 1 point increase above baseline EDSS sustained for 6 months. The MRI outcome measure was the change in T2 lesion volume. The ARR was significantly lower in patients treated with alemtuzumab than in patients who received interferon beta-1a (0.26 versus 0.52, $p<0.0001$). The proportion of patients with disability progression at year 2 was also significantly reduced in the alemtuzumab group (13% versus 21%; $p<0.0084$). There was no significant difference between the treatment groups for the change in T2 lesion volume (-1.3 versus -1.2; $p=0.14$).

The other alemtuzumab study was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously 3 times a week) controlled study in patients with RRMS. Patients entering Study 2 had EDSS scores of 3 or less and prior treatment for multiple sclerosis.¹⁷⁸ Patients were randomized to receive alemtuzumab (n=376) or interferon beta-1a (n=187). The clinical outcome measures were the ARR over 2 years and the time to confirmed disability progression, as defined in the first study. The MRI outcome measure was the change in T2 lesion volume. The ARR was significantly lower in patients treated with alemtuzumab than in patients who received interferon beta-1a (0.18 versus 0.39, $p<0.0001$). There was no statistically significant difference in the proportion of patients with disability progression at Year 2 (8% versus 11%; $p=0.22$) or between the treatment groups for the change in T2 lesion volume (-9.3 versus -6.5; $p=0.31$). A 5-year extension of this study with alemtuzumab demonstrated continued efficacy.¹⁷⁹

cladribine (Mavenclad) versus placebo

CLARITY was a 96-week, phase 3, double-blind, placebo-controlled trial that evaluated the efficacy of oral cladribine in 1,326 adults with relapsing-remitting MS based on the McDonald criteria.^{180,181} Included patients were required to have had ≥ 1 relapse in the previous 12 months and a Kurtzke EDSS score of ≤ 5.5 . Patients were randomized 1:1:1 to receive a cladribine cumulative dose of 3.5 mg/kg or 5.25 mg/kg or matching placebo. Patients randomized to the 3.5 mg/kg cumulative dose received the first treatment course at weeks 1 and 5, each over 4 to 5 days, of the first year. This was repeated as a second treatment course at weeks 1 and 5 of the second year. Patients in the cladribine 5.25 mg/kg group received additional treatment at weeks 9 and 13 of the first year. The primary efficacy measure was ARR at week 96. A relapse was defined as an increase of at least 2 points on the EDSS, in the absence of fever that lasted at least 24 hours and was preceded by ≥ 30 days of clinical stability or improvement. At baseline, the mean duration of MS was 8.7 years and median EDSS was 3. The median age was 39 years, and about twice as many females as males were enrolled. Patients were

excluded from the study if they had failed ≥ 2 previous disease-modifying therapies. The cladribine 3.5 mg/kg dose resulted in a 58% relative reduction in ARR compared to placebo (ARR, 0.14 versus 0.33, respectively; $p < 0.001$). A statistically lower percentage of patients in the cladribine 3.5 mg/kg group reported no relapse compared to the placebo group (81% versus 63%, respectively; $p < 0.05$). Notably, there was a significant decrease in the number of active T1 Gd-positive or T2 lesions with cladribine 3.5 mg/kg compared to placebo (T1 Gd+, 0 versus 0.33; T2, 0 versus 0.67; $p < 0.001$ for both). Compared to the 3.5 mg/kg regimen, the 5.25 mg/kg regimen did not provide additional clinically meaningful benefit and was associated with a higher incidence of grade ≥ 3 lymphopenia. In the 3.5 mg/kg group, 92% of patients completed the 96-week study.

A total of 806 patients who completed the CLARITY trial were enrolled in a blinded 2-year extension study.¹⁸² Placebo recipients from the original trial received cladribine 3.5 mg/kg; cladribine recipients (either dose) were re-randomized 2:1 to cladribine 3.5 mg/kg or placebo. In patients treated with cladribine 3.5 mg/kg in CLARITY, approximately 75% remained relapse-free when given placebo during the extension. No clinical improvement in efficacy was evident following further treatment with cladribine tablets after the initial 2-year treatment period in this trial setting. Patients treated with cladribine tablets in both CLARITY and the extension trials experienced the highest incidence of grade ≥ 3 lymphopenia (40.9% and 53.2%) and longest median time to recovery to grade 0 to 1 lymphopenia (212 and 168 days) during the extension.

dalfampridine (Ampyra) versus placebo

A phase 3 study assessed efficacy and safety of dalfampridine in patients with ambulatory deficits due to multiple sclerosis.¹⁸³ This was a randomized, multicenter, double-blind, controlled trial, 301 patients with any type of multiple sclerosis were assigned to 14 weeks of treatment with dalfampridine 10 mg or placebo twice daily. Patients who had a history of seizures or onset of an MS exacerbation within 60 days were excluded from the trial. A consistent improvement on a timed 25-foot walk was used to define response, with proportion of timed walk responders in each treatment group as the primary outcome. The proportion of timed walk responders was higher in the dalfampridine group (35%) than in the placebo group (8%; $p < 0.0001$). Improvement in walking speed in dalfampridine-treated patients was 25.2% and 4.7% in the placebo group. A 20% or greater improvement in walking speed is frequently considered clinically meaningful.^{184,185,186}

Another randomized, multicenter, double-blind trial included 229 patients with definite MS of any type.¹⁸⁷ Patients were randomized to dalfampridine 10 mg twice daily or placebo. Response was defined as consistent improvement on the timed 25-foot walk with the primary outcome the percent of timed walk responders in each group. The percentage of timed walk responders was 42.9% (51/119 patients) of patients receiving dalfampridine compared to 9.3% (11/118 patients) of patients receiving placebo ($p < 0.0001$). Average improvement in walking speed among dalfampridine-treated patients in the responders group was 24.7% from baseline (95% confidence interval [CI], 21 to 28.4). The mean improvement at the last treatment visit was 25.7% 8 to 12 hours after the previous dose. Adverse effects were consistent with previous studies.

dimethyl fumarate (Tecfidera) versus placebo

DEFINE study:¹⁸⁸ The DEFINE study was a 2-year, phase 3, randomized, double-blind, placebo-controlled study that compared dimethyl fumarate 240 mg twice daily, 240 mg thrice daily (not an

FDA-approved dosing frequency), and placebo to demonstrate the efficacy of dimethyl fumarate in patients with relapsing-remitting multiple sclerosis (RRMS). Patients who had experienced at least 1 relapse in the previous year or had a brain MRI scan demonstrating at least 1 Gd-enhancing lesion within 6 weeks of randomization were included. The primary endpoint was the proportion of patients who had relapses by 2 years. Neurological evaluations were conducted at baseline, every 3 months, and at the time of a suspected relapse and safety evaluations were conducted every 4 weeks. The study had balanced baseline demographic and disease characteristics. The median time on the study drug was 96 weeks with 69% in both dimethyl fumarate groups and 65% in the placebo group completing 96 weeks. A total of 1,234 patients received at least 1 dose of the medication including 410 in the twice daily arm, 416 in the thrice daily arm, and 408 in the placebo arm. Both dimethyl fumarate groups significantly reduced relapse of MS on the basis of Kaplan-Meier estimates of 27% for the twice daily group and 26% for the thrice daily group compared to 46% in the placebo group ($p < 0.001$). No additional benefit was shown in the thrice daily group compared to the twice daily group. The incidence of adverse events was similar across the 3 groups with flushing being the most common adverse effect in the dimethyl fumarate group. Dimethyl fumarate was also associated with a decrease in lymphocyte counts.

dimethyl fumarate (Tecfidera) versus placebo with glatiramer acetate (Copaxone) as an active comparator

CONFIRM study:¹⁸⁹ The CONFIRM study was a 2-year, phase 3, randomized, double-blind, placebo-controlled study that compared dimethyl fumarate 240 mg twice daily, 240 mg thrice daily (not a FDA-approved dosing frequency), open label glatiramer acetate 20 mg daily, and placebo to demonstrate the efficacy of dimethyl fumarate in patients with RRMS. Patients who had experienced at least 1 relapse in the previous year or had a brain MRI scan demonstrating at least 1 gadolinium-enhancing lesion within 6 weeks of randomization were included. The primary endpoint was ARR confirmed by an independent neurologic evaluation committee after 2 years. The study had balanced baseline demographic and disease characteristics. The ARR was calculated as the total number of relapses divided by patient years in the study. Standardized neurological assessments were performed every 12 weeks and at the time of suspected relapse. The median time on the study drug was 96 weeks with 72% in the dimethyl fumarate twice daily group, 70% in the dimethyl fumarate thrice daily group, 75% in the glatiramer acetate group, and 64% in the placebo group completing 96 weeks. One thousand four hundred seventeen patients were included in the intent to treat analysis including 359 in the twice daily group, 345 in the thrice daily group, 350 in the glatiramer acetate group, and 363 in the placebo group. All 3 treatment groups had a statistically significant reduction in ARRs compared to placebo including a 0.22 relapse rate ($p < 0.001$) in the twice daily group, a 0.2 ($p < 0.001$) relapse rate in the thrice daily group, and a 0.29 ($p = 0.01$) relapse rate in the glatiramer acetate compared to the 0.4 relapse rate in the placebo group. No additional benefit was shown in the thrice daily group compared to the twice daily group. Additional benefits were also seen in MRI measures (active lesions and total lesion volume).¹⁹⁰ Although the study was not designed to test the superiority or noninferiority of dimethyl fumarate to glatiramer acetate, the active comparator had similar results.¹⁹¹ The incidence of adverse events was similar across the groups with flushing being the most common adverse effect in the dimethyl fumarate groups. Dimethyl fumarate was also associated with a decrease in lymphocyte counts.

fingolimod (Gilenya) versus IFN β -1a IM (Avonex) in adults

TRANSFORMS:¹⁹² The first study was a 12-month, randomized, double-blind, double-dummy, multicenter study comparing fingolimod 0.5 mg or 1.25 mg daily and IFN β -1a 30 mcg IM weekly. A total of 1,292 patients had RRMS with a recent history of at least 1 relapse, median age of 36 years, and a score of 0 to 5.5 on the EDSS. The primary endpoint of ARR was significantly lower in the fingolimod groups compared to IFN β -1a: 0.16 (95% CI, 0.12 to 0.21) in the 0.5 mg group, 0.2 (95% CI, 0.16 to 0.26) in the 1.25 mg group, and 0.33 (95% CI, 0.26 to 0.42; $p < 0.001$ for both comparisons) in the IFN β -1a group. MRI results supported the primary findings as measured by the mean number of new and newly enlarged T2 lesions at 1 year (1.6 for fingolimod groups versus 2.6 for IFN β -1a, $p = 0.002$). There was no significant difference in the time to 3-month confirmed disability progression between fingolimod groups and IFN β -1a patients at 1 year. Two fatal infections occurred in the group that received the 1.25 mg dose of fingolimod: disseminated primary varicella zoster and herpes simplex encephalitis. Other adverse events in the fingolimod group were nonfatal herpes virus infections, bradycardia/atrioventricular block, hypertension, macular edema, skin cancer, and elevated liver enzymes.

A 2-year, double-blind extension of the TRANSFORMS study compared the second year with results from the first year with a focus on the patients who switched therapy from IFN β -1a and to evaluate efficacy of fingolimod at 24 months relative to fingolimod efficacy at 12 months.¹⁹³ A total of 1,027 patients entered the extension phase. Patients originally randomized to fingolimod 0.5 or 1.25 mg daily continued on the same treatment. Patients who originally received IFN β -1a 30 mcg IM weekly were re-randomized to fingolimod 0.5 mg or 1.25 mg daily. A total of 882 patients completed the 24 months of treatment. Endpoints included ARR, disability progression, and MRI outcomes. Patients receiving 24 months of fingolimod had persistent benefits in ARR (0.5 mg fingolimod [$n = 356$], 0.12 [95% CI, 0.08 to 0.17] in months 0 to 12 versus 0.11 [95% CI, 0.08 to 0.16] in months 13 to 24; 1.25 mg fingolimod [$n = 330$], 0.15 [95% CI, 0.1 to 0.21] versus 0.11 [95% CI, 0.08 to 0.16]. Patients who initially received IFN β -1a 30 mcg IM weekly had a lower ARR after switching to fingolimod compared to the first 12 months (IFN β -1a to 0.5 mg fingolimod [$n = 167$], 0.31 [95% CI, 0.22 to 0.43] in months 0 to 12 versus 0.22 [95% CI, 0.15 to 0.31] in months 13 to 24; $p = 0.049$; IFN β -1a to 1.25 mg fingolimod [$n = 174$], 0.29 [95% CI, 0.2 to 0.4] versus 0.18 [95% CI, 0.12 to 0.27], $p = 0.024$). After switching to fingolimod, numbers of new or newly enlarging T2 and gadolinium (Gd)-enhancing T1 lesions were significantly reduced compared with the previous 12 months of IFN β -1a therapy ($p < 0.0001$ for T2 lesions at both doses; $p = 0.002$ for T1 at 0.5 mg; $p = 0.011$ for T1 at 1.25 mg). Over the 2-year period, patients receiving continuous fingolimod had lower ARRs (0.18 [95% CI, 0.14 to 0.22] for 0.5 mg; 0.2 [95% CI, 0.16 to 0.25] for 1.25 mg; 0.33 [95% CI, 0.27 to 0.39] for the switch group; $p < 0.0001$ for both comparisons), fewer new or newly enlarged T2 lesions ($p = 0.035$ for 0.5 mg, $p = 0.068$ for 1.25 mg), and fewer patients with Gd-enhancing T1 lesions ($p = 0.001$ for 0.5 mg fingolimod versus switch group; $p = 0.002$ for 1.25 mg fingolimod versus switch group). There was no benefit on disability progression. Adverse events were consistent with those observed for fingolimod. The manufacturer of fingolimod supported the study. In an extension study of the TRANSFORMS trial and the above 2-year extension study, data were reported for patients receiving fingolimod for up to 4.5 years and suggested sustained efficacy of fingolimod following a switch from IFN β -1a.¹⁹⁴

fingolimod (Gilenya) versus IFN β -1a IM (Avonex) in pediatrics

PARADIGMS:^{195,196} A double-blind, randomized, clinical trial established the safety and efficacy of fingolimod in 215 pediatric patients ages 10 to 17 years (mean, 15.3 years) with RRMS with an EDSS score from 0 to 5.5 (median, 1.5). Included patients who had experienced > 1 clinical relapse during the past year, 2 relapses during the past 2 years, or evidence of ≥ 1 Gd-enhancing lesions on MRI. Patients were randomized 1:1 to fingolimod (0.25 mg or 0.5 mg) orally once daily or to IFN β -1a IM. Patients were permitted to have used an interferon-beta product, dimethyl fumarate, or glatiramer acetate up to the time of randomization. The ARR, the primary endpoint, was lower in patients treated with fingolimod (0.122) compared to patients who received IFN β -1a (0.675; absolute difference, 0.55 relapses; relative difference, 82%; $p < 0.001$). The relative reduction in ARR was 81.9%. In addition, the annualized rate of the number of new or newly enlarged T2 lesions (4.393 versus 9.269, respectively) and number of Gd-enhancing T1 lesions per scan (0.436 to 1.282, respectively) to month 24, both secondary endpoints, were lower in patients treated with fingolimod compared to those treated with IFN β -1a (both $p < 0.001$).

glatiramer acetate (Copaxone) and IFN β -1a IM (Avonex) versus glatiramer acetate (Copaxone) or IFN β -1a IM (Avonex)

CombiRx study:¹⁹⁷ The CombiRx study was a National Institutes of Health (NIH) sponsored 3-year, randomized, double-blind, controlled study comparing combined use of glatiramer acetate and IFN β -1a IM compared to each agent alone. Patients were randomized to 3 treatment arms of glatiramer acetate 20 mg subcutaneously daily plus placebo (GA), IFN β -1a 30 μ mg intramuscularly weekly plus placebo (IFN), or 20 mg subcutaneously daily plus IFN β -1a 30 μ mg intramuscularly weekly (GA + IFN). Participants were 18 to 60 years of age with an EDSS of 0 to 5.5 with an RRMS diagnosis and at least 2 exacerbations within the last 3 years. Patients received neurological assessment every 12 weeks for 3 years during the study and MRIs at months 6, 12, 24, and 36. The primary outcome of the study was the Annualized Relapse Rate (ARR) based on protocol-defined exacerbations. A total of 1,008 patients were randomized to the treatment arms with 499 patients in the GA + IFN arm, 250 in the IFN arm, and 259 in the GA arm. The patients' baseline characteristics were similar with the exception of age which was accounted for with adjustments for age. The GA + IFN treatment was not significantly better than GA treatment with 150 relapses compared to 70 relapses ($p = 0.27$), but it was significantly better than the IFN treatment with 97 relapses ($p = 0.022$). The GA treatment was significantly better than the IFN treatment with 70 relapses compared to 97 relapses ($p = 0.027$). There were no additional safety issues resulting from combination therapy and the adverse events reported were the usual adverse events associated with the single agents.

glatiramer acetate (Copaxone) (three times weekly) versus placebo

GALA study:¹⁹⁸ A randomized, double-blind, placebo-controlled study was conducted to assess the efficacy and safety of glatiramer acetate 40 mg administered 3 times weekly compared with placebo in patients with RRMS. Patients with RRMS with at least 1 documented relapse in the 12 months before screening, or at least 2 documented relapses in the 24 months before screening, and an EDSS score ≤ 5.5 , were randomized 2:1 to receive either glatiramer acetate 40 mg 3 times weekly subcutaneously or placebo for 12 months. Of 1,524 patients screened, 1,404 were randomized to receive glatiramer acetate 40 mg 3 times weekly ($n = 943$) or placebo ($n = 461$). Ninety-three percent and 91% of patients in the placebo and glatiramer acetate groups, respectively, completed the 12-month study. Glatiramer

acetate 40 mg 3 times weekly was associated with a 33.1% ARR compared to a 50.5% rate in the placebo group for a 34% reduction in annualized relapses (mean ARR, 0.331 versus 0.505; $p < 0.0001$). The most common adverse event in the glatiramer acetate group was injection site reaction (35.5% of the glatiramer acetate 40 mg 3 times weekly patients versus 5% of the patients on placebo).

glatiramer acetate (Glatopa) versus glatiramer acetate (Copaxone) and placebo

GATE: A randomized, double-blind, active and placebo-controlled phase 3 trial compared the efficacy of Glatopa and Copaxone to placebo ($n=794$).¹⁹⁹ Adult patients with RRMS, ≥ 1 relapse in the prior year, EDSS scores of 0 to 5, and 1 to 15 Gd-enhancing lesions on MRI were randomized 4.3:3.1:1 to Glatopa 20 mg, Copaxone 20 mg, and placebo once daily by SC injection for 9 months. Patients with prior exposure to glatiramer or other immunosuppressive treatments were excluded. The primary outcome was the total number of Gd-enhancing lesions during the final 3 months. ARR and EDSS were also measured. Gd-enhancing lesions were lower with both glatiramer products compared to placebo (ratio, 0.488; 95% CI, 0.365 to 0.651; $p < 0.001$). The ratio of Glatopa to Copaxone Gd-enhancing lesions was 1.095 (95% CI, 0.883 to 1.36), falling within the prespecified equivalence margin (0.727 to 1.375). The authors concluded that Glatopa was comparable in efficacy, as measured by Gd-enhancing lesions, to Copaxone.

IFN β -1a IM (Avonex) versus IFN β -1a SC (Rebif)

The EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) trial was a randomized, 64-week dose effect trial of IFN β -1a 44 mcg SC 3 times weekly or IFN β -1a 30 mcg IM once weekly in 677 patients with RRMS.²⁰⁰ Patients were aware of their treatment assignment; blinded clinical evaluators performed neurologic and MRI evaluations. At 24 weeks, the proportion of relapse-free patients (primary endpoint) was 75% in the SC arm and 63% in the IM arm ($p < 0.001$). At 48 weeks, the proportion of relapse-free patients was 62% in the SC group and 52% in the IM group ($p=0.006$). Fewer active MRI lesions (principal MRI endpoint) were observed in the SC arm at 24 weeks ($p < 0.001$). The 48-week MRI results were similar to those at 24 weeks, with nearly 40% fewer active MRI lesions in the SC group ($p < 0.001$). There was no significant difference in drug discontinuations, the rate of adverse events, or severity of adverse events; the majority of adverse events were rated mild by investigators. Hepatic and hematological adverse events and laboratory abnormalities were more common with the SC regimen. Flu-like symptoms were more common with the IM dosage.

In an extension of the EVIDENCE study, patients were all given IFN β -1a 44 mcg SC 3 times weekly and were followed for an average additional 32 weeks.²⁰¹ At the transition visit, 223 (73%) of 306 patients originally receiving 30 mcg IM weekly converted to 44 mcg SC 3 times weekly, and 272 (91%) of 299 receiving 44 mcg SC 3 times weekly continued the same therapy. The post-transition ARR decreased from 0.64 to 0.32 for patients switching to the SC dosage ($p < 0.001$), and from 0.46 to 0.34 for patients continuing the 3 times weekly SC dosage ($p=0.03$). The change was greater in those switching to the SC dosage ($p=0.047$). Patients converting to the 3-time weekly SC regimen had fewer active lesions on T2-weighted MRI compared to before the transition ($p=0.02$), whereas those continuing the higher dose had no significant change in T2 active lesions. Patients who converted to high-dose/high-frequency IFN β -1a therapy had increased rates of adverse events and treatment terminations consistent with the initiation of high-dose SC IFN therapy.

IFNβ-1a IM (Avonex) versus IFNβ-1b (Betaseron)

The Independent Comparison of Interferon (INCOMIN) trial was a single-blinded, randomized comparison of IFNβ-1a IM and IFNβ-1b in 188 patients with RRMS.²⁰² IFNβ-1a was given at a dose of 30 mcg IM once weekly, and IFNβ-1b was administered at a dose of 250 mcg SC every other day. Over the 2-year study period, 36% of patients randomized to IFNβ-1a IM were relapse-free compared to 51% of patients receiving IFNβ-1b ($p=0.03$). More patients remained free from new T2 lesions, which indicate inflammatory damage on MRI, in the IFNβ-1b group (55% versus 26%, $p<0.0003$). Delay of confirmed disease progression was significantly higher in the IFNβ-1b group. Discontinuation of therapy due to disease progression was more prevalent in the IFNβ-1a IM group. Significantly more patients withdrew from therapy with IFNβ-1b due to adverse events or laboratory abnormalities. It should be noted that, while MRI was assessed blindly, the physician evaluating clinical outcomes was unblinded.

IFNβ-1a IM (Avonex) versus IFNβ-1a SC (Rebif) versus IFNβ-1b (Betaseron)

In a parallel group, single-blind study, 90 patients with RRMS were randomized to receive IFNβ-1a 30 mcg IM once weekly, IFNβ-1a 44 mcg SC 3 times weekly, or IFNβ-1b 250 mcg SC every other day for 24 months.²⁰³ The EDSS scores remained stable in patients in the IFNβ-1a IM group and decreased in the groups receiving IFNβ-1a SC ($p<0.05$ versus baseline) and IFNβ-1b ($p<0.001$). In the patients treated with IFNβ-1a IM, the mean 2-year relapse rate decreased from 2 to 1.2 episodes ($p<0.001$ compared to baseline). In the patients treated with IFNβ-1a SC, the mean relapse rate decreased from 2.4 to 0.6, while the rate in those treated with IFNβ-1b decreased from 2.2 to 0.7 ($p<0.001$ for both changes from baseline). After 2 years, 20% of patients receiving IFNβ-1a IM remained relapse-free. In comparison, 56.7% of patients receiving IFNβ-1a SC and 43.3% of those receiving IFNβ-1b remained relapse-free ($p<0.05$ for both comparisons to IFNβ-1a IM).

IFNβ-1a SC (Rebif) versus IFNβ-1b (Betaseron)

In an open-label study, 301 patients with RRMS were randomized to receive IFNβ-1a 22 mcg SC once weekly or IFNβ-1b 250 mcg SC every other day for 2 years.²⁰⁴ The annual relapse rates were virtually equal in the 2 arms of the randomized study (IFNβ-1a: 0.7; IFNβ-1b: 0.71), as were the time to first relapse and the time to sustained progression. In addition, no significant difference existed in proportions of relapse-free patients, 40.8% in the IFNβ-1a SC group and 45.2% in the IFNβ-1b group. Subsequent intent-to-treat analysis indicated a statistically insignificant difference in the proportion of relapse-free patients, 35% and 41% in the IFNβ-1a SC and IFNβ-1b groups, respectively.²⁰⁵ The IFNβ-1a dosing interval in the study was less frequent than the FDA-approved dosing regimen.

IFNβ-1a SC (Rebif) versus glatiramer acetate (Copaxone)

In the multicenter, parallel, open-label REGARD (REbif versus Glatiramer Acetate in Relapsing MS Disease) trial, 764 patients with RRMS were randomized to receive IFNβ-1a SC 44 mcg 3 times weekly ($n=386$) or glatiramer acetate SC 20 mg daily ($n=378$) for 96 weeks.²⁰⁶ Patients had a history of at least 1 relapse within the previous 12 months. The primary outcome of time to first relapse was similar in both groups (hazard ratio 0.94; 95% CI 0.74 to 1.21; $p=0.64$). Relapse rates were lower than expected: 258 patients (126 in the IFNβ-1a group and 132 in the glatiramer acetate group) had 1 or more relapses. A secondary analysis using 460 patients (230 from each group) from the study was completed

to compare T2-weighted and gadolinium-enhanced lesion number and volume. There were no significant differences noted in the outcomes for the number and change in volume of T2 lesions or change in the volume of gadolinium-enhanced lesions. However, the IFN β -1a group had significantly fewer gadolinium-enhancing lesions (0.24 versus 0.41 lesions per patients per scan; 95% CI, -0.4 to 0.1; p=0.0002) versus the glatiramer acetate group. Both therapies were well tolerated.

IFN β -1b SC (Betaseron) versus glatiramer acetate (Copaxone)

The BEYOND trial compared the efficacy, safety, and tolerability of IFN β -1b 250 mcg or 500 mcg with glatiramer acetate 20 mg for treating RRMS.²⁰⁷ A total of 2,244 patients were enrolled in a prospective, multicenter, randomized trial. Patients were randomly assigned to receive IFN β -1b or glatiramer acetate SC every day. The primary outcome was relapse risk, defined as new or recurrent neurological symptoms separated by at least 30 days from the preceding event and that lasted at least 24 hours. Clinical outcomes were assessed quarterly for 2 to 3.5 years. No differences were determined in relapse risk, as well as for secondary endpoints such as EDSS progression, T1-hypointensive lesion volume, or normalized brain volume among treatment groups. Flu-like symptoms were more common in patients treated with IFN β -1b (p<0.0001), whereas injection site reactions were more common in patients treated with glatiramer acetate (p=0.0005). The source of funding for this study was Bayer HealthCare Pharmaceuticals.

IFN β -1a SC pegylated (Plegridy) versus placebo

ADVANCE study:²⁰⁸ The efficacy of pegylated IFN β -1a SC (Plegridy) was demonstrated in a randomized, double-blind, placebo-controlled trial. The trial compared clinical and MRI outcomes at 48 weeks in patients who received pegylated IFN β -1a SC 125 mcg (n=512) or placebo (n=500) subcutaneously once every 14 days. The study enrolled patients who had a baseline EDSS score from 0 to 5, who had experienced at least 2 relapses within the previous 3 years, and had experienced at least 1 relapse in the previous year. The trial excluded patients with progressive forms of multiple sclerosis. The mean age of the study population was 37 years, the mean disease duration was 3.6 years, and the mean EDSS score at baseline was 2.46. The majority of the patients were women (71%). The trial scheduled neurological evaluations at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI evaluations were scheduled at baseline, week 24, and week 48. The primary outcome was the ARR over 1 year. Secondary outcomes included the proportion of patients relapsing, number of new or newly enlarging T2 hyperintense lesions, and time to confirmed disability progression. Pegylated IFN β -1a SC was associated with a 26% relapse rate compared to 40% in the placebo group for a 36% relative reduction in annualized relapses (p=0.0007). Two-year extension study results suggest sustained efficacy as well.²⁰⁹

natalizumab (Tysabri) versus placebo

The efficacy of natalizumab was established in 2 randomized, double-blind, placebo-controlled trials in MS patients with at least 1 clinical relapse in the prior year and an EDSS score of 0 to 5 (AFFIRM and SENTINEL).^{210,211,212} AFFIRM included 942 patients without IFN β or glatiramer exposure within the prior 6 months, but most had not received treatment from either agent previously. Patients in AFFIRM were randomized 2:1 to natalizumab 300 mg as an IV infusion every 4 weeks for up to 28 months (30 infusions) or placebo. SENTINEL included 1,171 patients with ≥ 1 relapse while on treatment with weekly IFN β -1a (Avonex) during the prior year. Patients were randomized 1:1: to natalizumab 300 mg

as an IV infusion every 4 weeks for up to 28 months (30 infusions) or placebo and all continued IFN β -1a treatment. The primary endpoint was time to onset of sustained increase in disability (≥ 1 point on the EDSS from baseline for at least 12 weeks). In both studies, the time to onset of increased and sustained disability was longer with natalizumab than with placebo. Likewise, the proportion of patients with increased and sustained disability was lower with natalizumab than with placebo (AFFIRM: 17% versus 29% at 120 months, respectively [relative risk reduction, 42%; 95% CI, 23 to 57]; SENTINEL: 23% versus 29% at 120 months, respectively [relative risk reduction, 25%; 95% CI, 4 to 39]).

ocrelizumab (Ocrevus) versus IFN β -1a SC (Rebif)

OPERA I and II: Two replicate, phase 3, double-blind, double-dummy, randomized, active-controlled trials established the safety and efficacy of ocrelizumab for the treatment of patients with RMS (OPERA I, n=821; OPERA II, n=835).^{213,214} The trials included patients ages 18 to 55 years old with a diagnosis of MS (based on the 2010 revised McDonald criteria), an EDSS score of 0 to 5.5 at screening, ≥ 2 documented relapses within the past 2 years or 1 documented relapse within the past year, MRI of the brain consistent with MS, and no neurologic worsening for ≥ 30 days prior to both screening and baseline. Patients were randomized 1:1 to an ocrelizumab 600 mg IV infusion every 24 weeks with 2 initial doses of 300 mg on days 1 and 15 or IFN β -1a (Rebif) 44 mcg administered SC 3 times weekly. All patients were premedicated with 100 mg IV methylprednisolone prior to every infusion. An analgesic or antipyretic and antihistamine was also recommended, but use was at the discretion of the infusion center. The primary endpoint was the ARR at 96 weeks based on intent-to-treat (ITT) analysis.

In OPERA I, baseline characteristics were similar among groups and included a mean age of 37 years, 66% female, a mean duration of MS diagnosis of 3.8 years, mean number of relapses in the prior year of 1.3, a mean EDSS of 2.8, 74% of patients had not been treated previously with a non-steroid therapy in the past 2 years, and a mean of 1.8 T₁ Gd-enhancing lesions on MRI.^{215,216} In OPERA II, baseline characteristics also were similar among groups and included a mean age of 37 years, 66% female, a mean duration of MS diagnosis of 4.1 years, mean number of relapses in the prior year of 1.3, a mean EDSS of 2.8, 74% of patients had not been treated previously with a non-steroid therapy in the past 2 years, and a mean of 1.9 T₁ Gd-enhancing lesions on MRI.

In OPERA I, the ARR at 96 weeks was 0.16 (95% confidence interval [CI], 0.12 to 0.2) with ocrelizumab compared to 0.29 (95% CI, 0.24 to 0.36) with interferon β -1a, resulting in a rate ratio (RR) of 0.54 (95% CI, 0.4 to 0.72; p<0.001) and a relative reduction of 46%. In OPERA II, the ARR at 96 weeks was 0.16 (95% CI, 0.12 to 0.2) with ocrelizumab compared to 0.29 (95% CI, 0.23 to 0.36) with interferon β -1a, resulting in a RR of 0.53 (95% CI, 0.4 to 0.71; p<0.001) and a relative reduction of 47%.^{217,218} The proportion of patients with 12-week confirmed disability progression was 7.6% for ocrelizumab and 12.2% for interferon β -1a in OPERA I (HR, 0.57; 95% CI, 0.37 to 0.9; p=0.01) and 10.6% for ocrelizumab and 15.1% for interferon β -1a in OPERA II (HR, 0.63; 95% CI, 0.42 to 0.92; p=0.02). The mean number of T₁ Gd-enhancing lesions per MRI scan was 0.02 for ocrelizumab and 0.29 for interferon β -1a in OPERA I (RR, 0.06; 95% CI, 0.03 to 0.1; p<0.001) and 0.02 for ocrelizumab and 0.42 for interferon β -1a in OPERA II (RR, 0.05; 95% CI, 0.03 to 0.09; p<0.001). The mean number of new and/or enlarging T₂ hyperintense lesions per MRI scan was 0.32 for ocrelizumab and 1.41 for interferon β -1a in OPERA I (RR, 0.23; 95% CI, 0.17 to 0.3; p<0.001) and 0.33 for ocrelizumab and 1.9 for interferon β -1a in OPERA II (RR, 0.17; 95% CI, 0.13 to 0.23; p<0.001).

Subgroup analyses of efficacy endpoints from the pooled OPERA I and OPERA II clinical trials were presented in a separate publication.²¹⁹ Prespecified subgroups included study, age, sex, body mass index (BMI), region, baseline EDSS score, baseline gadolinium-enhancing T1 lesion status, and pre-treated patients with active disease or highly active disease. The treatment benefit of ocrelizumab versus IFN β -1a was maintained across the majority of subgroup-levels for all endpoints, including ARR, disability progression, and MRI outcomes.

siponimod (Mayzent) versus placebo

EXPAND:^{220,221} A phase 3, multinational, randomized, double-blind, parallel-group, placebo-controlled, time-to-event study evaluated the safety and efficacy of siponimod in patients with SPMS (n=1,651). Included patients were 18 to 60 years old and had evidence of disability progression in the past 2 years, no evidence of relapse within 3 months prior to study entry, and an EDSS score of 3 to 6.5. Patients were randomized 2:1 to daily oral siponimod 2 mg following titration or placebo for up to 3 years (median, 21 months; range, 1 day to 37 months) or until the occurrence of a prespecified number of confirmed disability progression (CDP) events. The primary outcome was the time to 3-month CDP, which was defined as a \geq 1-point increase in EDSS (a \geq 0.5-point for baseline EDSS \geq 5.5) that is sustained for 3 months. Other endpoints included the time to 3-month confirmed worsening of \geq 20% from baseline on the timed 25-foot walk test, the change from baseline in T2 lesion volume, ARR, and select MRI measures. Evaluations occurred at screening, every 3 months during treatment, and at the time of suspected relapse. MRI evaluations occurred at screening and every 12 months. At baseline, the median disease duration was 16 years (mean, 16.8 years), the median EDSS score was 6, 36% had \geq 1 relapses in the prior 2 years, 22% of those with available imaging had \geq 1 gadolinium-enhancing lesions on MRI, and 78% had previous MS treatment. Siponimod was found to be superior to placebo in reducing the risk of CDP (26% versus 32%, respectively), resulting in a hazard ratio of 0.79 (95% CI, 0.65 to 0.95; relative risk reduction, 21%; p=0.013). The ARR was 0.071 with siponimod versus 0.16 with placebo (relative reduction, 55%; p<0.01). On MRI, the change from baseline in T2 lesion volume (mm³) was 184 (95% CI, 54 to 314) with siponimod versus 879 (95% CI, 712 to 1,047) with placebo (p<0.01). No statistical difference was found in the 25-foot walk test; the proportion of patients with confirmed worsening in timed 25-foot walk test were 40% with siponimod versus 41% with placebo (p=not significant). Notably, while a significant difference on disability progression was found in patients with active SPMS, defined as those with a relapse in the prior 2 years (hazard ratio, 0.67; 95% CI, 0.49 to 0.91), the effect on those with non-active SPMS was not statistically significant (hazard ratio, 0.87; 95% CI, 0.68 to 1.11). No significant differences were found in the following subgroup analyses: relapses during study (yes/no) or gender; however, differences were seen in subgroups when evaluated by the number of gadolinium-enhancing T1 lesions at baseline (\geq 1, statistically different; 0, not different), baseline age, and EDSS, which are detailed in the prescribing information. Eight-two percent and 78% of siponimod- and placebo-treated patients, respectively, completed the study. Adverse events occurred in 89% of siponimod-treated patients versus 82% of placebo-treated patients; serious adverse events occurred in 18% of siponimod-treated patients versus 15% of placebo-treated patients.

teriflunomide (Aubagio) versus placebo

TEMPO Study:^{222,223} A double-blind, placebo-controlled study evaluated 7 mg and 14 mg doses of teriflunomide in relapsing forms of MS for 108 weeks with a primary endpoint of ARR. All patients had

a relapsing form of MS and had 1 relapse in the previous year or 2 relapses in the previous 2 years. Patients had not received interferon-beta for at least the past 4 months or any preventive medications in the past 6 months, nor were they permitted to receive those medications during the trial. Neurological evaluations were performed every 12 weeks during the trial in addition to visits for suspected relapse and MRIs were performed at weeks 24, 48, 72, and 108. A total of 1,088 patients were randomized to receive 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n=363). The mean age for the study was 37.9 years with a mean disease duration of 5.33 years and an EDSS of 5.5 or below with a mean baseline level of 2.68. Of the patients studied, 91.4% of the patients had RRMS and 8.6% had a progressive form of MS with relapses. A total of 796 (73.2%) of the patients completed the trial with similar dropout rates in all 3 groups. The APR and relative risk (RR) reduction were significantly reduced in the 14 mg (0.369 relapses, 31.5% RR, p=0.0005) and 7 mg (0.37 relapses, 31.2% RR, p=0.0002) teriflunomide groups compared to placebo (0.539 relapses). The reductions were noted in subgroups defined by sex, age group, prior MS therapy, and baseline disease. Although the study was not designed to demonstrate efficacy in secondary outcomes, disability progression after 12 weeks was reduced by teriflunomide 14 mg (p=0.03) and not by the 7 mg (p=0.08) arm compared to placebo. The treatment groups showed statistically favorable secondary outcomes in total lesion volume from baseline on magnetic resonance imaging (MRI).

The TOWER trial, an international, randomized, double-blind, placebo-controlled trial, reinforced the results of the TEMSO, with teriflunomide 7 mg and 14 mg showing significant reduction in ARRs and teriflunomide 14 mg with a significant reduction in the accumulation of disability.²²⁴ Another randomized, placebo-controlled trial, TOPIC, showed patients in the teriflunomide 7 mg and 14 mg groups had a significant reduction in time to relapse indicating clinically definite MS, relapses, and new MRI lesions, in clinically isolated syndrome indicative of early MS.²²⁵ A 9-year follow up of the TEMSO trial reported similar safety outcomes as found in the core TEMSO study.²²⁶

teriflunomide (Aubagio) versus IFN β -1a SC (Rebif)

TENERE Study:²²⁷ The TENERE study was a 48-week, randomized, rater-blinded study that compared teriflunomide 7 mg daily, 14 mg daily, and IFN β -1a 44mcg 3 times weekly. Patients 18 years of age and older who met McDonald criteria for MS, had a relapsing clinical course, with or without progression, and an EDSS score \leq 5.5 at screening were included. The primary composite endpoint was time to failure, defined as first occurrence of confirmed relapse or permanent treatment discontinuation for any cause. Relapse criteria required the appearance of a new clinical sign or symptom or clinical worsening of a previous sign or symptom that persisted for at least 24 hours without fever and each relapse was confirmed by the treating neurologist. A total of 324 patients were randomized (IFN β -1a: 104; teriflunomide 7 mg: 109; teriflunomide 14 mg: 111) and no difference in time to failure was observed. At Week 48, the cumulative percentage of estimated failures using the Kaplan–Meier method was 37% in the IFN β -1a group, and 36% and 33% in the teriflunomide 7 mg and 14 mg groups. The contribution of permanent treatment discontinuation to the failure rate was highest in the IFN β -1a group and lowest in the teriflunomide 7 mg group. In contrast, the fewest confirmed relapses were observed in the IFN β -1a group. Overall occurrences of adverse effects were similar across groups. Common adverse effects (greater than 10% in any group) reported more frequently with teriflunomide included nasopharyngitis, diarrhea, hair thinning, paresthesia, and back pain. Influenza-like symptoms, ALT increases, and headache occurred more frequently with IFN β -1a.

Neutralizing Antibodies: IFN β -1a IM (Avonex) versus IFN β -1a SC (Rebif) versus IFN β -1b (Betaseron)

One difference among the 3 IFN β products is the associated production of neutralizing antibodies (NAb). Data suggest that the presence of NAb against IFN β reduces the bioavailability and clinical efficacy of the drug leading to an increase in relapse rates.²²⁸ These findings also indicate that patients develop NAb independent of age, sex, disease duration, and progression index at start of treatment. Some studies suggest that NAb, once present, might disappear over time even though treatment continues.^{229,230,231}

To evaluate the incidence and the prevalence of NAb in each of the 3 IFN β products, sera were tested from 125 patients with RRMS.²³² Patients were treated with IFN β -1b 250 mcg SC every other day, IFN β -1a 30 mcg IM once weekly, or IFN β -1a 22 mcg SC 3 times weekly. Patients with 2 or more consecutive positive samples were considered to be persistently NAb-positive (NAb+). Over 18 months of treatment, the risk of developing persistent NAb was 31% for IFN β -1b, 15% for IFN β -1a SC, and 2% for IFN β -1a IM ($p=0.001$ for IFN β -1b versus IFN β -1a IM; $p=0.19$ for IFN β -1b versus IFN β -1a SC; $p=0.04$ for IFN β -1a SC versus IFN β -1a IM). In all patients with at least 1 NAb+ sample, the risk of becoming persistent NAb+ was 38% for IFN β -1b, 18% for IFN β -1a SC, and 7% for IFN β -1a IM ($p=0.0007$ for IFN β -1b versus IFN β -1a IM; $p=0.1$ for IFN β -1b versus IFN β -1a SC; $p=0.07$ for IFN β -1a SC versus IFN β -1a IM). At month 18, the prevalence of persistent NAb+ patients was 31.6% for IFN β -1b, 18.7% for IFN β -1a SC, and 4% for IFN β -1a IM.

In the EVIDENCE trial, NAb developed in 25% of the patients who received IFN β -1a SC compared with 2% of the patients given IFN β -1a IM.²³³ The incidence of NAb development appears to be less with IFN β -1a than with IFN β -1b and less when given IM in comparison to SC.

Primary Progressive MS

ocrelizumab (Ocrevus) versus placebo

ORATORIO: A phase 3, double-blind, randomized, placebo-controlled trial established the safety and efficacy of ocrelizumab for the treatment of patients with PPMS ($n=732$).^{234,235} The trial included patients ages 18 to 55 years old with a diagnosis of PPMS (based on the 2005 revised McDonald criteria), an EDSS score of 3 to 6.5 at screening, a score on the pyramidal functions component of the Functional Systems Scale of ≥ 2 , duration of MS symptoms of < 15 years in patients with an EDSS score of > 5 or < 10 years in patients with an EDSS ≤ 5 at screening, and a documented history or the presence at screening of an elevated IgG index or ≥ 1 IgG oligoclonal band detected in the cerebrospinal fluid. Patients were randomized 2:1 to an ocrelizumab 600 mg IV infusion every 24 weeks (administered as 2 doses of 300 mg 14 days apart for each dose round) or placebo. As the trial was event-driven, treatment continued for at least 5 doses and until the occurrence of 253 events of 12-week confirmed disability progression. All patients were premedicated with 100 mg IV methylprednisolone prior to every infusion. An analgesic or antipyretic and antihistamine was also recommended but use was at the discretion of the infusion center. The primary endpoint was the percentage of patients with 12-week confirmed disability progression, defined as a 12-week, sustained increase in EDSS ≥ 1 in patients with a baseline score ≤ 5.5 or ≥ 0.5 in patients with a baseline score > 5.5 , in a time-to-event, ITT analysis. Key secondary endpoints included worsening of timed 25-foot walk test and percentage change in T₂ hyperintense lesion volume. Baseline characteristics were similar among groups and included a mean age of 45 years, 49% female, a mean duration since

symptom onset of 6.7 years, a mean EDSS of 4.7, 88% of patients had not been treated previously with a non-steroid therapy, and 26% had $\geq T_1$ Gd-enhancing lesions on MRI.^{236,237} The proportion of patients with 12-week confirmed disability progression, the primary endpoint, was 32.9% with ocrelizumab and 39.3% with placebo (HR, 0.76; 95% CI, 0.59 to 0.98; $p=0.0321$). The adjusted geometric mean percent change in total volume on T₂-weighted lesions through week 120 was -3.37% and 7.43%, in the ocrelizumab and placebo groups, respectively (HR; 0.9; 95% CI, 0.88 to 0.92; $p<0.0001$). Twenty percent worsening of the timed 25-foot walk test at 12 weeks occurred in 49% of patients treated with ocrelizumab compared to 59% of patients treated with placebo.

META-ANALYSES

A Cochrane review of 6 clinical trials with 5 contributing to results ($n=2,904$) assessed the efficacy of RRMS patients randomly assigned to interferons and to glatiramer acetate.²³⁸ At 2 years of treatment, the number of participants with relapse (risk ratio [RR], 1.04; 95% CI, 0.87 to 1.24) and progression (RR, 1.11; 95% CI, 0.91 to 1.35) were comparable between the 2 groups. At 3 years, a single study suggested that relapse may be higher with interferons than with glatiramer (RR, 1.4; 95% CI, 1.13 to 1.7; $p=0.002$). Dropouts due to adverse effects were similar in both groups (RR, 0.95; 95% CI, 0.64 to 1.4). MRI results were also considered. At 2 years, the effects on new or enlarging T₂- or contrast-enhancing T₁ lesions at 24 months (mean difference [MD], -0.15; 95% CI, -0.68 to 0.39; and MD, -0.14; 95% CI, -0.3 to 0.02; respectively) were similar, but they differed in reduction in T₂- and T₁-weighted lesion volume as it was significant greater with interferon than with glatiramer (MD, -0.58; 95% CI, -0.99 to -0.18; $p=0.004$; and MD, -0.2; 95% CI, -0.33 to -0.07; $p=0.003$; respectively). A network meta-analysis and systematic review of 24 trials published between 1987 and 2015 also compared various formulations of IFN β to glatiramer acetate in RRMS patients; however, the authors found little evidence that any 1 drug was superior to another, despite all agents demonstrating a general delay in progression.²³⁹ Notably, a minor difference were found in time to confirmed progression at 6 months, but this was driven primarily by a single study and overall data were sparse for this outcome. Thus, the authors determined bias was too large to draw conclusions for the outcome.

Another Cochrane review compared alemtuzumab to IFN β -1a for RRMS utilizing 3 double-blind, randomized, controlled trials including 1,694 patients, all of which compared alemtuzumab 12 mg or 24 mg per day in annual cycles to IFN β -1a 44 mcg 3 times weekly.²⁴⁰ The authors found that, compared to IFN β -1a, alemtuzumab 12 mg demonstrated a reduced risk of relapses (RR, 0.6; 95% CI, 0.52 to 0.7), improvement in disease progression prevention (RR, 0.6; 95% CI, 0.45 to 0.79), and improvement in new T₂ lesion development (RR, 0.75; 95% CI, 0.61 to 0.93) at 2 and 3 years. No statistical difference was found in EDSS score or in the number of patients experiencing ≥ 1 adverse event or serious adverse events.

A network meta-analysis of 28 randomized, placebo-controlled trials compared the efficacy of various medications used to treat RRMS.²⁴¹ ARR reduction varied from 15% to 36% for various interferon- β products, glatiramer acetate, and teriflunomide and 50% to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. Most hazard ratios for 3-month and 6-month progression were superior to placebo; however, results for 3-month progression rates for interferon β -1a 30 mcg, glatiramer acetate 20 mg, interferon β -1a 22 mcg, and IFN β 250 mcg and 6-month progression with IFN β -1a 44 mcg were not statistically significant (confidence intervals included 1). Limitations of a network meta-analysis and the limited population per medication should be considered when interpreting results.

Another network meta-analysis of 14 studies indirectly compared the efficacy, as measured by ARR, of various monoclonal antibodies (e.g., natalizumab, alemtuzumab, daclizumab, ocrelizumab) for the treatment of MS (with IFN β -1a the most common direct comparator used).²⁴² The authors found that all were associated with significant reductions in ARR and similar safety risks; thus, the authors concluded direct comparisons are needed.

A network meta-analysis of 23 randomized controlled trials compared the relapse rate and treatment discontinuation due to adverse events of 12 disease-modifying therapies (DMTs) for MS.²⁴³ All therapies were significantly more effective in reducing the relapse rate compared to placebo over 2 years of follow-up. Alemtuzumab, ocrelizumab, and natalizumab were among the most effective DMTs, while teriflunomide, glatiramer acetate, IFN β -1a (Avonex, Rebif), and IFN β -1b (Betaseron) were among the least efficacious drugs. Regarding treatment discontinuation due to adverse events, glatiramer acetate, dimethyl fumarate, peginterferon beta-1a and IFN β -1a (Rebif) were worse than placebo. Overall, alemtuzumab, ocrelizumab, natalizumab, and fingolimod demonstrated better efficacy and lower discontinuation rates compared to the other DMTs. Glatiramer acetate, IFN β -1a (Rebif), and IFN β -1b (Betaseron) were associated with inferior efficacy and acceptability outcomes compared to the other DMTs.

A network meta-analysis included 33 trials that evaluated the efficacy and safety of ocrelizumab compared to 17 other DMTs approved to treat MS.²⁴⁴ The majority of trials were conducted in patients with relapsing forms of MS. Ocrelizumab was found to be more effective in reducing the risk of 12-week confirmed disability progression compared to 10 other treatments, including placebo. The probability that ocrelizumab was more effective in the remaining treatments (e.g., alemtuzumab, pegylated IFN β -1a, daclizumab, natalizumab, cladribine) was greater than 50% in each case. Ocrelizumab was also more effective in reducing the ARR compared to 12 other treatments, including placebo. The remaining treatment comparisons that did not favor ocrelizumab with regard to the ARR included alemtuzumab, natalizumab, and cladribine. Comparisons of ocrelizumab versus other DMTs showed no difference in the risk of serious adverse events and discontinuations due to adverse events.

SUMMARY

According to the American Academy of Neurology (AAN), disease-modifying therapy (DMT) should be offered to people with relapsing forms of multiple sclerosis (MS) with recent clinical relapses or MRI activity or those with a single clinical demyelinating event and ≥ 2 brain lesions characteristic of MS if desired. They caution that prescribers should counsel patients that treatments are intended to reduce relapses and new MRI lesion activity; they are not intended for symptom improvement. AAN recommends specific medications based on disease activity, treatment access, and adverse effect profiles. In addition, the recommendations emphasize a discussion of the importance of adherence in order to provide full efficacy. Guidelines recommend that stable patients continue treatment indefinitely, unless both the patient and prescriber feel that a trial off of medication is warranted, but discontinuation may be appropriate for select patients with secondary progressive MS (SPMS).

There is sufficient evidence to indicate that either the dose or the frequency of IFN β administration, or both, significantly influences the short-term outcome in patients with relapsing-remitting MS (RRMS). The route of administration of IFN β is not of clinical importance with regard to efficacy, but does have an impact on the side-effect profile. Questions remain as to comparable and optimal dosages and

frequencies for the various interferons. Plegridy, is a pegylated formulation of interferon beta 1a, which allows for a longer duration; therefore, Plegridy is dosed subcutaneously (SC) once every 2 weeks.

Data suggest neutralizing antibodies (NAb) against IFN β reduce the bioavailability and clinical efficacy of the drug leading to an increase in relapse rates. In the EVIDENCE trial, the incidence of NAb development appeared to be less with IFN β -1a than with IFN β -1b and less when given IM in comparison to SC. Some studies suggest that NAb, once present, might disappear over time with continued treatment.

Based on trial evidence, interferons and glatiramer acetate have similar clinical utility in MS. The results of the CombiRx trial suggest that combination glatiramer acetate (Copaxone) and IFN β -1a IM (Avonex) is not more effective than glatiramer acetate therapy alone, but glatiramer acetate may be more effective than IFN β -1a IM in reducing risk of exacerbations. Additional trials are needed to confirm this result and the comparative efficacy of glatiramer acetate to other IFN β s.

Six oral agents, cladribine (Mavenclad), dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), fingolimod (Gilenya), siponimod (Mayzent), and teriflunomide (Aubagio), are available for the treatment of MS. All have demonstrated superiority over placebo, but comparative data are limited. Despite its effectiveness, cladribine should be reserved for patients who have had an inadequate response to or are unable to tolerate an alternate drug. Even with its broad indication language for relapsing forms of MS, it should not be used for clinically isolated syndrome (CIS), and most of its data were completed in patients with RRMS. Dimethyl fumarate had similar results to glatiramer acetate in a study, although the study was not designed to test its superiority or noninferiority. Diroximel fumarate (Vumerity) contains the same active metabolite of dimethyl fumarate and was approved via an expedited approval pathway, utilizing some safety and efficacy data of dimethyl fumarate for approval. Compared to IFN β -1a (Avonex), fingolimod has shown significant efficacy in regard to relapse rate and MRI activity, but the risk of disease progression did not differ significantly between the treatment groups. Due to fingolimod's adverse event profile, significant monitoring is required. Notably, fingolimod offers the first FDA-approved treatment for pediatric patients with relapsing forms of MS who are 10 years of age and older. Similarly, significant monitoring is required for siponimod. Siponimod's broad indication wording states it may be used for CIS, RRMS, and active SPMS; however, its key, phase 3 clinical efficacy data versus placebo were primarily in patients with SPMS. Teriflunomide appears similar to IFN β -1a (Rebif) based on the results of the TENERE trial. The long-term safety and efficacy of these oral agents are unknown.

Another oral agent, dalfampridine (Ampyra), improves walking speed but it has no effect on the underlying disease. Alemtuzumab (Lemtrada), administered by intravenous infusion, is approved only for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS due to its adverse effect profile. Natalizumab (Tysabri), which as administered by intravenous infusion, is available for relapsing forms of MS but use also is limited due to serious safety concerns. In March 2018, the interleukin-2 blocking antibody, daclizumab (Zinbryta), was voluntarily withdrawn from the market worldwide following 7 reports of serious inflammatory encephalitis and meningoencephalitis.

Ocrelizumab marks the first medication approved for the treatment of primary progressive MS (PPMS) and is also approved for relapsing MS. Multiple treatment strategies which are not FDA-approved for

PPMS have been used historically, but few provide significant benefit on disease progression. Thus, it is likely that ocrelizumab will play a significant role in the treatment of PPMS. The 2018 AAN guidelines state clinicians should offer ocrelizumab to PPMS patients who are likely to benefit unless the risks outweigh the benefit.

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