



Multiple Sclerosis Agents Therapeutic Class Review (TCR)

February 2, 2022

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MANAGEMENTSM

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 <i>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 MS</i> <i>Due to its safety profile, alemtuzumab is not recommended for patients with clinically isolated syndrome (CIS)</i>
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 <i>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</i> <i>Due to its safety profile, cladribine is not recommended for patients with CIS</i>
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	generic, 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 MS, 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/IM (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	
monomethyl fumarate (Bafiertam®) ¹³	Banner Life Sciences	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults

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
ofatumumab (Kesimpta®) 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
ozanimod (Zeposia®) ¹⁷	Celgene	<ul style="list-style-type: none"> Relapsing form of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults Moderately to severely active ulcerative colitis (UC) in adults
ponesimod (Ponvory™) ¹⁸	Janssen	<ul style="list-style-type: none"> Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease, in adults
siponimod (Mayzent®) ¹⁹	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®) ²⁰	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.

OVERVIEW

Multiple sclerosis (MS) is a complex human autoimmune-type inflammatory disease of the central nervous system (CNS).^{21,22,23} 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).^{24,25} MS occurs most commonly in Caucasians, with rare cases in African Americans, Asian Americans, and Hispanics/Latinos. Like many 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 approximately 85% of patients) or primary progressive MS (observed in 15% of patients).²⁶ Relapses or “attacks” typically present sub-acutely, 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.²⁷ Detailed guidelines on the diagnosis of MS are available.^{28,29,30} 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:^{31,32,33}

- **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.³⁴ 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. A recent global study involving patients with RIS showed more than half of the patients progressing to MS within 10 years. Trials are currently in progress to determine if disease-modifying therapies (DMT) can play a role in disease prevention or delay.³⁵

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.³⁶

Ocrelizumab marks the first medication approved for the treatment of PPMS and is also approved for relapsing MS. Multiple treatment strategies that are not approved by the United States (US) Food and Drug Administration (FDA) for PPMS have been used historically, but few provide significant benefit on disease progression; thus, treatment of PPMS is often primarily symptomatic.³⁷

In 2018, the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology (AAN) developed and published practice guidelines for DMT for adults with MS and this guideline was reaffirmed in 2021.³⁸ 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). Diroximel fumarate, monomethyl fumarate, ofatumumab, ozanimod, **ponesimod**, and siponimod, 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).³⁹ 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 [Gd]-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.^{40,41} 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 an 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.⁴² 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 IM formulation of IFN β -1a (Avonex) appeared less immunogenic than the subcutaneous (SC) 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.⁴³ The AAN recommends clinicians discuss immunization options with patients to develop an optimal strategy for each patient, considering 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 (TB), 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 and the use of ozanimod (Zeposia) for the treatment of ulcerative colitis (UC) is not addressed in this therapeutic class review.

Ofatumumab is available through an oncology patient access program under the trade name Arzerra®.⁴⁴ The use of ofatumumab for indications other than MS will not be addressed in this Therapeutic Class Review.

PHARMACOLOGY^{45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64}

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 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.⁶⁵ This study and other published data indicate that 30 mcg IFN β -1a is equivalent to approximately 220 to 280 mcg IFN β -1b.⁶⁶

Alemtuzumab (Lemtrada) is a CD52 directed cytolytic monoclonal antibody. While 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 increased conduction of action potentials in demyelinated axons through inhibition of potassium channels. Dalfampridine is a broad-spectrum potassium channel blocker.

Dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), and monomethyl fumarate (Bafiertam) 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 (S1P) 1, 3, 4, and 5. Siponimod (Mayzent) and ozanimod (Zeposia) bind to S1P receptors 1 and 5. Ponesimod (Ponvory) binds with high affinity to S1P receptor 1. S1P receptor binding inhibits lymphocyte egress from lymph nodes, reducing their number in the peripheral blood.⁶⁷ While the exact mechanism of action of these agents is 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).^{68,69,70} 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.⁷¹

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) and ofatumumab (Kesimpta) are recombinant humanized CD20 monoclonal antibodies. Their precise mechanism in the treatment of MS are unknown; however, they target and bind to CD20, a cell surface antigen present on pre-B and mature B lymphocytes, resulting 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^{72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91}

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 SC administration.⁹² Yet, several studies demonstrated no difference in biologic effects between the different routes of administration.^{93,94,95} 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/IM (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
monomethyl fumarate oral (Bafiertam)	4-11	0.5	nd	nd
natalizumab (Tysabri)	nd	7-15 days	nd	nd
ocrelizumab (Ocrevus)	nd	26 days	nd	nd
ofatumumab injection (Kesimpta)	nd	16 days	nd	nd
ozanimod oral (Zeposia)	6-8	11 days	nd	nd
ponesimod oral (Ponvory)	2-4	~33 hrs	nd	nd
siponimod oral (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^{96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111, 112,113,114,115}

alemtuzumab (Lemtrada)

Alemtuzumab is contraindicated in patients who have active infections or are infected with human immunodeficiency virus (HIV) because it causes prolonged reductions of CD4+ lymphocyte. Alemtuzumab also is contraindicated in patients with a hypersensitivity to alemtuzumab or any of its other excipients.

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, which may be life-threatening. 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. It is also recommended to obtain thyroid function tests prior to initiating therapy and every 3 months thereafter. 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. **Sarcoidosis also has been reported in postmarketing cases with alemtuzumab.**

Alemtuzumab also causes cytokine release syndrome resulting in infusion reactions, some of which may be serious and life-threatening. Patients should only receive alemtuzumab in a certified healthcare facility with on-site access to personnel and equipment necessary to manage these serious infusion reactions. Patients should be premedicated with a corticosteroid and monitored during treatment. Cases of alveolar hemorrhage, myocardial ischemia, and myocardial infarction have also been reported within 48 hours of treatment. In addition, cases 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). 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.¹¹⁶ Physicians should alert patients that these 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 IFN β -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.

Alemtuzumab may increase the risk of hemophagocytic lymphohistiocytosis (HLH), which can be life-threatening if not treated early. Patients and healthcare providers should monitor for signs and symptoms of HLH, including lymphadenopathy, hepatosplenomegaly, fever, and neurologic symptoms, which have been reported to occur within 13 to 33 months after infusion. Diagnosis of HLH and discontinuation of alemtuzumab should be considered in patients who develop early manifestations without an established alternate etiology.

Postmarketing cases of acquired hemophilia A (anti-Factor VIII antibodies) have been reported, with patients experiencing extensive bruising, bleeding, and spontaneous SC hematomas. It is recommended for physicians to alert patients to promptly seek medical attention for evaluation if these signs and symptoms occur.

Infections were more common in alemtuzumab-treated patients compared to patients treated with IFN β -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, cytomegalovirus infections, and Epstein-Barr virus, have been reported. 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) was 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.

Serious, potentially life-threatening, cases of thrombotic thrombocytopenic purpura (TTP), a blood clotting disorder, have also been reported with alemtuzumab. Alemtuzumab should be discontinued if TTP is confirmed or an alternate etiology cannot be established. Patients should be monitored for signs and symptoms of TTP (e.g., purpura, jaundice, feel tired or weak, pallor, fever, tachycardia, dyspnea, headache, speech changes, confusion, vision changes, seizure, low amount of urine or dark urine, or blood in urine, abdominal pain, nausea, vomiting, or diarrhea).

Adult Onset Still's Disease (AOSD), a rare inflammatory condition, has been reported in postmarketing surveillance of patients treated with alemtuzumab. Patients should be monitored for signs and symptoms of AOSD (e.g., fever, arthritis, rash, leukocytosis in the absence of infections, malignancies, other rheumatic conditions). Alemtuzumab should be discontinued in patients with manifestations of AOSD and if an alternate etiology cannot be established.

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 has caused a dose-dependent reduction in lymphocyte count. In clinical trials, 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.

Dalfampridine can cause CNS-related adverse events (e.g., vertigo, dizziness), and impair a patient's ability to drive or operate machinery; patients should be counseled.

dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), monomethyl fumarate (Bafiertam)

Dimethyl fumarate, diroximel fumarate, and monomethyl 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, diroximel fumarate, and monomethyl fumarate may decrease lymphocyte counts. In clinical trials with dimethyl fumarate, 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 these three agents, 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, diroximel fumarate, and monomethyl fumarate may cause flushing (e.g., redness, itching, burning sensation). In clinical trials with dimethyl fumarate, 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 postmarketing 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 and monomethyl fumarate. Signs and symptoms of liver injury, including elevated serum aminotransferases and total bilirubin, have occurred. Liver 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 diroximel fumarate and monomethyl fumarate as these agents share an active metabolite.¹¹⁷ 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. Postmarketing cases of PML occurred predominantly in patients with lymphocyte counts of $< 0.8 \times 10^9/L$ for more than 6 months. 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, which may occur at any time during treatment. This risk is also possible with diroximel fumarate and monomethyl 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 postmarketing data including reports of patients who died of cardiovascular events or unknown causes.¹¹⁸ 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 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 atrioventricular block (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.^{119,120} 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.¹²¹ 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.¹²²

Relapses with tumefactive demyelinating lesions (solitary demyelinating lesions > 2 cm) 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 infection site. Lipoatrophy also can occur at various times throughout treatment and is thought to be permanent.

Postmarketing cases of hepatic injury, including severe cases of hepatitis with jaundice and liver failure, have been reported in patients using glatiramer. Physicians should alert patients to seek medical attention promptly if signs and symptoms of hepatic injury occur. Discontinuation of treatment may be warranted.

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 IFN β or any component of the formulation. Except for IFN β -1a SC/IM (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/IM (Plegridy) and prefilled syringes of IFN β -1a IM (Avonex) do not contain albumin. IFN β -1a IM (Avonex), pegylated IFN β -1a SC/IM (Plegridy), and IFN β -1b (Betaseron) have also been associated with rare reports of anaphylaxis. **Rarely, serious allergic reactions, such as angioedema or urticaria, can occur with IFN β -1a SC/IM (Plegridy).**

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/IM (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 postmarketing reports have documented injection site necrosis occurring over 1 year after initiation of therapy. It generally affects the SC 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 **IFN β -1a IM (Avonex), IFN β -1b (Betaseron, Extavia), and pegylated IFN β -1a SC/IM (Plegridy) treatment; In clinical studies with pegylated IFN β -1a SC/IM (Plegridy), incidence was higher with SC administration compared to IM administration (32% versus 14%, respectively). Patients**

should be monitored for injection site reactions including necrosis (e.g., breaks in skin associated with blue-black skin discoloration, swelling, or drainage of fluid from injection site). Patients should be warned against injecting in areas that are inflamed, edematous, erythematous, ecchymotic, or has any signs of infection. Patients should be advised of aseptic self-injection techniques and procedures, to rotate injection sites with each dose, or discontinue therapy until healing of lesions occurs. Post marketing cases of injection site abscesses and cellulitis requiring treatment with hospitalization for surgical drainage and IV antibiotics have been reported with use of interferon beta.

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

The removable cap of the diluent pre-filled syringe for Extavia and the protective rubber cover of the Plegridy prefilled syringe for IM administration 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 (PLEX) 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). Three main factors are thought to contribute to the increased risk of PML which include presence of anti-JCV antibodies, treatment durations longer than 2 years, and prior treatment with immunosuppressants. 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. Although there are no known interventions to treat PML adequately, PLEX therapy has been shown to accelerate natalizumab clearance from the body based on data in a study of 12 patients. Evidence does not support the benefit of PLEX to treat opportunistic infections, as it has not been studied specifically in natalizumab-treated patients with 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.

Natalizumab may cause thrombocytopenia, including ITP, which may lead to serious or life-threatening sequelae. Appropriate monitoring of symptoms, including abnormal bleeding and easy bruising, may be necessary to prevent any delay in diagnosis and treatment of thrombocytopenia. In post marketing surveillance, cases of thrombocytopenia, occasionally associated with anemia, have been reported in neonates exposed to natalizumab *in utero*. Complete blood counts should be monitored in neonates.

ocrelizumab (Ocrevus)

Ocrelizumab is contraindicated in patients with a history of life-threatening infusion reactions to ocrelizumab. Hepatitis B virus (HBV) reactivation has been reported in the postmarketing setting in patients with MS. 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. Serious cases

of herpes simplex virus and VZV have been reported in postmarketing data. 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.

Decreased immunoglobulin levels were reported with ocrelizumab. Pooled clinical trial data with up to approximately 7 years of exposure revealed decreased levels of immunoglobulin G below the lower limit of normal (IgG<LLN) and increased rates of serious infections. Assess serum immunoglobulin levels prior to starting treatment and consult immunology experts if levels are low. Quantitative serum immunoglobulins levels should be monitored during treatment and after discontinuation, until B-cell repletion is demonstrated. Consider discontinuing ocrelizumab in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

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.

ofatumumab (Kesimpta)

Ofatumumab is contraindicated in patients with active HBV infections. While there were no cases of HBV reactivation in patients in clinical trials with ofatumumab for MS, reactivation has been reported in patients treated with higher doses of ofatumumab for chronic lymphocytic leukemia (CLL) and in patients treated with other anti-CD20 antibodies. An HBV screening prior to initiation is required and should include hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HbcAb) testing. Providers should consult with a liver disease expert prior to initiating therapy for patients who are negative for HbsAg and positive for HbcAb or who are carriers of HBV (HbsAg+).

Cases of PML have not been reported in clinical studies with ofatumumab use in MS; however, high-doses of ofatumumab for CLL has been reported to cause PML resulting in death. Cases of PML may occur as these have been reported with other anti-CD20 antibodies and other MS therapies. Ofatumumab should be discontinued if PML is confirmed in the patient.

In clinical trials, the rate of infections and serious infections were similar in patients treated with ofatumumab and patients treated with teriflunomide (51.6% versus 52.7% and 2.5% versus 1.8%, respectively). Ofatumumab increased the risk of upper respiratory tract infections and urinary tract infections. Therapy should be delayed in patients with active infections until the infection has resolved. The safety of immunization with live or live-attenuated vaccines following ofatumumab 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 ofatumumab for live or live-attenuated vaccines and at least 2 weeks prior to initiation of ofatumumab for non-live vaccines. Live-attenuated or live vaccines are not recommended during treatment and until B-cell repletion upon discontinuation of ofatumumab. Do not

administer live or live-attenuated vaccines before confirming B-cell count recovery in infants of mothers exposed to ofatumumab during pregnancy. Non-live vaccines may be administered to these infants, but the risk of possible altered immune response should be considered.

Ofatumumab carries a warning for injection-related reactions including fever, myalgia, chills, headache, fatigue, and erythema. Pre-medication (e.g., methylprednisolone or equivalent corticosteroid and an antihistamine) prior to the injections has shown limited benefit. In clinical trials, the infusion reactions occurred in 21% of the patients, with the highest incidence associated with the first injection (14.4%). Most reactions were mild to moderate in severity.

Ofatumumab may decrease immunoglobulin levels. In clinical trials, 7.7% of the patients treated with ofatumumab compared to 3.1% of the patients treated with teriflunomide exhibited a reduction in immunoglobulin M (IgM) levels. Reductions in immunoglobulin G (IgG) levels were not seen in the study. It is recommended for healthcare providers to monitor the levels of quantitative serum immunoglobulin levels during treatment and after discontinuation until B-cell repletion, particularly in patients with opportunistic or recurrent infections. Discontinuation should be considered in patients with low immunoglobulins resulting in the development of serious infections or in patients with prolonged hypogammaglobulinemia requiring treatment with intravenous immunoglobulins.

In addition, ofatumumab may cause fetal harm based on the results of animal studies. Females of reproductive potential should use effective contraception during ofatumumab use and for at least 6 months following discontinuation.

ozanimod (Zeposia)

Ozanimod is contraindicated in 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; patients with Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome (unless patient has a functioning pacemaker); patients who are taking monoamine oxidase (MAO) inhibitors; and patients who have severe untreated sleep apnea.

Ozanimod increases the susceptibility to infections, including herpes-related infections, cryptococcal infections, PML, urinary tract infections, and respiratory tract infections. In clinical trials, the overall rate of infections and serious infections in patients treated with ozanimod were similar to those treated with IFN β -1a (35% versus 34% and 1% versus 0.8%, respectively). Interruption of treatment and additional monitoring should be considered for patients who develop serious infections. PML has been reported in patients treated with S1P receptor modulators and other MS therapies. Although rare, suspected cases of PML and cryptococcal infections require prompt evaluation, treatment, and ozanimod discontinuation. Monitoring should continue for an additional 3 months after discontinuation of ozanimod. Before initiating therapy, it is recommended for healthcare providers to obtain a recent CBC within 6 months or after discontinuation of their prior MS therapy. Patients who have active infections should delay the initiation of treatment until the infection has resolved. Vaccination status and antibody testing for VZV should be obtained prior to initiating treatment.

Cases of transient reduction in heart rate and AV conduction delays in patients taking ozanimod have been reported. Healthcare providers should use an up-titration schedule in patients to reach the goal maintenance dosage of ozanimod. The heart rate decrease generally begins within 5 hours of the initial dose and returns to near baseline by hour 6. The maximum decrease in heart rate is typically reached on

day 8. A similar pattern was seen in transient AV conduction delays. First- and second-degree type 1 AV blocks were reported in patients using ozanimod at doses higher than the recommendation without titration. A cardiologist's advice should be sought in the following situations: male patients with QTc > 450 msec; female patients with QTc > 470 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. Notably, ozanimod 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; significant QT prolongation (QTc > 450 msec in males, QTc > 470 msec in females); severe untreated sleep apnea, and a resting heart rate < 55 beats per min (bpm) at baseline.

Elevations of aminotransferases have been seen in patients taking ozanimod. Transaminase and bilirubin levels should be obtained before initiation of therapy. In clinical trials, elevations of 3-fold the upper limit of normal (ULN) or greater occurred in 5.5% and 3.1% of ozanimod-treated and IFN β -1a-treated patients, respectively, with the majority of the elevations occurring within 6 months. Approximately 79% of the ozanimod-treated patients continued therapy with values returning to less than 3 times the ULN within 2 to 4 weeks. Liver function assessments should be completed in patients who develop symptoms associated with hepatic dysfunction (e.g., nausea, vomiting, abdominal pain, rash with eosinophilia, anorexia, jaundice, or dark urine). Discontinuation of therapy should be considered in patients with confirmed significant liver injury.

In clinical trials, ozanimod-treated patients had an average increase of approximately 1 to 2 mm Hg systolic pressure and no difference in diastolic pressure over IFN β -1a-treated patients, with the first detection occurring 3 months following initiation and continued during treatment. Blood pressure should be monitored, and clinically managed if appropriate, during treatment.

Ozanimod causes a dose-dependent reduction in absolute FEV₁ that can be seen in patients as early as 3 months following treatment initiation. Similar responses were seen in absolute value and percent-predicted forced vital capacity (FVC) reductions in patients following 3 months of treatment initiation. Respiratory function should be monitored via spirometry during therapy with ozanimod if indicated.

Cases of macular edema have been observed in patients treated with ozanimod and other S1P modulators. The risk is greater in patients with a history of diabetes mellitus and/or uveitis are at increased risk of macular edema. Patients experiencing changes in visions are recommended to complete ophthalmic evaluations while taking ozanimod with regular follow-up evaluations.

Rare cases of 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 ozanimod 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, ozanimod should be discontinued, a complete physical and neurological examination should occur, and an MRI scan should be considered.

Concomitant ozanimod therapy with anti-neoplastic, immunosuppressive, or immune-modulating therapies should be used and monitored with caution. Unintended additive immunosuppressive effects must be considered when switching from these agents to ozanimod and upon discontinuation of ozanimod. Treatment with ozanimod following treatment with alemtuzumab is not recommended. Although rare, discontinuation of ozanimod and other S1P treatments may cause severe exacerbations of disease, including disease rebound. Healthcare providers should observe and properly treat patients for a severe increase in disability upon ozanimod discontinuation. Caution should be taken when patients begin other therapies within 4 weeks of ozanimod discontinuation, as it takes approximately 30 days for peripheral blood lymphocytes to return to normal. The safety of immunization with live or live-attenuated vaccines following ozanimod use has not been evaluated. Administer live-attenuated vaccines at least 4 weeks prior to initiation and at least 3 months following treatment with ozanimod.

Ozanimod carries a warning for fetal harm. Effective contraception is recommended during treatment and for 3 months following ozanimod discontinuation.

Hypersensitivity, including rash and urticaria, has been reported with ozanimod in active-controlled MS clinical trials.

An increased risk of cutaneous malignancies has been reported with another S1P receptor modulator. Clinical trials reported malignancies (e.g., melanoma, basal cell carcinoma, breast cancer, and seminoma) with ozanimod.

ponesimod (Ponvory)

Ponesimod is contraindicated in patients who have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure during the previous 6 months. Unless the patient has a functioning pacemaker, ponesimod is also contraindicated in patients who have presence of Mobitz Type II second-degree or third-degree AV block, or sick sinus syndrome, or sino-atrial block.

Initiation of ponesimod can cause bradyarrhythmia and atrioventricular conduction delays. Therefore, an up-titration schedule is recommended to reduce the cardiac effects while reaching the maintenance dosage of ponesimod (20 mg). An ECG is recommended in all patients to determine the presence of any preexisting conduction abnormalities. Also, 4-hour first-dose monitoring is recommended in patients with sinus bradycardia, first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure with onset > 6 months prior to initiation. Bradycardia occurred at treatment initiation and sinus bradycardia on ECG (heart rate < 50 bpm) in 5.8% of patients in clinical trial compared to 1.6% with teriflunomide 14 mg. The heart rate decrease generally begins within an hour of first dose initiation and returns to baseline within 4 to 5 hours. The average decrease in heart rate was 6 bpm and resolved in all patients without intervention or discontinuation of ponesimod. Transient AV conduction delays also occur at dose titration. AV conduction delays appeared as first-degree AV block (prolonged PR interval on ECG) and occurred in 3.4% of ponesimod patients compared to 1.2% of teriflunomide patients. These conduction abnormalities were transient, asymptomatic, resolved within 24 hours, and resolved without intervention or discontinuation of ponesimod. A cardiology consult is recommended for patients with significant QT prolongation (QTc > 500 msec), atrial flutter/fibrillation or arrhythmia treated with Class Ia or Class III antiarrhythmic agent, unstable ischemic heart disease, cardiac decompensated failure occurring > 6 months prior to therapy initiation, history of cardiac arrest,

cerebrovascular disease (transient ischemic attack, stroke occurring > 6 months prior to therapy initiation), or uncontrolled hypertension, or history of Mobitz Type II second degree or higher-grade AV block, sick-sinus syndrome, or sino-atrial heart block. Bradycardia may be poorly tolerated in the following patients: patients with a history of cardiac arrest, cerebrovascular disease (e.g., transient ischemic attack, stroke occurring > 6 months prior to therapy initiation), uncontrolled hypertension, or severe untreated sleep apnea; therefore, use of ponesimod is not recommended and advice from a cardiologist should be considered with treatment in these populations. A cardiologist's advice also should be sought for initiation of ponesimod in patients with a history of recurrent syncope or symptomatic bradycardia, patients receiving concurrent therapy with drugs that decrease heart rate (e.g., beta-blocker, non-dihydropyridine calcium channel blockers [diltiazem, verapamil], digoxin).

Ponesimod increases the susceptibility to infections, including herpes viral infection and other infections (cryptococcal meningitis, disseminated cryptococcal infections, PML) reported with other S1P receptor modulators and other multiple sclerosis therapies. In clinical trials, the overall rate of infections in patients treated with ponesimod were similar to those treated with teriflunomide (54.2% versus 52.1%, respectively). The risk of upper respiratory tract infections is increased with ponesimod. Ponesimod-treated patients experienced serious or severe infections at 1.6% compared to teriflunomide 0.9%. Ponesimod should not be initiated in patients with active infection and therapy should be suspended or discontinued for patients who develop serious infections. Prior to initiating therapy, healthcare providers should obtain a recent CBC (within the last 6 months or after discontinuation of prior MS therapy), and patients should be monitored for infection during treatment and for 1 to 2 weeks after discontinuation of therapy. Vaccination status or a history of chickenpox should be confirmed prior to initiating ponesimod. Full vaccination with varicella vaccine is recommended in antibody-negative patients prior to treatment, and treatment should be postponed for 4 weeks after vaccination. Live attenuated vaccines should be avoided during and for 1 to 2 weeks after treatment with ponesimod.

Initiate ponesimod with caution in patients with prior or concomitant therapy with anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) due to the risk of additive immune system effects. Unintended additive immunosuppressive effects must be considered when switching from drugs with prolonged immune effects to ponesimod. Ponesimod should not be initiated after treatment with alemtuzumab. Residual lowering effects on peripheral lymphocyte count lasting up to 1 to 2 weeks following the last dose of ponesimod can cause additive an additive effect on the immune system; therefore, use of immunosuppressants during this period should be used with caution.

Ponesimod causes dose-dependent reductions in FEV₁ and reductions in diffusion lung capacity for carbon monoxide; this was seen mostly in the first month following treatment initiation in clinical trials. In patients with severe respiratory disease (pulmonary fibrosis, asthma, chronic obstructive pulmonary disease), ponesimod should be used with caution and patients should be monitored via spirometry during therapy if clinically indicated.

Ponesimod can cause elevations in transaminases; Therefore, providers should obtain recent transaminases and bilirubin levels (e.g., within last 6 months) prior to initiation of therapy. In clinical trials, elevations of 5-fold the ULN or greater occurred in 4.6% and 2.5% of ponesimod-treated and teriflunomide-treated patients, respectively. Elevations of 3-fold the ULN or greater occurred in 17.3% and 8.3% of ponesimod-treated and teriflunomide-treated patients, with a median time to elevation of

3 months. The majority of patients (89%) with ALT increases of ≥ 3 -fold the ULN continued ponesimod therapy with values returning to < 3 times the ULN within 2 to 4 weeks. Liver enzymes should be evaluated in patients who develop symptoms associated with hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice, and/or dark urine). Therapy should be discontinued with confirmed significant liver injury.

Ponesimod can cause increases in blood pressure, and blood pressure should be monitored during therapy and managed appropriately. In clinical trials, hypertensive events occurred in 10.1% and 9% in patients receiving ponesimod and teriflunomide, respectively, with an average increase of systolic blood pressure/diastolic blood pressure (SBP/DBP) for ponesimod (2.9 mm Hg/2.8 mm Hg) compared to teriflunomide (2.8 mm Hg/3.1 mm Hg).

Ponesimod can cause cutaneous malignancies, and cases of basal cell carcinoma and other skin malignancies have been reported in patients treated with ponesimod as well as with other S1P receptor modulators. In clinical trials, basal cell carcinoma occurred in 0.4% and 0.2% of ponesimod-treated and teriflunomide-treated patients, respectively. Skin examinations are recommended periodically, especially in patients with risk factors for skin cancer. Patients with increased risk for skin cancer should be advised to limit exposure to sunlight and ultraviolet (UV) light, wear protective clothing, and use high protection factor sunscreen. Phototherapy with UV-B radiation or psoralen and ultraviolet A (PUVA)-photochemotherapy is not recommended in patients while taking ponesimod.

Ponesimod can cause fetal harm. Effective contraception is recommended during treatment and for 1 week following ponesimod discontinuation.

Ponesimod and other S1P receptor modulators have been associated with increased risk of macular edema. An ophthalmic examination prior to initiating therapy and regular follow-up examinations of the fundus, including the macula, is recommended during treatment with ponesimod. Patients have a higher risk of macular edema if they have a history of uveitis and diabetes mellitus, and changes in vision should be monitored and evaluated regularly.

S1P receptor modulators have been associated with rare cases of PRES. Patients should be monitored for neurological and psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs). The healthcare provider should complete a physical and neurological examination and consider an MRI with any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurologic deterioration. Although symptoms of PRES are usually reversible, it can lead to ischemic stroke or cerebral hemorrhage. Ponesimod should be discontinued if PRES is suspected.

Severe increase in disability after stopping ponesimod can lead to rare occasions of severe exacerbation of disease, including disease rebound. Patients should be monitored closely upon discontinuation of therapy.

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 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 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 coadministered 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 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 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 mm Hg systolic and 1.2 mm Hg 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.

Siponimod can cause respiratory effects, and patients should be advised to contact their provider if they experience new onset or worsening of dyspnea.

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. Evaluation of respiratory function by spirometry 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 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 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 an 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.

An increased risk of basal cell carcinoma has been associated with long-term use of S1P modulators, including siponimod, at an incidence of 1%. Clinical trials reported malignancies (e.g., malignant melanoma *in situ*, seminoma, squamous cell carcinoma) with siponimod and another S1P modulator. Patients should be monitored for suspicious skin lesions. Exposure to sunlight and UV light should be limited and concomitant phototherapy is not recommended.

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

A severe increase in disability has been reported after discontinuation of another S1P receptor modulator like siponimod, and patients should be advised to contact their provider if they develop worsening symptoms of MS following discontinuation of Siponimod.

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, toxic epidermal necrolysis, and drug reaction with eosinophilia, and systemic symptoms (DRESS), which can be fatal. Cases of If signs and symptoms of serious skin reactions occur, patients should discontinue teriflunomide, seek immediate medical attention, and begin an accelerated elimination procedure immediately.

Teriflunomide can cause hypersensitivity reactions, anaphylaxis, and severe allergic reactions. Patients should be advised of signs and symptoms of severe allergic reactions, such as dyspnea, urticaria, and angioedema (e.g., lips, eyes, throat, tongue).

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. In the postmarketing setting, cases of clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, have been reported. In addition, in a clinical trial, adult patients exhibited ALT greater than 3 times the ULN within the first years of treatment. One adult patient developed ALT 32 times the ULN and jaundice within 5 months of initiation of therapy. 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 childbearing 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 **in adult patients**; 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 in **adult patients**. 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, **including polyneuropathy and mononeuropathy, have been reported in adult patients. In addition, elevated blood pressure has been reported in adult patients.**

Acute renal failure/hyperkalemia and interstitial lung disease are among other reported warnings.

Cases of pancreatitis were reported in clinical trials with adult and pediatric patients receiving teriflunomide with 1 case being serious. Pancreatitis appears to occur at a higher frequency in pediatric patients. Teriflunomide should be discontinued with an accelerated elimination procedure if pancreatitis is suspected and should not be given to pediatric patients.

Patients should be advised to stop taking teriflunomide if they experience difficulty breathing, itching, swelling on any part of the body (e.g., lips, eyes, throat, tongue) and if they experience these symptoms in combination with a fever or a rash.

Risk Evaluation and Mitigation Strategy (REMS) Programs¹²³

Agents in this review assigned REMS programs are 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. **Pharmacies can obtain authorization to ship product online. A communication plan is no longer required, but a Patient Transfer of Care Form has been added to the REMS material.**

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^{124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143}

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 organic cation transporter 2 (OCT2) inhibitors (e.g., cimetidine) may increase dalfampridine (Ampyra) exposure, potentially increasing the risk of seizures.

Coadministration of dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), or monomethyl fumarate (Bafiertam) with one another 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) and ofatumumab (Kesimpta) should not be used with other immunosuppressants. 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 ocrelizumab is coadministered with drugs with prolonged immune effects (e.g., daclizumab, fingolimod, natalizumab, teriflunomide, mitoxantrone). 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.

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. Coadministration 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 (Mayzent), ozanimod (Zeposia), and ponesimod (Ponvory) have not been studied with concomitant antineoplastic, immune-modulating, or immunosuppressive therapies.

Vaccinations may be less effective during and for a period of time after treatment with sphingosine 1-phosphate receptor modulators. Live attenuated vaccines should be avoided during treatment with these agents and for 2 months after discontinuation of fingolimod, 3 months following ozanimod, and 1 to 2 weeks following treatment with ponesimod. Siponimod should be interrupted 1 week prior and 4 weeks after a planned vaccination. If a live immunization is required, administer the vaccine at least 1 month prior to ponesimod initiation.

Coadministration of ozanimod with strong CYP2C8 inhibitors, CYP2C8 inducers, or BCRP inhibitors is not recommended due to the increased risk of adverse reactions. Ozanimod has not been studied with concomitant use of MAO inhibitors (e.g., selegiline, phenelzine, linezolid); however, its coadministration with one of these agents is contraindicated. Initiation of MAO inhibitors should follow at least 14 days after discontinuing treatment with ozanimod. Likewise, concomitant use of ozanimod with medications that can increase norepinephrine or serotonin levels (e.g., opioids, selective serotonin reuptake inhibitors [SSRIs], selective norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants, tyramine) may cause serious adverse reactions, including hypertensive crisis, and their use with ozanimod is not recommended. If used concurrently, adequate monitoring is required.

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. Concomitant use of ponesimod and strong CYP3A4 and uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) inducers is not recommended.

Neither siponimod nor ponesimod have been studied in patients using QT-prolongating drugs; due to potential additive effects, siponimod and ponesimod should generally not be initiated in patients using concomitant QT-prolongating agents or other agents that can decrease heart rate without consultation from a cardiologist. Caution should be used, as described above, in patients using beta-blockers. 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), ozanimod, or ponesimod. Coadministration of ketoconazole can increase fingolimod exposure by 70%; a higher risk of adverse effects is possible. Avoid use of live attenuated vaccines during fingolimod treatment and for 2 months following discontinuation. Pediatric patients, if possible, should be brought up to date with all immunizations according to current immunization guidelines prior to initiation of fingolimod.

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 coadministered 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 coadministered with teriflunomide due to an increase in contraceptive drug levels after repeated doses of teriflunomide.

ADVERSE EFFECTS^{144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163}

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)†	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/IM (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

† Lymphopenia

‡ Influenza

§ Glatiramer 40 mg versus 20 mg incidence of injection site erythema (22% versus 43%, respectively), pain (10% versus 40%, respectively), and pruritus (6% versus 27%, respectively) as reported in the package insert

¶ 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
monomethyl fumarate (Bafiertam)	nr	nr	nr	n/a	reported	reported	reported
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)
ofatumumab (Kesimpta)	nr	nr	nr	21	nr	nr	8
ozanimod (Zeposia)	nr	nr	nr	n/a	10	nr	4
ponesimod (Ponvory)	nr	reported	nr	n/a	23** (12)	nr	reported
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

** Ponesimod 20 mg versus teriflunomide 14 mg incidence of increased liver enzymes (23% versus 12%), respectively

Additional adverse effects reported with alemtuzumab (Lemtrada) ($\geq 10\%$ of patients and more than IFN β -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 IFN β -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%). Postmarketing adverse reactions of vertigo have been reported.

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. Postmarketing experience shows reports of rhinorrhea in dimethyl fumarate and diroximel fumarate. Adverse effects of diroximel fumarate (Vumerity) and monomethyl fumarate (Bafiertam) 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 AV 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 to assess the bioequivalence of IFN β -1a (Plegridy) IM and SC, the most common adverse reactions in study population (> 10%) were chills (36% IM versus 27% SC), pain (22% IM versus 14% SC), headache (36% IM versus 41% SC), injection site pain (11% IM versus 15% SC), and injection site erythema (2% IM versus 25% SC). Injection site reactions (erythema, pain, pruritis, or edema) occurred in IFN β -1a (Plegridy) IM (14%) versus SC (32%).

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.¹⁶⁴ 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.

Hemolytic anemia has been reported in postmarketing cases with IFN β -1a (Rebif) and IFN β -1b (Betaseron, Extavia).

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%). Incidence, intensity, and types of symptoms of infusion reactions with ocrelizumab 2-hour infusion were consistent with infusion reactions reported with 3.5 hour infusions in patients who did not experience any previous serious infusion reactions.

The most common adverse reactions not reflected in the above table (incidence \geq 5%) and reported with ofatumumab (Kesimpta) in clinical trials were upper respiratory tract infections (39%), systemic injection-related reactions (21%), headache (13%), urinary tract infection (10%), and blood immunoglobulin M reduction (6%).

Upper respiratory infection, orthostatic hypotension, urinary tract infection, and hypertension (not reported above with incidence \geq 4% and greater than IFN β -1a) have also been reported with ozanimod (Zeposia).

In a clinical trial of ponesimod compared to teriflunomide, the most common adverse reactions (\geq 10%) experienced with ponesimod with at least 2% higher rate compared to teriflunomide, respectively, included upper respiratory infection (37% versus 34%), hepatic transaminase elevation (23% versus 12%), and hypertension (10% versus 9%). ALT elevations \geq 5 times the ULN occurred in 4.6% versus 2.5% of patients that received ponesimod versus teriflunomide, respectively. In addition, ALT elevation, \geq 3-fold the ULN, occurred in 17.3% versus 8.3% of patients treated with ponesimod versus teriflunomide, respectively. An elevation of 3-fold the ULN occurred at a median time of 3 months. Increases in ALT \geq 3-fold the ULN values returned to $<$ 3 times the ULN within approximately 2 to 4 weeks in majority of patients (89%).

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^{165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181}

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

Previously, alemtuzumab (Lemtrada), dalfampridine (Ampyra), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), IFN β -1a IM (Avonex), IFN β -1a SC (Rebif), IFN β -1a SC/IM (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 dimethyl fumarate and 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 β -1a IM (Avonex), and IFN β -1a SC/IM (Plegridy) in pregnant women have not generally indicated a drug-associated risk of major birth defects. All references to the pregnancy registry for IFN β -1a (Plegridy) have been removed from labeling. Patients taking natalizumab (Tysabri) should inform their healthcare provider if they become pregnant or plan to become pregnant.

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 diroximel fumarate (Vumerity), monomethyl fumarate (Bafiertam), ozanimod (Zeposia), siponimod (Mayzent), and ponesimod (Ponvory) in pregnancy are inadequate to advise of maternal or fetal risk; however, based on pharmacology and animal data, these agents can cause fetal harm. Labeling for ozanimod, siponimod, and ponesimod advise that women of reproductive potential should use effective contraception during treatment; continue contraception for 3 months, 10 days, and 1 week after discontinuation of MS therapy for ozanimod, siponimod, and ponesimod, respectively.

Data in pregnant women receiving ocrelizumab (Ocrevus) or ofatumumab (Kesimpta) are not available 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 and ofatumumab are humanized monoclonal antibodies of an IgG1 subtype, and immunoglobulins are known to cross the placenta. Women of childbearing potential should use contraception while on treatment with both products and for 6 months following the last dose. A pregnancy exposure registry has been added to monitor outcomes in women exposed to ocrelizumab during pregnancy.

Teriflunomide (Aubagio) is contraindicated in pregnant women or women of childbearing 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. Likewise, no dose adjustment of siponimod (Mayzent) is needed in patients with hepatic impairment. **No dosage adjustment is required for ponosimod (Ponvory) in patients with mild hepatic impairment; however, use with ponosimod is not recommended in moderate to severe hepatic impairment.** Pharmacokinetics of ozanimod (Zeposia) are unknown; however, it is not recommended to initiate treatment with ozanimod in patients with hepatic impairment.

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 studies of dimethyl fumarate (Tecfidera), **diroximel fumarate (Vumerity), or monomethyl fumarate (Bafiertam)** have been conducted in patients with hepatic impairment; however, hepatic impairment would not be expected to affect exposure of any of these agents, 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), natalizumab (Tysabri), and ofatumumab (Kesimpta) in patients with hepatic impairment have not been studied. Hepatic impairment is not expected to significantly affect dalfampridine pharmacokinetics or recommended dosing. Pharmacokinetics of IFN β -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.

No dosage adjustments of dimethyl fumarate (Tecfidera) or monomethyl fumarate (Bafiertam) are needed in patients with renal impairment. While renal impairment can increase exposure of diroximel fumarate's (Vumerity) 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. Blood levels of ozanimod (Zeposia) were increased in a dedicated renal impairment trial; however, no dosing adjustments are advised. There are no clinically important effects on pharmacokinetics of ozanimod in patients with renal impairment. 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. Ponesimod does not require dosage adjustments in patients with renal impairment. The effects of dialysis on ponesimod have not been studied.

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 dosage adjustments of teriflunomide (Aubagio) are necessary in patients with renal impairment.

The pharmacokinetics of glatiramer (Copaxone), IFNβ 1-a (Rebif), natalizumab (Tysabri), or ofatumumab (Kesimpta) 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.

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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-dose vial (SDV): 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
diroximel fumarate (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) Warm to room temperature before use Ensure device compatibility when using an optional autoinjector	Single-dose prefilled syringes*: 20 mg/mL, 40 mg/mL 20 mg and 40 mg strengths are <i>not</i> interchangeable
IFNβ-1a (Avonex prefilled syringe)	30 mcg IM once weekly	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 Rebidose®)			Prefilled autoinjector: 22 mcg/0.5 mL, 44 mcg/0.5 mL, titration pack
IFN β-1a SC/IM (pegylated) (Plegridy)	125 mcg SC/IM every 14 days after dose titration; titrate over 4 weeks with a dose of 63 mcg at initiation on day 1, and 94 mcg 2 weeks later on day 15, and 125 mcg on day 29	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	SC Prefilled syringes: 125 mcg, starter pack (63 mcg and 94 mcg) SC Prefilled autoinjectors/pens: 125 mcg, starter pack (63 mcg and 94 mcg) IM prefilled syringe: 125 mcg/0.5mL
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.²⁰²

† The Betaconnect electronic autoinjector is approved for use with Betaseron.²⁰³ 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
monomethyl fumarate (Bafiertam)	95 mg orally twice daily for 7 days, then increase to the maintenance dose of 190 mg orally twice daily	Should not be crushed, chewed, or sprinkled on food; can be taken with or without food; administration with non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior may reduce the incidence of flushing A temporary dose reduction to 95 mg orally twice daily may be considered for tolerability; however, the recommended maintenance dose of 190 mg orally twice daily should be resumed within 4 weeks (consider discontinuation if unable to tolerate)	Delayed-release capsules: 95 mg
natalizumab (Tysabri)	300 mg IV infusion over 1 hour every 4 weeks In Crohn's disease, if no therapeutic benefit seen by 12 weeks of induction therapy and chronic concomitant steroids cannot be discontinued within 6 months of starting therapy, discontinue natalizumab therapy.	Observe for 1 hour following infusion completion for the first 12 infusions and use clinical judgement for 13 th and subsequent infusions if no hypersensitivity reactions were observed; 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: Option 1: 600 mg as an IV infusion over at least 3.5 hours every 6 months beginning 6 months after the first infusion Option 2: (if no prior serious infusion reaction with any previous Ocrevus infusion) 600 mg IV infusion of approximately 2 hours duration	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
ofatumumab (Kesimpta)	Initial dose: 20 mg as a SC injection at weeks 0, 1, and 2 Maintenance dose: 20 mg as a SC injection once a month starting at week 4	First injection should be performed under the guidance of a healthcare professional Refrigerate; must allow medication to reach room temperature for 15 to 30 minutes before administration without removing the needle cover Protect from light until time of use	Prefilled syringes/pens: 20 mg/0.4 mL

Dosages (continued)

Drug	Dosage	Comments	Availability																						
ozanimod (Zeposia)	0.23 mg orally once daily on days 1 to 4, followed by 0.46 mg orally once daily on days 5 to 7, and 0.92 mg once daily on days 8 and thereafter	Re-initiation of titration regimen is only required if 1 titration dose is missed during the first 2 weeks of treatment	Capsules: 0.92 mg, 7-day starter pack (four 0.23 mg capsules, three 0.46 mg capsules) Starter kit (four 0.23 mg capsules, three 0.46 mg capsules, thirty 0.92 mg capsules)																						
ponesimod (Ponvory)	20 mg orally once daily, beginning on day 15, following an initial titration Titration (all doses administered orally once daily): <table border="1" data-bbox="324 714 722 1144"> <thead> <tr> <th>Dose</th> <th>Day(s)</th> </tr> </thead> <tbody> <tr> <td>2 mg</td> <td>1 to 2</td> </tr> <tr> <td>3 mg</td> <td>3 to 4</td> </tr> <tr> <td>4 mg</td> <td>5 to 6</td> </tr> <tr> <td>5 mg</td> <td>7</td> </tr> <tr> <td>6 mg</td> <td>8</td> </tr> <tr> <td>7 mg</td> <td>9</td> </tr> <tr> <td>8 mg</td> <td>10</td> </tr> <tr> <td>9 mg</td> <td>11</td> </tr> <tr> <td>10 mg</td> <td>12 to 14</td> </tr> <tr> <td>20 mg</td> <td>15+</td> </tr> </tbody> </table>	Dose	Day(s)	2 mg	1 to 2	3 mg	3 to 4	4 mg	5 to 6	5 mg	7	6 mg	8	7 mg	9	8 mg	10	9 mg	11	10 mg	12 to 14	20 mg	15+	Re-initiation with Day 1 titration regimen recommended if ≥ 4 consecutive doses are missed during titration or maintenance	Tablets: 20 mg Starter kit (two 2 mg tablets, two 3 mg tablets, two 4 mg tablets, 1 each of 5 mg, 6 mg, 7 mg, 8 mg, and 9 mg tablets, and three 10 mg tablets)
Dose	Day(s)																								
2 mg	1 to 2																								
3 mg	3 to 4																								
4 mg	5 to 6																								
5 mg	7																								
6 mg	8																								
7 mg	9																								
8 mg	10																								
9 mg	11																								
10 mg	12 to 14																								
20 mg	15+																								
siponimod (Mayzent)	Dosing recommendations based on CYP2C9 genotypes which must be confirmed 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 until dispensing to patient Once dispensed, unopened containers may be stored at room temperature for up to 3 months; opened containers of siponimod may be stored at room temperature for up to 3 months in the original starter pack and 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 \geq 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 and monomethyl 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.

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 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 CBC and obtain serum transaminases and total bilirubin levels within 6 months prior to initiation. See product labeling for additional details.

Initiation with ozanimod requires first-dose cardiac monitoring in male patients with QTc > 450 msec; female patients with QTc > 470 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. Prescribers should review results of a recent CBC and obtain serum transaminases and total bilirubin levels within 6 months prior to initiation. Cardiac and ophthalmic evaluation should be assessed prior to initiation. See product labeling for additional details.

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)	
	Titration Day	Titration Dose
CYP2C9 Genotypes: *1/*1, *1/*2, or *2/*2	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)

For siponimod, first dose, 4-hour monitoring 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 infarction or heart failure occurring > 6 months prior to treatment initiation who are in a stable condition. All patients must be observed for signs and symptoms of bradycardia for at least 4 hours after first dose with hourly pulse and blood pressure measurement. An ECG should be obtained prior to dosing and the end of the 4-hour monitoring period. Appropriate management should be initiated if symptomatic bradycardia, arrhythmias, conduction-related symptoms, corrected QT ≥ 500 msec, or new onset second degree or higher AV blocker at 4 hours post-dose occur. If pharmacologic management is needed, monitoring should continue overnight and 4-hour monitoring should also occur with the second dose. The most appropriate monitoring recommendations should be obtained via consultation with a cardiologist in select patient populations, as described above.

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.²⁰⁴

Diroximel fumarate (Vumerity) and monomethyl fumarate (Bafiertam) were 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 these agents.^{205,206}

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 RRMS.^{207,208} 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. MRI evaluations were performed annually.

The first study was a 2-year randomized, open-label, rater-blinded, active comparator (IFN β -1a 44 micrograms administered SC 3 times a week) controlled study in patients with RRMS.²⁰⁹ Patients entering the study had EDSS scores of 5 or less and had to have experienced at least 1 relapse while on IFN β or glatiramer acetate therapy. Patients were randomized to receive alemtuzumab (n=426) or IFN β -1a (n=202). The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression (CDP). 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 IFN β -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 (IFN β -1a 44 micrograms administered SC 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 MS.²¹⁰ Patients were randomized to receive alemtuzumab (n=376) or IFN β -1a (n=187). The clinical outcome measures were the ARR over 2 years and the time to CDP, 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 IFN β -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.²¹¹

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 RRMS based on the McDonald criteria.^{212,213} 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.²¹⁴ 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 MS.²¹⁵ This was a randomized, multicenter, double-blind, controlled trial, 301 patients with any type of MS 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.^{216,217,218}

Another randomized, multicenter, double-blind trial included 229 patients with definite MS of any type.²¹⁹ 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:²²⁰ 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 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:²²¹ 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 Gd-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 (ITT) 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 ARR 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).²²² Although the study was not designed to test the superiority or noninferiority of dimethyl fumarate to glatiramer acetate, the active comparator had similar results.²²³ 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:²²⁴ 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 (CDP) 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/AV 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.²²⁵ 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 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.²²⁶

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

PARADIGMS:^{227,228} 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:²²⁹ 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 SC daily plus placebo (GA), IFN β -1a 30 μ g IM weekly plus placebo (IFN), or 20 mg SC daily plus IFN β -1a 30 μ g IM 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:²³⁰ 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 SC 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).²³¹ 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.²³² 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.²³³ 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.

IFN β -1a IM (Avonex) versus IFN β -1b (Betaseron)

The Independent Comparison of Interferon (INCOMIN) trial was a single-blinded, randomized comparison of IFN β -1a IM and IFN β -1b in 188 patients with RRMS.²³⁴ IFN β -1a was given at a dose of 30 mcg IM once weekly, and IFN β -1b was administered at a dose of 250 mcg SC every other day. Over the 2-year study period, 36% of patients randomized to IFN β -1a IM were relapse-free compared to 51% of patients receiving IFN β -1b ($p=0.03$). More patients remained free from new T2 lesions, which indicate inflammatory damage on MRI, in the IFN β -1b group (55% versus 26%, $p<0.0003$). Delay of confirmed disease progression was significantly higher in the IFN β -1b group. Discontinuation of therapy due to disease progression was more prevalent in the IFN β -1a IM group. Significantly more patients withdrew from therapy with IFN β -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.

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

In a parallel group, single-blind study, 90 patients with RRMS were randomized to receive IFN β -1a 30 mcg IM once weekly, IFN β -1a 44 mcg SC 3 times weekly, or IFN β -1b 250 mcg SC every other day for 24 months.²³⁵ The EDSS scores remained stable in patients in the IFN β -1a IM group and decreased in the groups receiving IFN β -1a SC ($p<0.05$ versus baseline) and IFN β -1b ($p<0.001$). In the patients treated with IFN β -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 IFN β -1a SC, the mean relapse rate decreased from 2.4 to 0.6, while the rate in those treated with IFN β -1b decreased from 2.2 to 0.7 ($p<0.001$ for both changes from baseline). After 2 years, 20% of patients receiving IFN β -1a IM remained relapse-free. In comparison, 56.7% of patients receiving IFN β -1a SC and 43.3% of those receiving IFN β -1b remained relapse-free ($p<0.05$ for both comparisons to IFN β -1a IM).

IFN β -1a SC (Rebif) versus IFN β -1b (Betaseron)

In an open-label study, 301 patients with RRMS were randomized to receive IFN β -1a 22 mcg SC once weekly or IFN β -1b 250 mcg SC every other day for 2 years.²³⁶ The annual relapse rates were virtually equal in the 2 arms of the randomized study (IFN β -1a: 0.7; IFN β -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 IFN β -1a SC group and 45.2% in the IFN β -1b group. Subsequent ITT analysis indicated a statistically insignificant difference in the proportion of relapse-free patients, 35% and 41% in the IFN β -1a SC and IFN β -1b groups, respectively.²³⁷ The IFN β -1a dosing interval in the study was less frequent than the FDA-approved dosing regimen.

IFN β -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 IFN β -1a SC 44 mcg 3 times weekly ($n=386$) or glatiramer acetate SC 20 mg daily ($n=378$) for 96 weeks.²³⁸ 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 [HR], 0.94; 95% CI 0.74 to 1.21; p=0.64). Relapse rates were lower than expected: 258 patients (126 in the IFN β -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 Gd-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 Gd-enhanced lesions. However, the IFN β -1a group had significantly fewer Gd-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.²³⁹ 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:²⁴⁰ 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) SC 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 MS. 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 CDP. 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.²⁴¹

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 a an EDSS score of 0 to 5 (AFFIRM and SENTINEL).^{242,243,244} 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).^{245,246} 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 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.^{247,248} 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% 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%.^{249,250} The proportion of patients with 12-week CDP 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.²⁵¹ Prespecified subgroups included study, age, sex, body mass index (BMI), region, baseline EDSS score, baseline Gd-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.

ocrelizumab (Ocrevus) shorter infusions

SaROD.²⁵² A phase 3b, open-label, 2-cohort study evaluated the safety of ocrelizumab in a shorter infusion protocol in 141 adult patients ages 18 to 55 years with PPMS and RMS per the 2017 revised McDonald criteria. Patients were enrolled, 2:1, into 2 cohorts if they had an EDSS score of 0 to 6.5, no prior exposure to other B-cell-targeted therapies, and no prior exposure to alemtuzumab. Patients were excluded if they had a prior serious or life-threatening IRR with the initial dose of ocrelizumab. Prior to start of ocrelizumab infusion, all patients received a premedication with a corticosteroid approximately 30 minutes prior to infusion and an antihistamine within 60 minutes before each infusion, an antipyretic was optional. . The safety of administering dose 2 or dose 3 of ocrelizumab 600 mg (infused over approximately 2 hours) (Cohort 1) or dose 1 of 300 mg of ocrelizumab (infused over 1.5 hours) (Cohort 2) was evaluated compared with US prescribing information for ocrelizumab dose 1 or doses 1 and 2 at US label infusion rates. The primary outcome was the number and proportion of patients in the 2-hour infusion group that experienced \geq grade 3 IRRs. The secondary endpoints for both cohorts included any grade IRRs and cohort 2 included \geq grade 3 IRRs. For patients in the 2-hour 600 mg infusion group, mean infusion time decreased by approximately 1.09 hours and the 1.5- hour 300 mg infusion group by 0.79 hours compared with US prescribing information (USPI). Infusion-related reactions (IRRs), reported by 36% of patients in the study were mild-to-moderate, and there were no grade 3 or 4 IRRs observed. The most common types of IRRs, occurring in 32.6% of patients, were systemic reactions (e.g., throat irritation, pruritis, headaches, nausea, fatigue). There were no discontinuations, serious adverse effects, deaths, or new safety signals. The ocrelizumab infusion time can be reduced from 3.5 hours to 2 hours without sacrificing patient safety or increase (IRRs).

ofatumumab (Kesimpta) versus teriflunomide (Aubagio)

ASCLEPIOS:^{253,254} Two randomized, double-blind, double-dummy, active-comparator controlled phase 3 trials compared the safety and efficacy of ofatumumab versus teriflunomide in patients with relapsing MS. Patients between the ages of 18 and 55 years were included in the study if they had a diagnosis of MS with RRMS or SPMS and an EDSS score of 0 to 5.5. Patients must have experienced \geq 1 relapse during the previous year, \geq 2 relapses during the previous 2 years, or a positive Gd-enhancing MRI in the previous year to be eligible for participation. Patients were randomized to receive SC ofatumumab 20 mg injections every 4 weeks after appropriate loading doses (n=946) with daily oral placebo or the active comparator oral teriflunomide 14 mg capsules (n=936). Treatment duration was for up to 30 months (median, 1.6 years). Patients received neurologic evaluations at baseline, every 3 months during treatment, and at the time of suspected relapse, while brain MRI scans were completed at baseline and ever year thereafter. The primary outcome was ARR. Other endpoints included 3-month CDP, 6-month

CDP, 3-month serum neurofilament light chain levels, changes in brain volume, and select MRI measures. The study defined disability progression as an increase in EDSS of ≥ 1.5 , 1, or 0.5 points in patients with baseline scores of 0, 1 to 5, ≥ 5.5 , respectively. The ARR from the ofatumumab and teriflunomide groups in ASCLEPIOS I were 0.11 and 0.22, respectively (treatment difference from teriflunomide, -0.11; 95% CI, -0.16 to -0.06; $p < 0.001$). In ASCLEPIOS II, the ARRs in the ofatumumab and teriflunomide groups were 0.1 and 0.25 (treatment difference from teriflunomide, -0.15; 95% CI, -0.2 to -0.09; $p < 0.001$). In pooled trials, the 3-month CDP for ofatumumab-treated patients was 10.9% and 15% for teriflunomide-treated patients, respectively (HR, 0.66; $p = 0.002$). The 6-month CDP for ofatumumab-treated and teriflunomide-treated patients were 11% and 8.1% (HR, 1.35; $p = 0.09$). Notably, 2.5% of ofatumumab-treated patients and 1.8% of teriflunomide-treated patients experienced serious infections, while injection-related reactions occurred in 20.2% of patients in the ofatumumab group and 15% of patients in the teriflunomide group. Both studies demonstrated that ofatumumab significantly lowered the ARR compared to teriflunomide, while also significantly reducing the risk of 3-month CDP.

ozanimod (Zeposia) versus IFN β -1a IM (Avonex)

SUNBEAM:^{255,256} A phase 3, randomized, double-blind, double-dummy, active-controlled trial assessed the safety and efficacy of ozanimod versus IFN β -1a in patients with relapsing MS. Patients enrolled in the study were between the ages of 18 and 55 years, with baseline EDSS scores ≤ 5 , and had either ≥ 1 relapse within the 12 months prior to screening, or ≥ 1 relapse within 24 months prior to screening and ≥ 1 Gd-enhancing lesion within 12 months prior to screen. The mean age of this population was 35.4 years, with the mean time since MS symptom onset being 6.9 years. Patients were randomized 1:1:1 to receive ozanimod 0.5 mg ($n = 451$), ozanimod 1 mg ($n = 447$), or IM IFN β -1a ($n = 448$). The primary objective assessed the ARR during the treatment period in the ITT population. The adjusted ARR for patients treated with IFN β -1a was 0.35 (95% CI, 0.28 to 0.44); the adjusted ARR for patients treated with ozanimod 0.5 mg was 0.24 (95% CI, 0.19 to 0.31; RR, 0.69 [95% CI, 0.55 to 0.86] versus IFN β -1a; $p = 0.0013$); and the adjusted ARR for patients treated with ozanimod 1 mg was 0.18 (95% CI, 0.14 to 0.24; RR, 0.52 [95% CI, 0.41 to 0.66] versus IFN β -1a; $p < 0.0001$). The ARRs from the ozanimod groups were significantly lower than in the IFN β -1a group.

RADIANCE:^{257,258} A phase 3, multinational, randomized, double-blind, double-dummy, active comparator-controlled clinical trials evaluated the safety and efficacy of ozanimod compared to IFN β -1a in patients with relapsing MS. Similar to the SUNBEAM study, patients included in the study were between the ages of 18 to 55 years, had confirmed MS diagnosis per the 2010 McDonald criteria, a relapsing clinical course, an EDSS ≤ 5 , and brain MRI lesions that are consistent with MS. Patients also had experienced ≥ 1 relapse within the last year prior to screening or ≥ 1 relapse within the 2 years prior and ≥ 1 Gd-enhancing lesion within the year prior to randomization. Patients were randomized 1:1:1 to receive daily oral ozanimod 0.5 mg ($n = 439$), daily oral ozanimod 1 mg ($n = 433$), or weekly IM IFN β -1a ($n = 441$). Patients received neurological evaluations at baseline, every 3 months, and at the time of suspected relapse, with brain MRI scans completed throughout the studies. The primary outcome was the ARR over the 24-month period. Other outcome measures included the number of MRI T1 Gd-enhancing lesions, number of new or enlarging MRI T2 hyperintense lesions, and the time to CDP, which is defined as ≥ 1 point increase from baseline EDSS after 3 and 6 months of treatment. Adjusted ARRs were 0.28 (95% CI, 0.23 to 0.32) with IFN β -1a; 0.22 (95% CI, 0.18 to 0.26) with ozanimod 0.5 mg; and 0.17 (95% CI, 0.14 to 0.21) with ozanimod 1 mg. The RR versus IFN β -1a was 0.79 (95% CI, 0.65 to 0.96;

p=0.0167) for ozanimod 0.5mg and 0.62 (96% CI, 0.51 to 0.77; p<0.0001) for ozanimod 1 mg. The study resulted in a statistically significantly lower ARR in the ozanimod-treated patients compared to the IFN β -1a-treated patients; however, it did not conclude any statistically significant differences in the 3-month and 6-month CDP among the patients treated with ozanimod and IFN β -1a over the 24 months. Treatment emergent adverse events occurred in more patients in the IFN β -1a group (365 [83%] of 440 patients) than in the ozanimod 1 mg group (324 [74.7%] of 434 patients) or the ozanimod 0.5 mg group (325 [74.3%] of 439 patients). Across 3 groups, incidences of infections and serious adverse events were similar.

ponesimod versus teriflunomide

OPTIMUM:^{259,260} A randomized, double-blind, active comparator, superiority study compared the efficacy and safety of ponesimod and teriflunomide in patients with RMS. Patients enrolled were adults aged 18 to 55 years with a diagnosis of MS (per the 2010 McDonald criteria) with a relapsing course from onset, an EDSS score of 0 to 5.5, had experienced at least 1 relapse within the year prior or 2 relapses within the prior 2 years, or had at least 1 Gd-enhancing lesion on a brain MRI within the prior 6 months or at baseline. Patients were excluded if they had a diagnosis of primary progressive MS. Patients were randomized 1:1 to 20 mg ponesimod, following a 14-day titration, or 14 mg teriflunomide once daily for 108 weeks. The primary outcome was ARR, based on the number of confirmed relapses per patient-year to the end of the study based on ITT. Secondary outcomes included symptom domain changes, as measured by the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS; range, 0 to 100; higher scores represent more fatigue) at week 108, time to 12-week and 24-week confirmed disability accumulation (CDA; new Gd+ T1 lesions or new or enlarging T2 lesions), and the number of combined unique active lesions (CUAL) per year on MRI. There were 1,133 patients enrolled in the study (n=567 ponesimod; n=566 teriflunomide). The mean age of patients enrolled in the trial was 37 years, 97% were White, and 64.9% were female. Included patients had a mean duration of disease of 7.6 years, with 1.3 mean relapses in the previous year and a mean EDSS score of approximately 2.6. Fifty-seven percent of the patients had no prior non-steroid treatments for MS. There were 42.6% of patients with ≥ 1 Gd-enhancing T1 lesions (mean 2) at baseline on MRI. At study completion, the ARR was 0.202 with ponesimod and 0.29 with teriflunomide (rate ratio, 0.695; 99% confidence interval [CI], 0.536 to 0.902; p<0.001), resulting in a 30.5% relative reduction in ARR for ponesimod compared to teriflunomide. The change from baseline in the FSIQ-RMS weekly symptom score at week 108 was lower with ponesimod than teriflunomide (difference, -3.57; 95% CI, -5.83 to -1.32; p=0.002). The mean number of CUAL per year using annual MRIs at week 108 was 1.405 with ponesimod versus 3.164 with teriflunomide (rate ratio, 0.444; 95% CI, 0.364 to 0.542; p<0.001). The investigators found no difference in 12-week and 24-week CDA (p=0.29 and p=0.37, respectively). Treatment-emergent adverse effects (TEAEs) were similar in both groups; however, TEAEs leading to discontinuation occurred more frequently in the ponesimod group compared to teriflunomide (8.7% versus 6%, respectively).

siponimod (Mayzent) versus placebo

EXPAND:^{261,262} 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 CDP events. The primary outcome was the time to 3-month CDP, which was defined as a ≥ 1 -point increase in EDSS (a ≥ 0.5 -point for baseline EDSS ≥ 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 ≥ 1 relapses in the prior 2 years, 22% of those with available imaging had ≥ 1 Gd-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 (mm^3) 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 (HR, 0.67; 95% CI, 0.49 to 0.91), the effect on those with non-active SPMS was not statistically significant (HR, 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 Gd-enhancing T1 lesions at baseline (≥ 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:^{263,264} 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 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.²⁶⁵ 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 CIS indicative of early MS.²⁶⁶ A 9-year follow up of the TEMSO trial reported similar safety outcomes as found in the core TEMSO study.²⁶⁷

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

TENERE Study:²⁶⁸ 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 ≤ 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.²⁶⁹ 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.^{270,271,272}

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.²⁷³ 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.²⁷⁴ 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).^{275,276} 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 CDP. 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 CDP, 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.^{277,278} The proportion of patients with 12-week CDP, 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.²⁷⁹ 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.²⁸⁰ 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.²⁸¹ 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.²⁸² 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 (CI 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).²⁸³ 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.²⁸⁴ 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.²⁸⁵ 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 CDP 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.

A network meta-analysis was applied, comparing cladribine to oral disease-modifying drugs, fingolimod, dimethyl fumarate, and teriflunomide.²⁸⁶ It utilized 6 randomized clinical trials to evaluate disease control with no evidence of disease activity (NEDA-3) as a composite endpoint in patients with RRMS. NEDA-3 was significantly higher with cladribine compared to dimethyl fumarate (odds ratio [OR], 1.76; 95% credible intervals [CrI], 1.02 to 3.03) and teriflunomide (OR, 2.78; 95% CrI, 1.6 to 4.83), but not compared to fingolimod. Cladribine was more effective compared with the other oral agents with regards to MRI NEDA, cladribine versus dimethyl fumarate (OR, 1.87; 95% CrI, 1.18 to 2.97), versus teriflunomide (OR, 6.59; 95% CrI, 4.32 to 10.09), and versus fingolimod (OR, 1.58; 95%CrI, 1.1 to 2.29). The authors concluded that cladribine was significantly more effective compared to other first-line oral agents, dimethyl fumarate and teriflunomide; however, there were no significant differences seen compared to fingolimod.

A network analysis of 33 mixed-treatment comparisons (MTCs) evaluated the safety and efficacy of DMTs compared to placebo in adults with RRMS.²⁸⁷ The ARR in 28 of the trials was significantly reduced in all treatments compared to placebo. Alemtuzumab was found to have the highest probability (63%) of being the most effective treatment with regards to ARR compared to placebo (RR, 0.28; 95% CrI, 0.21 to 0.38), followed by natalizumab (30% probability; RR, 0.32; 95% CrI, 0.23 to 0.43). The authors confirmed the benefit of all DMTs with regards to ARR compared with placebo. The authors also concluded comparable rates of serious adverse events for DMTs compared to placebo.

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 IFN β -1a, which allows for a longer duration; therefore, Plegridy is dosed subcutaneously (SC) or intramuscularly (IM) 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.

Nine oral agents, cladribine (Mavenclad), dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), fingolimod (Gilenya), monomethyl fumarate (Bafiertam), ozanimod (Zeposia), siponimod (Mayzent), teriflunomide (Aubagio), and ponesimod (Ponvory) are available for the treatment of MS. Most 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 and monomethyl fumarate (Bafiertam) contain the same active metabolite of dimethyl fumarate and were approved via an abbreviated 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 only 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. Unlike the other sphingosine 1-phosphate receptor modulators, ozanimod and ponesimod do not require genetic testing or first-dose observations upon initiation; however, first-dose monitoring is recommended for select patient populations using ponesimod. 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 is 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 (Ocrevus), a CD20-directed cytolytic antibody, 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 (reaffirmed in 2021) state clinicians should offer ocrelizumab to PPMS patients who are likely to benefit unless the risks outweigh the benefit. Ofatumumab (Kesimpta), another recombinant humanized CD20 monoclonal antibody approved for relapsing forms of MS in 2020, has been associated with lower annualized relapse rate (ARR) in patients with relapsing MS compared to teriflunomide in clinical trials. Comparative efficacy of ofatumumab SC injections and intravenous (IV) ocrelizumab have not been compared. Notably, ofatumumab is not approved for PPMS.

REFERENCES

- 1 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
- 2 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
- 3 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
- 4 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021.
- 5 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
- 6 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
- 7 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
- 8 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
- 9 Rebif [package insert]. Rockland, MA; Serono; November 2021.
- 10 Plegridy [package insert]. Cambridge, MA; Biogen; November 2021.
- 11 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
- 12 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
- 13 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
- 14 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
- 15 Ocrevus [package insert]. South San Francisco, CA; Genentech; March 2021.
- 16 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
- 17 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
- 18 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
- 19 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
- 20 Aubagio [package insert]. Cambridge, MA; Genzyme; April 2021.
- 21 Lutton JD, Winston R, Rodman TC. Multiple sclerosis: etiological mechanisms and future directions. *Exp Biol Med* (Maywood). 2004; 229:12-20.
- 22 Calabresi PA. Diagnosis and management of multiple sclerosis. *Am Fam Physician*. 2004; 70:1935-44.
- 23 Multiple Sclerosis. Last updated January 3, 2022. Available at: <https://emedicine.medscape.com/article/1146199-overview>. Accessed February 4, 2022.
- 24 Available at: <https://www.nationalmssociety.org/About-the-Society/MS-Prevalence/MS-Prevalence-FAQ>. Accessed February 4, 2022.
- 25 Multiple Sclerosis. Last updated September 2, 2020. Available at: <https://emedicine.medscape.com/article/1146199-overview>. Accessed February 4, 2022.
- 26 National Multiple Sclerosis Society. Available at: <https://www.nationalmssociety.org/What-is-MS/Types-of-MS>. Accessed February 4, 2022.
- 27 Hafler DA. Multiple sclerosis. *J Clin Invest*. 2004; 113:788-794.
- 28 Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. DOI: 10.1016/S1474-4422(17)30470-2.
- 29 Saslow L, Li DKB, Halper J, et al. An international standardized magnetic resonance imaging protocol for diagnosis and follow-up of patients with multiple sclerosis: Advocacy, dissemination, and implementation strategies. *Int J MS Care* (2020) 22 (5): 226-232. Available at: https://www.ms-care.org/page/MRI_protocol. Accessed February 7, 2022.
- 30 2020. An International Standardized Magnetic Resonance Imaging Protocol for Diagnosis and Follow-up of Patients with Multiple Sclerosis: Advocacy, Dissemination, and Implementation Strategies. 2018. Available at: <https://www.ms-care.org/>. Accessed February 4, 2022.
- 31 Mitchell G. Update on multiple sclerosis therapy. *Med Clin North America*. 1993; 77:231-249.
- 32 Holland NJ. Basic MS Facts. *Clinical Bulletin: Information for Health Professionals*. National Multiple Sclerosis Society; 2002.
- 33 National Multiple Sclerosis Society. Available at: <https://www.nationalmssociety.org/What-is-MS/Types-of-MS>. Accessed February 4, 2022.
- 34 National Multiple Sclerosis Society. Available at: <https://www.nationalmssociety.org/What-is-MS/Types-of-MS>. Accessed February 4, 2022.
- 35 National Multiple Sclerosis Society. Available at: <https://www.nationalmssociety.org/What-is-MS/Types-of-MS>. Accessed February 4, 2022.
- 36 Goodin DS, Froman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for clinical practice guidelines. *Neurology*. 2002; 58:169-178.

-
- 37 Treating PPMS. Available at: <https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS/Treating-Primary-Progressive-MS>. Accessed February 4, 2022.
- 38 Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. 2018 (reaffirmed 2021). Available at: <https://www.aan.com/Guidelines/home/ByTopic?topicId=18>. Accessed February 4, 2022.
- 39 Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. 2018 (reaffirmed 2021). Available at: <https://www.aan.com/Guidelines/home/ByTopic?topicId=18>. Accessed February 4, 2022.
- 40 Ghezzi A, Amato MP, Makhani N, et al. Pediatric multiple sclerosis: Conventional first-line treatment and general management. *Neurology*. 2016; 30;87(9 Suppl 2):S97-S102. DOI: 10.1212/WNL.0000000000002823. Available at: http://n.neurology.org/content/87/9_Supplement_2#sthash.6u9TjZfM.dpuf. Accessed February 4, 2022.
- 41 Chitnis T, Ghezzi A, Bajer-Kornek B, et al. Pediatric multiple sclerosis: Escalation and emerging treatments. *Neurology*. 2016;87(9 Suppl 2):S103-9. DOI: 10.1212/WNL.0000000000002884. Available at: http://n.neurology.org/content/87/9_Supplement_2#sthash.6u9TjZfM.dpuf. Accessed February 4, 2022.
- 42 Goodin DS, Frohman EM, Hurwitz B, et al. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report. *Neurology*. 2007; 28(13): 977-984.
- 43 Farez MF, Correale J, Armstrong ML, et al. Practice guideline update: vaccine-preventable infections and immunizations in multiple sclerosis, a report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2019; 93(13): 584-594. Available at: <https://www.aan.com/Guidelines/Home/ByStatusOrType?status=all>. Accessed February 4, 2022.
- 44 Arzerra. Novartis. Available at: <https://www.us.arzerra.com/>. Accessed February 4, 2022.
- 45 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
- 46 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
- 47 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
- 48 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021.
- 49 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
- 50 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
- 51 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
- 52 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
- 53 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
- 54 Rebif [package insert]. Rockland, MA; Serono; November 2021.
- 55 Plegridy [package insert]. Cambridge, MA; Biogen; November 2021.
- 56 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
- 57 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
- 58 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
- 59 Ocrevus [package insert]. South San Francisco, CA; Genentech; March 2021.
- 60 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
- 61 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
- 62 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
- 63 Aubagio [package insert]. Cambridge, MA; Genzyme April 2021.
- 64 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
- 65 Deisenhammer F, Mayringer I, Harvey J, et al. A comparative study of the relative bioavailability of different interferon beta preparations. *Neurology*. 2000; 54:2055-2060.
- 66 Sturzebecher S, Maibauer R, Heuner A, et al. Pharmacodynamic comparison of single doses of IFNβ-1a and IFNβ-1b in healthy volunteers. *J Interferon Cytokine Res*. 1999; 19:1257-1264.
- 67 Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol*. 2010; 33(2):91-101.
- 68 Racke MK, et al. Copolymer-1-induced inhibition of antigen-specific T cell activation: Interference with antigen presentation. *J Neuroimmunology*. 1992; 37:75-84.
- 69 Teitelbaum D, et al. Synthetic copolymer 1 inhibits human T-cell lines specific for myelin basic protein. *Proc Natl Acad Sci*. 1992; 89:137-141.
- 70 Fridkis-Hareli M, et al. Synthetic copolymer 1 and myelin basic protein do not require processing prior to binding class II major histocompatibility complex molecules on living antigen-presenting cells. *Cellular Immunology*. 1995; 163:229-236.
- 71 Dhib-Jalbut S. Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis. *Neurology*. 2002; 58(8 Suppl 4):S3-9.
- 72 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
- 73 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
- 74 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
- 75 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021.
- 76 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
- 77 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
- 78 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
- 79 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
- 80 Rebif [package insert]. Rockland, MA; Serono; November 2021.
- 81 Plegridy [package insert]. Cambridge, MA; Biogen; November 2021.
- 82 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
- 83 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
- 84 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
-

-
- 85 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
- 86 Ocrevus [package insert]. South San Francisco, CA; Genentech; December 2020.
- 87 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
- 88 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
- 89 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
- 90 Aubagio [package insert]. Cambridge, MA; Genzyme April 2021.
- 91 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
- 92 Alam J, Goelz S, Rioux P, et al. Comparative pharmacokinetics and pharmacodynamics of two recombinant human interferon beta preparations. *Neurology*. 2000; 54:2055-2060.
- 93 Sturzebecher S, Maibauer R, Heuner A, et al. Pharmacodynamic comparison of single doses of IFN β -1a and IFN β -1b in healthy volunteers. *J Interferon Cytokine Res*. 1999; 19:1257-1264.
- 94 Salmon P, Le Cotonnee JY, Galazka A, et al. Pharmacokinetics and pharmacodynamics of recombinant human interferon-beta in healthy male volunteers. *J Interferon Cytokine Res*. 1996; 16:759-764.
- 95 Munafo A, Trinchard-Lugan I, Nguyen TXQ, et al. Comparative pharmacokinetics and pharmacodynamics of recombinant human interferon beta-1a after intramuscular and subcutaneous administration. *Eur J Neurol*. 1998; 5:1-7.
- 96 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
- 97 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
- 98 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
- 99 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021.
- 100 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
- 101 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
- 102 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
- 103 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
- 104 Rebif [package insert]. Rockland, MA; Serono; November 2021.
- 105 Plegridy [package insert]. Cambridge, MA; Biogen; November.
- 106 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
- 107 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
- 108 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
- 109 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
- 110 Ocrevus [package insert]. South San Francisco, CA; Genentech; December 2020.
- 111 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
- 112 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
- 113 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
- 114 Aubagio [package insert]. Cambridge, MA; Genzyme April 2021.
- 115 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
- 116 FDA Drug Safety Communication: FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug Lemtrada (alemtuzumab). Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-serious-risks-stroke-and-blood-vessel-wall-tears-multiple-sclerosis-drug>. Accessed February 4, 2022.
- 117 FDA Drug Safety Communication: Tecfidera (dimethyl fumarate) by Biogen Idec: Case of rare brain infection PDL reported. Available at: <https://www.fda.gov/drugs/drugsafety/ucm424625.htm>. Accessed February 4, 2022.
- 118 FDA Drug Safety Communication: Revised recommendations for cardiovascular monitoring and use of multiple sclerosis drug Gilenya (fingolimod). May 14, 2012. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm>. Accessed February 4, 2022.
- 119 FDA Drug Safety Communication: Revised recommendations for cardiovascular monitoring and use of multiple sclerosis drug Gilenya (fingolimod). Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm>. Accessed February 4, 2022.
- 120 FDA Drug Safety Communication: Safety review of a reported death after the first dose of Multiple Sclerosis drug Gilenya (fingolimod). Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm303192.htm>. Accessed February 4, 2022.
- 121 FDA Drug Safety Communication: FDA warns about cases of rare brain infection with MS drug Gilenya (fingolimod) in two patients with no prior exposure to immunosuppressant drugs. Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm456919.htm>. Accessed February 4, 2022.
- 122 FDA Safety Announcement: FDA warns about severe worsening of multiple sclerosis after stopping the medicine Gilenya (fingolimod). Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-severe-worsening-multiple-sclerosis-after-stopping-medicine-gilenya-fingolimod>. Accessed February 4, 2022.
- 123 REMS@FDA. Available at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>. Accessed February 4, 2022.
- 124 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
- 125 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
- 126 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
- 127 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021.
- 128 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
- 129 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
- 130 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
- 131 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
- 132 Rebif [package insert]. Rockland, MA; Serono; November 2021.
- 133 Plegridy [package insert]. Cambridge, MA; Biogen; November.
- 134 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
-

135 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
136 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
137 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
138 Ocrevus [package insert]. South San Francisco, CA; Genentech; December 2020.
139 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
140 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
141 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
142 Aubagio [package insert]. Cambridge, MA; Genzyme April 2021.
143 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
144 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
145 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
146 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
147 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021..
148 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
149 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
150 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
151 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
152 Rebif [package insert]. Rockland, MA; Serono; November 2021.
153 Plegridy [package insert]. Cambridge, MA; Biogen; November 2021.
154 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
155 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
156 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
157 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
158 Ocrevus [package insert]. South San Francisco, CA; Genentech; December 2020.
159 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
160 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
161 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
162 Aubagio [package insert]. Cambridge, MA; Genzyme April 2021.
163 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
164 Ruggieri RM, Settiani N, Viviano L, et al. Long-term interferon-beta treatment for multiple sclerosis. *Neurol Sci.* 2003; 24:361-4.
165 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
166 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
167 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
168 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021..
169 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
170 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
171 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
172 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
173 Rebif [package insert]. Rockland, MA; Serono; November 2021.
174 Plegridy [package insert]. Cambridge, MA; Biogen; November 2021.
175 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
176 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
177 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
178 Ocrevus [package insert]. South San Francisco, CA; Genentech; December 2020.
179 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
180 Aubagio [package insert]. Cambridge, MA; Genzyme April 2021.
181 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
182 Lemtrada [package insert]. Cambridge, MA; Genzyme; January 2022.
183 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
184 Ampyra [package insert]. Ardsley, NY; Acorda; November 2021.
185 Tecfidera [package insert]. Cambridge, MA; Biogen; January 2021..
186 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
187 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
188 Copaxone [package insert]. Parsippany, NJ; Teva; January 2022.
189 Avonex [package insert]. Cambridge, MA; Biogen; November 2021.
190 Rebif [package insert]. Rockland, MA; Serono; November 2021.
191 Plegridy [package insert]. Cambridge, MA; Biogen; November 2021.
192 Betaseron [package insert]. Whippany, NJ; Bayer; November 2021.
193 Extavia [package insert]. East Hanover, NJ; Novartis; November 2021.
194 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
195 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
196 Ocrevus [package insert]. South San Francisco, CA; Genentech; December 2020.
197 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.

-
- 198 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
- 199 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
- 200 Aubagio [package insert]. Cambridge, MA; Genzyme April 2021.
- 201 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
- 202 Glatopa [package insert]. Princeton, NJ; Sandoz; July 2020.
- 203 Available at: <https://www.betaseron.com/betaconnect-system/>. Accessed February 4, 2022.
- 204 Extavia [package insert]. East Hanover, NJ; Novartis; October 2020.
- 205 Vumerity [package insert]. Cambridge, MA; Biogen; January 2021.
- 206 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.
- 207 Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet*. 2012; 380(9856): 1829-1839. DOI: 10.1016/S0140-6736(12)61768-1.
- 208 Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatments for patients with relapsing-remitting multiple sclerosis: randomised controlled phase 3 trial. *Lancet*. 2012; 380(9856): 1819-1828. DOI: 10.1016/S0140-6736(12)61769-3.
- 209 Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet*. 2012; 380(9856): 1829-1839. DOI: 10.1016/S0140-6736(12)61768-1.
- 210 Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatments for patients with relapsing-remitting multiple sclerosis: randomised controlled phase 3 trial. *Lancet*. 2012; 380(9856): 1819-1828. DOI: 10.1016/S0140-6736(12)61769-3.
- 211 Havrdova E, Arnold DL, Cohen JA, et al. Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. *Neurology*. 2017;89(11):1107-1116. DOI: 10.1212/WNL.0000000000004313.
- 212 Mavenclad [package insert]. Rockland MA; EMD Serono; April 2019.
- 213 Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010;362:416-26. DOI: 10.1056/NEJMoa0902533.
- 214 Giovannoni G, Soelberg, Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. *Multiple Sclerosis Journal*. 2018, Vol. 24(12) 1594-1604. DOI: 10.1177/1352458518727603.
- 215 Goodman AD, Brown TR, Krupp LB, et al. Sustained release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. *Lancet*. 2009; 373(9665):732-8.
- 216 Kaufman M, Moyer D, Norton J. The significant change for the timed 25-foot walk in the multiple sclerosis functional composite. *Multiple Sclerosis*. 2000; 6:286-290.
- 217 Schwid SR, Goodman AD, McDermott MP, et al. Quantitative functional measures in MS: what is a reliable change? *Neurology*. 2002; 58: 1294-1296.
- 218 Kragt JJ, van der Linden FAH, Nielsen JM, et al. Clinical Impact of 20% worsening on timed 25 foot walk and 9 hole peg test in multiple sclerosis. *Multiple Sclerosis*. 2006; 12: 594-598.
- 219 Goodman AD, Brown TR, Edwards KR, et al for the MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol*. 2010; 68(4):494-502.
- 220 Gold R, Kappos L, Arnold D, et al. Placebo controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367:1098-107.
- 221 Fox R, Miller D, Phillips ST, et al. Placebo controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367:1087-97.
- 222 Miller DH, Fox RJ, Phillips JT, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study. *Neurology*. 2015; 84(11): 1145-1152. DOI: 10.1212/WNL.0000000000001360.
- 223 Fox R, Miller D, Phillips ST, et al. Placebo controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367:1087-97.
- 224 Cohen JA, Barkhof F, Comi G, et al. TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010; 362(5):402-415.
- 225 Khatri B, Barkhof F, Comi G, et al for the TRANSFORMS Study Group. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomized extension of the TRANSFORMS study. *Lancet Neurol*. 2011; 10(6):520-9.
- 226 Cohen JA, Khatri B, Barkhof F, et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. *J Neurol Neurosurg Psychiatry*. 2016; 87(5): 468-475. DOI: 10.1136/jnnp-2015-310597.
- 227 Chitnis T, Arnold DL, Banwell B, et al for the PARADIGMS study group. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379(11):1017-1027. DOI: 10.1056/NEJMoa1800149.
- 228 Gilenya [package insert]. East Hanover, NJ; Novartis; December 2019.
- 229 Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol*. 2013 Mar; 73(3):327-40.
- 230 Khan O, Rieckmann P, Boyko A, et al. For the GALA study group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol*. 2013; 73(6):705-713. DOI: 10.1002/ana.23938.
- 231 Cohen J, Belova A, Selmaj K, et al. Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial. *JAMA Neurol*. 2015; 72(12): 1433-1441. DOI: 10.1001/jamaneurol.2015.2154.
- 232 Sandberg-Wollheim M, Bever C, Carter J, et al. Comparative tolerance of IFN beta-1a regimens in patients with relapsing multiple sclerosis. *The EVIDENCE study*. *J Neurol*. 2005; 252:8-13.
- 233 Schwid SR, Thorpe J, Sharief M, et al. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis: the EVIDENCE Study. *Arch Neurol*. 2005; 785-92.
- 234 Durelli L, Verdun E, Barbero P, et al. Every-other-day IFN beta-1b versus once-weekly IFN beta-1a for multiple sclerosis: results of a two-year prospective randomized multicenter study (INCOMIN). *Lancet*. 2002; 359:1453-1460.
- 235 Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaseron, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. *Acta Neurol Scand*. 2006; 113:283-7.
- 236 Koch-Henriksen N, Sørensen PS, Christensen T, et al. A randomized study of two interferon- beta treatments in relapsing-remitting multiple sclerosis. *Neurology*. 2006; 66:1056-60.
-

- 237 Koch-Henriksen N, Sørensen PS, Christensen T, et al. Reply from the authors. *Neurology*. 2006; 67(7): 1313-1314.
- 238 Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the Rebif vs. Glatiramer Acetate in Relapsing MS Disease [REGARD] study; a multicentre, randomized, parallel, open-label trial. *Lancet Neurol*. 2008; 7(10):903-14.
- 239 O'Connor P, Filippi M, Arnason B, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurol*. 2009; 8(10):889-97.
- 240 Calabresi P, Kieseier B, Arnold D, et al. Pegylated Interferon Beta-1a for relapsing remitting multiple sclerosis (ADVANCE): A randomized, phase 3, double blind study. *Lancet Neurol* 2014;13:657-665.
- 241 Arnold DL, Calabresi PA, Kieseier BC, et al. Peginterferon beta-1a improves MRI measures and increases the proportion of patients with no evidence of disease activity in relapsing-remitting multiple sclerosis: 2-year results from the ADVANCE randomized controlled trial. *BMC Neurol*. 2017; 17(1): 29. DOI: 10.1186/s12883-017-0799-0.
- 242 Tysabri [package insert]. Cambridge, MA; Biogen; December 2021.
- 243 Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006; 354(9): 899-910.
- 244 Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006; 354(9): 911-923.
- 245 Ocrevus [package insert]. South San Francisco, CA; Genentech; March 2021.
- 246 Hauser SL, Bar-Or A, Comi G, et al for the OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017; 376 (3): 221-234. DOI: 10.1056/NEJMoa1601277.
- 247 Ocrevus [package insert]. South San Francisco, CA; Genentech; March 2021.
- 248 Hauser SL, Bar-Or A, Comi G, et al for the OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017; 376 (3): 221-234. DOI: 10.1056/NEJMoa1601277.
- 249 Ocrevus [package insert]. South San Francisco, CA; Genentech; December 2020.
- 250 Hauser SL, Bar-Or A, Comi G, et al for the OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017; 376 (3): 221-234. DOI: 10.1056/NEJMoa1601277.
- 251 Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J Neurol*. 2019 May;266(5):1182-1193. DOI: 10.1007/s00415-019-09248-6.
- 252 Vollmer TL, Cohen JA, Alvarez E, et al. Safety results of administering ocrelizumab per a shorter infusion protocol in patients with primary progressive and relapsing multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102454. DOI: 10.1016/j.msard.2020.102454.
- 253 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
- 254 Hauser S, Bar-Or A, Cohen J, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med*. 2020; 383(6):546-557. DOI: 10.1056/NEJMoa1917246.
- 255 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
- 256 Comi G, Kappos L, Selmaj K, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomized, minimum 12-month, phase 3 trial. *Lancet Neurol*. 2019; 18(11):1009-1020. DOI: 10.1016/S1474-4422(19)30239-X.
- 257 Zeposia [package insert]. Summit, NJ; Celgene; December 2021.
- 258 Cohen J, Comi G, Selmaj K, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomized, 24-month, phase 3 trial. *Lancet Neurol*. 2019; 18(11):1021-1033. DOI: 10.1016/S1474-4422(19)30238-8.
- 259 Ponvory [package insert]. Titusville, NJ; Janssen; April 2021.
- 260 Kappos L, Fox R, Burcklen, et al. Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis in the active-comparator phase 3 OPTIMUM study: a randomized clinical trial. *JAMA Neurol*. 2021 Mar 29. DOI: 10.1001/jamaneurol.2021.0405. [published online ahead of print]
- 261 Mayzent [package insert]. East Hanover, NJ; Novartis; September 2021.
- 262 Kappos L, Bar-Or A, Cree BAC, et al for the EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10127):1263-1273. DOI: 10.1016/S0140-6736(18)30475-6.
- 263 Aubagio [package insert]. Cambridge, MA; Genzyme; April 2021.
- 264 O'Connor P, Wolinsky J, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;365:1293-303.
- 265 Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with a relapsing multiple sclerosis (TOWER): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13(3):247-56. DOI: 10.1016/S1474-4422(13)70308-9.
- 266 Miller A, Wolinsky J, Kappos L, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13(10):977-86. DOI: 10.1016/S1474-4422(14)70191-7.
- 267 O'Connor P, Comi G, Freeman MS, et al. Long-term safety and efficacy of teriflunomide: nine-year follow-up of the randomized TEMSO study. *Neurology*. 2016; 86(10): 920-930. DOI: 10.1212/WNL.0000000000002441.
- 268 Vermersch P, Czlonskowska A, Grimaldi L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial. *Mult Scler*: 2013 Nov 21.
- 269 Sorensen PS, Ross C, Clemmesen KM, et al. Clinical importance of neutralizing antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. *Lancet*. 2003; 362:1184-91.
- 270 Polman C, Kappos L, White R, et al. Neutralizing antibodies during treatment of secondary progressive MS with interferon beta-1b. *Neurology*. 2003; 60:37-43.
- 271 Bellomi F, Scagnolari C, Tomassini V, et al. Fate of neutralizing and binding antibodies to IFN beta in MS patients treated with IFN beta for 6 years. *J Neurol Sci*. 2003; 215:3-8.
- 272 Sorensen PS, Koch-Henriksen N, Flachs EM, et al. Is the treatment effect of IFN-beta restored after the disappearance of neutralizing antibodies? *Mult Scler*. 2008; 14(6):837-42.
- 273 Bertolotto A, Malucchi S, Sala A. Differential effects of three interferon betas on neutralising antibodies in patients with multiple sclerosis: a follow up study in an independent laboratory. *J Neurol Neurosurg Psychiatry*. 2002; 73:148-153.

-
- 274 Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology*. 2002; 59:1496-1506.
- 275 Ocrevus [package insert]. South San Francisco, CA; Genentech; March 2021.
- 276 Montalban X, Hauser SL, Kappos L, et al for the ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017; 376(3): 209-220. DOI: 10.1056/NEJMoa1606468.
- 277 Ocrevus [package insert]. South San Francisco, CA; Genentech; March 2021.
- 278 Montalban X, Hauser SL, Kappos L, et al for the ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017; 376(3): 209-220. DOI: 10.1056/NEJMoa1606468.
- 279 La Mantia L, Di Peitranoni C, Rovaris M, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2016; 11: CD009333. DOI: 10.1002/14651858.CD009333.pub3.
- 280 Melendez-Torres GJ, Armoiry X, Court R, et al. Comparative effectiveness of beta-interferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages. *BMC Neurol*. 2018;18(1):162. DOI: 10.1186/s12883-018-1162-9.
- 281 Zhang J, Shi S, Zhang Y, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2017; 11:CD010968. DOI: 10.1002/14651858.CD010968.pub2.
- 282 Fogarty E, Schmitz S, Tubridy N, et al. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: systemic review and network meta-analysis. *Mult Scler Relat Disord*. 2016; 9:23-30. DOI: 10.1016/j.msard.2016.06.001.
- 283 Xu X, Chi S, Wang Q, et al. Efficacy and safety of monoclonal antibody therapies for relapsing remitting multiple sclerosis: A network meta-analysis. *Mult Scler Relat Disord*. 2018; 25:322-328. DOI: 10.1016/j.msard.2018.08.026.
- 284 Li H, Hu F, Zhang Y, et al. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. *J Neurol*. 2019 May 25. DOI: 10.1007/s00415-019-09395 [Epub ahead of print].
- 285 McCool R, Wilson K, Arber M, et al. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. *Mult Scler Relat Disord*. 2019;29:55-61. DOI: 10.1016/j.msard.2018.
- 286 Bartosik-Psujek H, Kaczyński L, Górecka M, et al. Cladribine tablets versus other disease-modifying oral drugs in achieving no evidence of disease activity (NEDA) in multiple sclerosis-A systematic review and network meta-analysis. *Mult Scler Relat Disord*. 2021;49:102769. DOI: 10.1016/j.msard.2021.102769.
- 287 Giovannoni G, Lang S, Wolff R, et al. A systematic review and mixed treatment comparison of pharmaceutical interventions for multiple sclerosis. *Neurol Ther*. 2020;9(2):359-374. DOI: 10.1007/s40120-020-00212-5.