CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209884Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209884
PDUFA Goal Date	March 26, 2019
OSE RCM #	2018-1288
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	March 26, 2019
Subject	Evaluation of Need for a REMS
Established Name	Siponimod
Trade Name	Mayzent
Name of Applicant	Novartis Pharmaceuticals Corp
Therapeutic Class	Sphingosine 1-phosphate receptor modulator
Formulation(s)	0.25 mg and 2 mg oral tablets
Dosing Regimen	Initial (5-day titration): 0.25 mg PO Qday on Days 1 and 2; 0.5 mg PO Qday on Day 3; 0.75 mg PO Qday on Day 4; 1.25 mg PO Qday on Day 5 Maintenance: 2 mg PO daily or 1 mg PO daily (patients with a CYP2C9 *1*3 or *2*3 genotype)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Mayzent (siponimod) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corp. submitted a New Drug Application (NDA 209884) for siponimod with the proposed indication: for the treatment of patients with secondary progressive multiple sclerosis (SPMS). If approved, siponimod labeling will be indicated for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

The serious risks associated with siponimod include infections, macular edema, bradyarrhythmias, respiratory effects, and liver injury. The applicant did not submit a proposed REMS or risk management plan with this application. If siponimod is approved, labeling should communicate the associated serious risks and their respective management. Currently, these risks are addressed in the Warnings and Precautions section of the proposed label. The likely prescribers of siponimod will be neurologists specializing in the treatment and management of multiple sclerosis. These prescribers are likely to be familiar with the management of adverse events associated with sphingosine 1-phosphate receptor modulators like siponimod and the currently approved fingolimod. DRISK and the Division of Neurology Products agree that a REMS is not necessary to ensure the benefits of siponimod outweigh its risk for the proposed indication of SPMS.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Mayzent (siponimod) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corp. submitted a New Drug Application (NDA 209884) for siponimod with the proposed indication: for the treatment of patients with secondary progressive multiple sclerosis (SPMS). This application is under review in the Division of Neurology Products. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION[1]

Mayzent (siponimod), a new molecular entity[a], is a sphingosine 1-phosphate (S1P) receptor modulator proposed for the treatment of patients with SPMS. Siponimod is proposed as 0.25 mg and 2 mg film-coated tablets for oral administration. The recommended dose includes initiation with a 5-day dose titration and a maintenance dose.

- Initial 5-day dose titration: 0.25 mg PO daily on Days 1 and 2; 0.5 mg PO daily on Day 3; 0.75 mg PO daily on Day 4; 1.25 mg PO daily on Day 5
- Maintenance: 2 mg PO daily or 1 mg PO daily (patients with a CYP2C9 *1*3 or *2*3 genotype)

Treatment is continued indefinitely or until unacceptable toxicity occurs.[b] Siponimod was granted Fast Track Designation for SPMS.[2] Siponimod is not currently approved in any jurisdiction. If approved, siponimod will be the second drug in the pharmacologic class of S1P receptor modulators. The S1P receptor modulator currently

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

available on the U.S. market is Gilenya (fingolimod); it is approved for relapsing forms of MS only. Fingolimod was initially approved with a communication plan REMS that was released on November 29, 2016 after meeting its goals. See table 1 in the appendix for additional details.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209884 relevant to this review:

- 09/24/2012: Fast Track Designation granted for SPMS
- 01/25/2018: Rolling review granted for siponimod NDA 209884
- 06/28/2018: NDA 209884 submission complete for siponimod for the treatment of adults with SPMS
- 11/08/2018: A Post Mid-cycle meeting was held between the FDA and the Applicant via teleconference. The FDA informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for siponimod.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by chronic inflammation, demyelination, plaque formation, and neuroaxonal damage.[3] MS is the most common cause of neurological disability in young adults.[4] MS affects over 400,000 people in the US and over 2.3 million people globally. The prevalence of progressive MS is not well characterized but is estimated to be 1.3 million.[5] Approximately 85% of patients present with relapsing-remitting multiple sclerosis (RRMS). The majority of these patients will gradually evolve into having secondary progressive multiple sclerosis (SPMS). SPMS is characterized by a progressive worsening of neurologic function and disability independent of acute relapses. Patients with SPMS may or may not have continued disease activity (relapses, new MRI brain lesions).[6] The hallmark of this period is the gradual accumulation of significant, irreversible neurologic disability. Symptoms include reduced ambulation, vision impairment, cognitive impairment, fatigue, and bladder and bowel dysfunction. Rates of wheelchair use for SPMS patients are between 44-58%.[7] The disease has a significant impact on quality of life and productivity.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options for SPMS are limited as most FDA-approved therapies for MS are indicated for the relapsing form of MS. The only FDA-approved treatment for SPMS is mitoxantrone.[8] Mitoxantrone is rarely used due to the significant safety risks of cardiotoxicity and leukemia. The role of disease-modifying treatments (DMTs) in progressive disease is not well defined due to a lack of evidence in delaying progression of disability and low numbers of SPMS patients in studies. The treatment approach is highly individualized. Guidelines recommend DMT therapy in the subgroup of SPMS patients with disease activity (i.e. continued relapses and/or new MRI activity).[9] Options for patients who transition to SPMS include continuation of the DMT used in the RRMS stage or switching to another agent. There is some evidence for the use of interferon-beta, however, the evidence is mostly in younger patients with active disease. Other options such as interferon-beta, pulse doses of intravenous glucocorticoids, or immunosuppressive agents such as cyclophosphamide or methotrexate have limited evidence and/or serious risks.[10] There is a need for safe and effective treatment options that slow disability progression in patients with SPMS. See table 1 in the appendix for additional details.

4 Benefit Assessment

The efficacy and safety of siponimod for the treatment of SPMS is supported by two studies with each study consisting of two parts.[11]

4.1 STUDY CBAF312A2304

Study CBAF312A2304, referred to as A2304 (NCT 01665144), consists of a core part (A2304CP) and an extension part (A2304EP). The core part, A2304CP, was a Phase 3, randomized, double-blind, multi-center, placebo-controlled time to event study that evaluated siponimod 2 mg by mouth daily, titrated over 6 days, compared to placebo in 1651 patients with SPMS (siponimod, n = 1105; placebo, n = 546). The extension part, A2304EP, is ongoing and allows patients to continue siponimod or begin therapy if originally randomized to placebo. The same dose and frequency were used in both studies. As of May 2017, 1220 patients have entered Study 2304EP (74% from A2304CP).

Hierarchical testing and analysis was utilized for the primary and secondary endpoints. The primary endpoint of Study A2304 was time to 3-month confirmed disability progression (CDP) measured by the expanded disability status scale (EDSS). The key secondary endpoints of interest included time to 3-month confirmed worsening of at least 20% in the timed 25-foot walk test (T25FW) and the reduction in the increase in T2 lesion volume from baseline. Additional secondary endpoints included time to 6-month CDP, and annualized relapse rate (ARR). For the primary endpoint of time to 3-month CDP, Study A2304CP results showed a 21.2% reduction in favor of siponimod (HR=0.79, p=0.013) versus placebo. Regarding the key secondary endpoints, there was no significant difference in the time to 3-month confirmed worsening of the T25FW test between the groups (HR=0.94, p=0.44) and treatment with siponimod resulted in less accumulation of T2 lesion volume at both Month 12 and Month 24 (both p<0.0001). The additional secondary endpoints results showed a 25.9% reduction in the risk of time to 6-month CDP (HR=0.74, p=0.0058) and the ARR was reduced by 55.5% compared to placebo (ARR ratio 0.445, p<0.001) in both patients with and without pre-study relapses.

As of May 2017, Study A2304EP results showed the siponimod-siponimod group was significantly superior to the placebo-siponimod group for the 3-month CDP endpoint (p=0.0148). The incidence of relapses remained low in the extension period. The ARR for both treatment groups were similar during the extension period. This study will continue and provide up to an additional 7 years of data.

The Clinical Reviewer concluded that Study CBAF312A2304 does not support a benefit of siponimod in a population with predominantly progressive disease, e.g., non-relapsing SPMS, because siponimod's effect on 3-month confirmed disability progression is driven by its effect on relapses and inflammatory activity in this study.[13]

4.2 STUDY CBAF312A2201

Study CBAF312A2201, referred to as A2201 (NCT 00879658), was a Phase 2, double-blind, randomized, multi-center, placebo-controlled dose-ranging study evaluating the efficacy and safety of siponimod compared to placebo in 297 patients with RRMS. The purpose of this study was to determine the optimal dose of siponimod based on its effect on inflammatory activity.

The entry criteria included patients with RRMS, defined as evidence of recent inflammatory activity (2 relapses in the past 2 years, 1 relapse in the past 1 year or a positive gadolinium (Gd)-enhanced MRI scan at screening)

and an EDSS score of 0 to 5 at screening. Patients in period one (N=188) were randomly assigned in a 1:1:1:1 ratio to one of three siponimod doses (10 mg, 2 mg, or 0.5 mg) or placebo for 6 months. Patients in period two (N=109) were randomly assigned (4:4:1) to siponimod 1.25 mg, 0.25 mg, or placebo for 3 months. Period two included a dose titration to the target doses to mitigate bradyarrhythmia effects seen when starting at the doses in period one. The primary endpoint was the percentage reduction in the number of MRI combined unique active lesions (CUALs) for each siponimod dose compared to placebo at 3 months.

The percent reduction of CUALs compared to placebo at month 3 was dose-dependent – of 74.3%, 69.7%, 86.1%, 61.5%, and 44.3% for the siponimod 10 mg, 2 mg, 1.25 mg, 0.5 mg, and 0.25 mg treatment groups, respectively. Secondary endpoints of annualized relapse rate and proportion of patients free of confirmed relapses were significant in the siponimod 2 mg group compared to placebo. The Applicant selected the optimal dose of siponimod, 2 mg, due to the MRI dose response curve and the significant reduction in ARR compared to placebo. There was no significant improvement in efficacy at the 10 mg dose and adverse events were more frequent compared to the 2 mg dose.

The extension part of Study A2201 (A2201E1) allowed patients enrolled in the core study to continue treatment with siponimod or begin treatment if they had originally received placebo. The first phase was a double-blind phase (N=184) for 24 months. Patients in the placebo group were randomized to one of the five siponimod doses. The mean number of Gd-enhancing lesions remained low at month 24 in all dose groups. The annualized relapse rates were higher in the siponimod 0.5 mg and 0.25 mg groups compared to the higher doses demonstrating a dose-dependent effect. The proportion of patients free of Gd-enhanced lesions was 67%. After month 24, the study converted to an open-label phase (N=159) where all patients switched to the 2 mg daily dose. The median duration of exposure in this phase was around 41 months. MRI Lesion activity and annual relapse rates remained low in this phase. Mean EDSS scores remained stable during the extension and at month 60 most patients were free of CDP. This extension provided about 5 years of data, although the results were limited by the small size and lack of a placebo comparator group.

The Clinical Reviewer concluded siponimod's effect on relapses and MRI metrics suggest that it may offer a benefit to people with relapsing MS, although the data are not convincing because only 13.1% of subjects in CBAF312A2304 experienced a relapse; CBAF312A2201 was not powered to show an effect on relapses, and ARR was a secondary endpoint in both trials.[13]

Overall, the Clinical Reviewer did not find that this application contains substantial evidence of effectiveness to support siponimod's approval for SPMS. Siponimod's treatment effect appears to be much greater for reducing worsening disability (from relapses and new MRI lesions) than for reducing disability progression (independent of inflammatory activity).[13] However, factoring in the efficacy of other immunomodulatory and immunosuppressive agents (including the approved S1P receptor modulator, fingolimod), the Clinical Reviewer finds that there is likely substantial evidence of effectiveness to support the approval of siponimod with an indication of relapsing MS.[15] If approved, siponimod labeling will include the following revised indication: for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[16]

5 Risk Assessment & Safe-Use Conditions[c]

The safety profile of siponimod was derived from Studies A2304 and A2201 including the core and extension parts. There were 1737 patients in the safety set which included all patients who were enrolled and took at least one dose of siponimod. The comparator group for the safety set included 607 patients receiving placebo. The most common treatment-emergent adverse events (TEAEs) were infections/infestations and nervous system disorders.[17] The serious adverse events (referred to as risks) determined to be associated with siponimod include infections, macular edema, bradyarrhythmias, respiratory effects, and liver injury.[d] These risks are addressed in the proposed siponimod label under Warnings and Precautions and are discussed below.

5.1 INFECTIONS

Overall, 1004/1737 (57.8%) experienced an adverse event of infection or infestation in the siponimod group compared to 301/607 (49.6%) in the placebo group. The most common events were due to upper respiratory infections (nasopharyngitis, etc.), urinary tract infections, influenza, and herpetic infections.[18] The proposed label advises to obtain a complete blood count before initiating treatment and to not start siponimod in patients with active infections.[1]

5.2 BRADYARRHYTHMIA

5.2.1 Reduction in Heart Rate

Sinus bradycardia events occurred in 92/1737 (5.3%) of patients in the siponimod group compared to 10/607 (1.7%) in the placebo group. Events of bradycardia occurred in 81/1737 (4.7%) of patients in the siponimod group compared to 16/607 (2.6%) in the placebo group. The proposed label advises siponimod may result in a transient decrease in heart rate (b) (4) .[1] Because of the reduction in heart rate, the proposed label recommends first-dose monitoring for patients with sinus bradycardia (HR less than 55 bpm), first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure. It's also recommended to obtain an ECG in these patients at the end of the Day 1 observation period (b) (4) .[16]

5.2.2 Atrioventricular Conduction

First-degree atrioventricular (AV) block occurred in 31/1737 (1.8%) of patients on siponimod compared to 5/607 (0.8%) in the placebo group. Second-degree AV block occurred in 10/1737 (0.6%) patients receiving siponimod compared to 4/607 (0.7%) in the placebo group. The proposed label advises siponimod has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. (b) (4) titration of siponimod is recommended to help reduce these cardiac effects.[1]

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[d] *Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

5.3 RESPIRATORY EFFECTS

In Study A2304, patients treated with siponimod (n = 1099) experienced a decline in baseline of forced expiratory volume over 1 second (FEV1) by 88 mL (95% CI: 139, 37) at two years compared to placebo (n = 546).[1] The mean difference between siponimod-treated patients and patients receiving placebo in percent predicted FEV_1 at 2 years was 2.8% (95% CI: -4.5, -1.0).[19] The proposed label advises spirometric evaluation of respiratory function should be performed during therapy if clinically indicated.

5.4 LIVER INJURY

Overall, adverse events of increased hepatic tests (any) occurred in 255/1737 (14.7%) of patients in the siponimod group compared to 24/607 (4%) in the placebo group. Any hepatic tests refers to: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and bilirubin. In the siponimod group, 104 (6%) had increases in ALT, 24 (1.4%) increases in AST, 95 (5.5%) increases in GGT, and 17 (1%) increases in bilirubin. None of these adverse events were determined to be Hy's Law events. The proposed label advises to obtain liver enzyme results before initiation, closely monitor patients with severe hepatic impairment, and to discontinue if significant liver injury occurs.[1]

5.5 DEATHS

As of the 120-day safety report (December 31, 2017), including late breaking deaths, there were 20 deaths in the completed studies (siponimod = 16; placebo = 4).[20] Of the 16 patients who were exposed to siponimod, the Applicant attributed the deaths to lung adenocarcinoma, pneumonia, pulmonary embolism (n = 2), myocardial infarction, cardiac arrest, suicide, urosepsis, malignant melanoma, craniocerebral injury, amyotrophic lateral sclerosis, respiratory paralysis, cardiorespiratory arrest, septic shock, and two deaths of unknown causes.

6 Expected Postmarket Use

Siponimod will likely be primarily prescribed in the outpatient setting. The likely prescribers include neurologists who specialize in the treatment of multiple sclerosis. These prescribers are likely to be familiar with the management of adverse events associated with S1P receptor modulators like siponimod and fingolimod. Fingolimod has similar risks as siponimod and was approved with a Communication Plan (CP) REMS which included informing healthcare professionals about risks including bradyarrhythmia and atrioventricular block at treatment initiation, infections, respiratory effects, and liver injury, similar to those found with this drug. In 2016, the Agency determined that the communication plan was complete and the goal of educating prescribers had been satisfied, and therefore eliminated the REMS.[21] These similar risks are currently addressed in Warnings and Precautions of the proposed siponimod label.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for siponimod.

8 Discussion of Need for a REMS

While the Clinical Reviewer did not find that this application contains substantial evidence of effectiveness to support siponimod's approval for SPMS, the overall risk/benefit assessment for siponimod appears favorable when used in patients with relapsing forms of MS.[15] After factoring in the efficacy of other immunomodulatory and immunosuppressive agents (including the approved S1P receptor modulator, fingolimod), the Clinical Reviewer finds that there is likely substantial evidence of effectiveness to support the approval of siponimod with an indication of relapsing MS.[15]

MS is a serious disease and is the most common cause of neurological disability in young adults. Progressive forms of MS, like SPMS, are estimated to affect 1.3 million people worldwide. There is no standard treatment for SPMS. The one FDA-approved treatment for SPMS, mitoxantrone, is associated with serious toxicities. Therefore, treatment is highly individualized with prescribers relying heavily on off-label use for DMTs that may have been effective during the relapsing state of the disease. There is an unmet clinical need for treatment options for patients with SPMS.

The serious risks associated with siponimod include infections, macular edema, bradyarrhythmias, respiratory effects, and liver injury. The healthcare providers prescribing siponimod should be familiar with managing these risks as they are well known to be associated with S1P receptor modulators. Labeling will be used to communicate and manage these risks. DRISK recommends that, should siponimod be approved, a REMS is not necessary to ensure its benefits outweigh its risks for the treatment of SPMS in adults.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. In general, healthcare providers who treat MS are familiar with the risks of S1P receptor modulators and the importance of patient monitoring.

Should the Division of Neurology Products have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

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10.2 TABLE 1: TREATMENT OPTIONS FOR MULTIPLE SCLEROSIS[8]

Drug (Approval Date)	Indication	Dosing and Administration	Important Safety and Tolerability Issues	Risk Management Approaches
Interferons				
Avonex (1996) (interferon-beta-1a)	Relapsing forms of multiple sclerosis (RMS) to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability	30 mcg intramuscularly weekly	Depression, suicide, hepatic injury, anaphylaxis and other allergic reactions, decreased peripheral blood counts, seizures, congestive heart failure (Avonex, Plegridy), thrombotic microangiopathy (Rebif, Plegridy), new autoimmune disorders - hyper/hypothyroidism, autoimmune hepatitis (Avonex, Plegridy)	Labeling – Warnings and Precautions
Rebif (2002) (interferon-beta-1a)		22 or 44 mcg subcutaneously 3 times per week		
Plegridy (2014) (pegylated interferon-beta-1a)	RMS	125 mcg subcutaneously every 14 days		

Betaseron (1993) Extavia (2009) (interferon-beta-1b)	RMS to reduce the frequency of clinical exacerbations	0.25 mg subcutaneously every other day	Hepatic injury, anaphylaxis and other allergic reactions, depression and suicide, congestive heart failure, injection site skin necrosis and reactions, leukopenia, thrombotic microangiopathy, flu-like symptoms, drug-induced lupus erythematosus	Labeling – Warnings and Precautions
Copaxone (1996) Glatopa (2015) (glatiramer acetate)	RMS	20 mg subcutaneously once daily or 40 mg 3 times per week at least 48 hours apart	Immediate post-injection reaction, chest pain, lipoatrophy and skin necrosis at injection site, modify immune response	Labeling – Warnings and Precautions
Tysabri (2004) (natalizumab)	RMS	300 mg IV infusion every 4 weeks	Progressive multifocal leukoencephalopathy	REMS with medication guide, elements to assure safe use; Labeling – Boxed Warning
			Herpes infections, hepatotoxicity, hypersensitivity reactions (e.g. anaphylaxis), antibody formation, immunosuppression, infections	Labeling – Warnings and Precautions
Gilenya (2010) (fingolimod)	RMS in patients 10 years of age and older	Adults and pediatric patients (10 years and above) and weighing more than 40 kg: 0.5 mg orally daily Pediatric patients (10 years of age and above) weighing less than or equal to 40 kg: 0.25 mg orally daily	Infections, progressive multifocal leukoencephalopathy, macular edema, posterior reversible encephalopathy syndrome, respiratory effects, liver injury, fetal risk, severe increase in disability after stopping fingolimod, increased blood pressure, cutaneous malignancies	REMS with communication plan (*released 2016*) Labeling – Warnings and Precautions
			First-dose monitoring required (risk of bradyarrhythmia, atrioventricular blocks)	Labeling – Dosage and Administration
Aubagio (2012) (teriflunomide)	RMS	7 mg or 14 mg orally once daily	Hepatotoxicity, Teratogenicity	Labeling – Boxed Warning
			Accelerated elimination if co-administered with cholestyramine or activated charcoal for 11 days, may decrease WBC, monitor for infections, peripheral neuropathy, acute renal failure, hyperkalemia, severe skin reactions including Stevens-Johnson syndrome, increased blood pressure	Labeling – Warnings and Precautions
Tecfidera (2013) (dimethyl fumarate)	RMS	120 mg orally twice daily for 7 days, then 240 mg orally daily	Anaphylaxis and angioedema, progressive multifocal leukoencephalopathy, lymphopenia, liver injury	Labeling – Warnings and Precautions
Lemtrada (2014) (alemtuzumab)	RMS, reserve for patients with inadequate response to two or more MS drugs	Initial treatment of two courses administered by intravenous infusion over 4 hours: First course: 12 mg/day for 5 days Second course (12	Autoimmune conditions, serious infusion reactions, administration must occur in appropriate setting to manage anaphylaxis, serious infusion reactions, stroke, increased risk of malignancies (e.g. thyroid cancer, melanoma, lymphoproliferative disorders)	REMS with communication plan and elements for safe use; Labeling – Boxed Warning

		months later): 12 mg/day for 3 days Subsequent treatments (12-month intervals): 12 mg/day for 3 days	Immune thrombocytopenia, glomerular nephropathies, thyroid disorders, other autoimmune cytopenias, infections	Labeling - Boxed Warnings
Ocrevus (2017) (ocrelizumab)	RMS or primary progressive MS	Start dose: 300 mg intravenous infusion, followed two weeks later by a 300 mg intravenous infusion Subsequent doses: 600 mg every 6 months	Infusion reactions, infections, increased risk of malignancy	Labeling – Warnings and Precautions
			Screening for viral hepatitis required prior to initiation, premedication with corticosteroid and antihistamine recommended	Labeling – Dosage and Administration
Mitoxantrone (1987)	Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing or worsening relapsing-remitting MS	12 mg/m^2 intravenous infusion every 3 months	Cardiotoxicity, secondary acute myeloid leukemia	Labeling - Boxed Warning
			Administration/extravasation, myelosuppression	Labeling - Warnings and Precautions

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