CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	209899
PDUFA Goal Date	March 25, 2020
OSE RCM #	2018-94
Reviewer Name	Yasmeen Abou-Sayed, PharmD
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD, MPH
Review Completion Date	March 24, 2020
Subject	Evaluation of Need for a REMS
Established Name	Ozanimod
Trade Name	Zeposia
Name of Applicant	Celgene International II Sarl (Celgene)
Therapeutic Class	Sphingosine 1-phosphate (S1P) receptor modulator
Formulation	Oral capsule, 0.23 mg, 0.46 mg, 0.92 mg
Dosing Regimen	0.92 mg orally once daily, following an initial 7-day dose escalation schedule (consisting of 0.23 mg for the first 4 days, followed by 0.46 mg for the next 3 days)

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EXECUTIVE SUMMARY

This review) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zeposia (ozanimod) is necessary to ensure the benefits outweigh its risks. Celgene submitted a New Drug Application (NDA) 209899 for Zeposia with the proposed indication for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The risks associated with ozanimod include: lymphopenia and infections, bradyarrhythmias, and hepatic transaminase elevations. The Applicant did not submit a proposed REMS or risk management plan with this application.

If ozanimod 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 ozanimod should be familiar with the management of adverse events associated with sphingosine 1-phosphate receptor modulators like currently approved siponimod and fingolimod. Therefore, a REMS is not needed to ensure the benefits of ozanimod outweigh its risks at this time.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zeposia (ozanimod) is necessary to ensure the benefits outweigh its risks. Celgene submitted a New Drug Application (NDA) 209899 for ozanimod with the proposed indication for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. This application is under review in the Division of Neurology 2. The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Ozanimod, a new molecular entity (NME) [a], is a sphingosine-1-phosphate (S1P) receptor modulator that is selective for S1P1 and S1P5. The Applicant's proposed indication for ozanimod is for the treatment of relapsing multiple sclerosis (RMS), to include clinically isolated syndrome (CIS), relapsing-remitting disease (RRMS), and active secondary progressive disease (SPMS), in adults. Ozanimod is formulated as an oral capsule (0.23, 0.46, and 0.92 mg strengths, expressed as Ozanimod HCl 0.25, 0.5, and 1 mg), to be titrated over a 7-day dose schedule (0.23 mg for the first 4 days, followed by 0.46 mg for the next 3 days) to a once daily dose of 0.92 mg, for maintenance.[b] Ozanimod is not currently approved in any jurisdiction.

There are currently two other S1P receptor modulators approved for the treatment of relapsing forms of

[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.*

multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. These are Gilenya (fingolimod), a relatively non-selective S1P receptor modulator, and Mayzent (siponimod), which is purportedly also selective for S1P1 and S1P5. Fingolimod was initially approved with a communication plan REMS that was released on November 29, 2016 after meeting its goals.[1]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209899 relevant to this review:

- 04/22/2019: NDA 209899 submission for the treatment of relapsing multiple sclerosis received
- 9/17/2019: A Mid-cycle communication was sent to the Applicant in which the Agency informed the Applicant that a REMS would likely not be necessary, and a final determination on the need for a REMS would be made at the completion of the review cycle[2]
- 1/14/2020: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for ozanimod[3]

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION[4]

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by chronic inflammation, demyelination, plaque formation, and neuroaxonal damage.[5] MS is the most common cause of neurological disability in young adults.[6] MS affects over 400,000 people in the US and over 2.3 million people globally.[c] The prevalence of progressive MS is not well characterized but is estimated to be 1.3 million.[7] 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).[8] 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%.[9] The disease has a significant impact on quality of life and productivity.[d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are over a dozen MS drugs that are FDA-approved to treat relapsing MS (RMS), including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active secondary progressive multiple sclerosis (SPMS). Table 1 in the Appendix provides a list of currently approved MS medications.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Currently available therapies reduce the relapse rate by 30 to 50%, but unfortunately achieve inconsistent results on disability progression.[10] Because they were the earliest approved therapies and because there have been few major safety concerns, either a β -interferon or glatiramer acetate are often the initial choice for treatment for new onset typical RMS. If the response is not adequate to one of these two treatments, then one of several approved alternative therapies can be used. Other approved therapies for MS target cells in the immune system, and work with efficacy at least comparable, and often superior, to the interferons and glatiramer acetate. Each therapy has a different benefit risk profile, and the choice of which agent to use is a matter of clinical judgement in balancing efficacy and safety for the individual patient.

4 Benefit Assessment

The efficacy and safety of ozanimod for the treatment of relapsing forms of multiple sclerosis (MS), is supported by two Phase 3 studies, RPC01-201B (201B, National Controlled Trial [NCT] 02047734) and RPC01-301 (301, NCT02294058). Both studies were global, randomized, double-blind, double-dummy, active-controlled, parallel studies, comparing 0.5 mg and 1 mg daily doses of ozanimod with a 30 mg weekly intramuscular injection of Avonex (interferon [IFN] β-1a). Because atrioventricular block is a known potential adverse event with S1P receptor modulators like ozanimod, patients followed a 7-day titration to the target dose; subjects randomized to treatment with ozanimod received 0.25 mg orally daily for days 1 to 4 and then 0.5 mg on days 5 to 7. Subjects received the target dose of ozanimod (0.5 mg or 1 mg) on day 8 and thereafter. Study 201B (n=1320) had a treatment period of 2 years, while study 301's (n=1346) duration varied by patient and the study ended when the last patient completed 12 months of treatment.

The two studies evaluated the same set of primary and key secondary endpoints. The primary efficacy endpoint of the two studies was the annualized relapse rate (ARR) of the protocol defined relapse (PDR)[e]. Secondary endpoints included a demonstration of a superior reduction in various MRI measures of MS disease activity and a reduction in the occurrence of progression of disability.

In both studies, treatment with ozanimod 1 mg and 0.5 mg resulted in statistically significant reductions in ARR compared with IFN β-1a (primary endpoint). A dose-dependent effect was observed, with improved efficacy seen with the 1 mg dose versus the 0.5 mg dose of ozanimod in both studies. In Study 301, the reduction in ARR at the end of the treatment period was approximately 48% with ozanimod 1 mg ($p<0.0001$) and 31% with ozanimod 0.5 mg ($p=0.0013$) compared to IFN β-1a. The reduction in ARR

[e] A relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening, based on examination by the blinded evaluator, consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on two or more of the appropriate FS scores. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications).

at Month 24 in Study 201B, as compared to IFN β-1a, was approximately 38% with ozanimod 1 mg ($p<0.0001$) and 21% with ozanimod 0.5 mg ($p=0.0167$).

In study 201, all secondary endpoints at the end of the 24 month study period were positive, with statistically significant results on both measures for both doses of ozanimod ($p < 0.001$ for 1 mg dose of ozanimod for both secondary endpoints, and $p = 0.002$ for 0.5 mg dose for reduction in MRI lesions, and $p = 0.003$ for progression of disability).

The clinical reviewer concluded that the Applicant provided substantial evidence of efficacy based on the primary endpoint of a reduction in the ARR.[f,11]

5 Risk Assessment & Safe-Use Conditions

The safety profile of ozanimod for the treatment of adults with RMS contains data from 2917 subjects enrolled in the two Phase 3 active-controlled (Studies 201B and 301) and one Phase 2 study (RPC01-201A [201A]). Study 201A was a randomized, double-blind, placebo controlled, 24-week study that enrolled 258 subjects and compared two doses of ozanimod (0.5 mg and 1 mg) with interferon β-1a. The majority of patients in the safety database were exposed to at least 6 months of ozanimod treatment (96.9%), 64.9% were exposed for at least 24 months, and some patients have over 5 years of exposure to ozanimod. Of note, patients with "clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease," including specific cardiac conditions, poorly controlled diabetes mellitus type 2, and a history of uveitis, were excluded from participating in the clinical trials of ozanimod in subjects with RMS[12].

Eight deaths (0.3%) occurred in ozanimod-treated adults with MS, including two from cancer (pancreatic with liver metastases and disseminated cancer with unknown primary), two from accidents (train and motorcycle), and single cases of drowning, pulmonary embolism after orthopedic surgery, bilateral pneumonia, and chronic kidney failure (in a woman with posterior reversible encephalopathy syndrome and flaccid paralysis). None of the deaths were attributed to ozanimod by the clinical reviewer.[13]

The most common adverse events (AEs) in subjects receiving ozanimod in the safety database were upper respiratory infection (26.2%), hepatic transaminase elevations (10.2%), headache (8.8%), influenza-like illness (5.0%), orthostatic hypotension (4.3%), urinary tract infection (4.1%), back pain (4.0%), and hypertension (3.4%). The following serious adverse events[g] (SAEs) were identified by the

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[g] 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.

clinical reviewer to be adverse events of special interest (AESIs) in ozanimod: lymphopenia and infections, bradyarrhythmia, and hepatic transaminase elevations.

5.1 LYMPHOPENIA AND INFECTIONS

Lymphopenia is an AESI due to the mechanism of S1P receptor modulators. The drug binds to S1P1 receptors in lymph nodes and prevents certain lymphoid immune cells from being excreted into the blood and reaching the central nervous system (CNS), leading to lymphopenia. Based on a reference range for lymphocytes of 0.9 – 3.6 x 109/L, 600 ozanimod patients (30.9%) had a lymphocyte count of $< 0.5 \times 10^9$/L and 25 ozanimod patients (1.3%) had a count $< 0.2 \times 10^9$/L. Lymphopenia can increase the risk of infections, and was a safety finding in the ozanimod safety database.[h]

Overall, In the safety pool, there were 656 (33.7%) reports of infections/infestations in ozanimod patients. The most common events were due to upper respiratory tract infections (nasopharyngitis, rhinitis, sinusitis, etc.), urinary tract infections, influenza, and herpetic infections.

The clinical reviewer agrees with the Applicant's proposed labeling that a CBC with lymphocyte count should be checked before initiating ozanimod.[14] Additionally, it is recommended that periodic assessments of complete blood cell (CBC) with lymphocyte counts be performed during treatment with ozanimod.

5.2 BRADYARRHYTHMIA (BRADYCARDIA AND ATRIOVENTRICULAR [AV] BLOCK)

S1P receptors are expressed on atrial myocytes cells of the cardiac conduction system, with fingolimod and siponimod demonstrating transient effects on heart rate and atrioventricular conduction at initiation of therapy. Both approved S1P modulators have labeled warnings for bradycardia and AV block. In the controlled RMS studies, ozanimod was initiated with an 8-day dose escalation, which appeared to reduce the rate of bradycardia and cardiac AEs when starting the drug. Subjects with a myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months, New York Heart Association Class III / IV heart failure, cardiac conduction or rhythm disorders, risk factors for QT prolongation, severe untreated sleep apnea, or a resting heart rate less than 55 bpm at baseline, were excluded from participation in the controlled RMS studies. With these exclusions and the dose escalation, there were no reported cases with a heart rate less than 40 bpm or Type 2 (or higher) AV block in the controlled RMS studies. There appears to be a slightly increased risk of 1st degree atrioventricular block and bradycardia six hours after the first dose of ozanimod 1mg compared to subsequent ECGs. Twenty-two (2.3%) patients on 1 mg had AV block at baseline, compared to 25 patients (2.6%) 6 hours after the first dose.

[h] 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.*

The Division of Cardiovascular and Renal Products (DCRP) was consulted during the review of this NDA, and their conclusions included that ozanimod results in mild dose dependent bradycardia.[15] They did not identify any events of bradycardia or AV block that were of concern. They also determined that titration helped reduce the cardiac effects of ozanimod.

The clinical reviewer recommends that all patients should have an ECG prior to initiation of ozanimod to determine whether a patient has an arrhythmia or to confirm an ongoing cardiac issue, and ozanimod should only be initiated with the labeled dose escalation. The risk of bradyarrhythmia and AV block and the exclusionary cardiac conditions from the clinical development program should be included in the Warnings and Precautions and Contraindications sections of the labeling of ozanimod, similar to the approved labeling of the other approved S1P receptor modulators .

5.3 Hepatic Transaminase Elevations

S1P receptor modulators are known to cause transaminase elevations; elevated transaminases and hepatic injury are in the warnings and precautions sections of labeling for siponimod and fingolimod, thus they are of interest in ozanimod. Ozanimod can cause elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT), but these elevations appeared reversible with discontinuation of the drug in the controlled RMS studies. Table 1 details laboratory values collected during the controlled RMS studies.

Table 1 - Hepatobiliary Labs, controlled RMS population

	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Alanine Aminotransferase (ALT); reference range: 6 – 41 U/L[1]					
Mean (std) (IU/L)	22.5 (28.0)	17.7 (8.8)	25.8 (29.7)	29.2 (31.5)	27.5 (30.7)
Median (IU/L)	16	16	19	21	20
Min, max (IU,L)	4, 828	4, 74	3, 1214	4, 1436	3, 1436
# subjects > 5x ULN	10 (1.1%)	0	8 (0.8%)	12 (1.2%)	20 (1.0%)
# subjects > 10x ULN	2 (0.2%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Aspartate Aminotransferase (AST); reference range: 9 – 43 U/L[1]					
Mean (std) (IU/L)	19.9 (18.4)	19.2 (5.5)	20.0 (16.1)	21.7 (16.3)	20.9 (16.3)
Median (IU/L)	17	19	17	19	18

	IFN β-1a 30 mcg n=885	Placebo n=88	Ozanimod 0.5 mg n=979	Ozanimod 1 mg n=965	Overall Ozanimod n=1944
Min, max (IU,L)	6, 579	8, 40	6, 778	6, 588	6, 778
# subjects > 5x ULN	7 (0.8%)	0	3 (0.3%)	5 (0.5%)	8 (0.4%)
# subjects > 10x ULN	2 (0.2%)	0	1 (0.1%)	3 (0.3%)	4 (0.2%)
Gamma Glutamyltransferase (GGT); reference range: 5– 52 U/L[1]					
Mean (std) (IU/L)	23.0 (27.0)	18.5 (13.3)	31.1 (38.5)	38.8 (44.4)	35.0 (41.7)
Median (IU/L)	16	13	19	24	21
Min, max (IU,L)	3, 1010	5, 78	4, 588	4, 627	4, 627
# subjects > 5x ULN	4 (0.5%)	0	15 (1.5%)	13 (1.3%)	28 (1.4%)
# subjects > 10x ULN	1 (0.1%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Total Bilirubin (TB); reference range: 1.7 – 18.8 umol/L					
Mean (std) (umol/L)	8.4 (4.4)	8.3 (4.6)	9.6 (5.5)	9.8 (6.2)	9.7 (5.9)
Median (umol/L)	7.5	7.2	8.4	8.4	8.4
Min, max (umol/L)	1.7, 42.4	1.9, 45	1.7, 52.5	2.6, 85.2	1.7, 85.2
# subjects > 2x ULN	1 (0.1%)	1 (1.1%)	14 (1.4%)	15 (1.6%)	29 (1.5%)
# subjects > 3x ULN	0	0	0	3 (0.3%)	3 (0.2%)
Alkaline Phosphatase (ALP); reference range: 30-116 U/L[1]					
Mean (std) (IU/L)	58.1 (17.1)	65.2 (19.7)	57.5 (20.3)	59.9 (23.6)	58.7 (22.1)
Median (IU/L)	55	61	55	55	55
Min, max (IU,L)	11, 165	29, 143	19, 336	5, 295	5, 336
# subjects > 2x ULN	0	0	4 (0.4%)	2 (0.2%)	6 (0.3%)

Most of the transaminase elevations in the ozanimod development program were asymptomatic, and there were no reported cases of fulminant hepatic failure in these studies.

The clinical reviewer therefore recommends that transaminases and total bilirubin should be checked before starting, and periodically during treatment with ozanimod. The labeling for ozanimod should include a statement regarding the risk and symptoms of transaminase elevation and liver injury in the Warnings and Precautions section of the labeling of ozanimod.

6 Expected Postmarket Use

Ozanimod will likely be primarily prescribed in the outpatient setting. The likely prescribers of ozanimod should be familiar with the management of adverse events associated with S1P receptor modulators like ozanimod, siponimod, and fingolimod, which have similar risks. Fingolimod 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.[16] Therefore, likely prescribers of this drug should be familiar with the risks associated with the class.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for ozanimod beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ozanimod on the basis of the efficacy and safety information currently available.[17]

MS is a serious disease and is the most common cause of neurological disability in young adults. Relapsing and progressive forms of MS are estimated to affect 2.3 million people worldwide. Several drugs are currently approved for the various forms of MS, however there remains an unmet clinical need for patients who may fail available therapies or experience serious toxicities with others.

The serious risks associated with ozanimod include lymphopenia and infections, bradyarrhythmias, and hepatic transaminase elevations. A currently approved S1P modulator, fingolimod, 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 goal of educating prescribers had been satisfied, and therefore eliminated the REMS.[18]

The healthcare providers prescribing ozanimod 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 the risks associated with ozanimod via the Warnings and Precautions and Contraindications,

similar to what is in the currently approved labels for drugs in the same class. Labeling will also communicate the appropriate titration schedule for ozanimod, to mitigate the risk of bradyarrhythmias. This reviewer recommends that, should ozanimod be approved, a REMS is not necessary to ensure its benefits outweigh its risks for the treatment of RMS 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 DN2 have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 TABLES

Product Trade Name (Generic) Year of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Betaseron (Beta interferon 1b) 1993	Relapsing forms of MS	subcutaneous every other day	Hepatotoxicity, depression	Labeling – Warnings and Precautions
Avonex (Beta interferon 1a) 1996	Relapsing forms of MS	IM weekly	Hepatotoxicity, depression	Labeling – Warnings and Precautions
Copazone (Glatiramer acetate) 1996	Relapsing forms of MS	subcutaneous daily	None	Labeling – Warnings and Precautions
Novantrone (Mitoxantrone) 2000	Relapsing forms of MS	IV every 3 months	Cardiotoxicity, leukemia	Labeling – Boxed Warning

Rebif (Beta interferon 1a) 2002	Relapsing forms of MS	subcutaneous 3 times weekly	Hepatotoxicity, depression	Labeling – Warnings and Precautions
Tysabri (Natalizumab) 2004	Relapsing forms of MS	IV every 4 weeks	Progressive Multifocal Leukoencephalopathy,	REMS with medication guide, elements to assure safe use; Labeling – Boxed Warning
Extavia (Beta interferon 1b) 2009	Relapsing forms of MS	subcutaneous every other day	Hepatotoxicity, depression	Labeling – Warnings and Precautions
Gilenya (Fingolimod) 2010	Relapsing forms of MS	orally once daily	1st dose bradycardia, macular edema, fetal risk	REMS with communication plan (released 2016) Labeling – Warnings and Precautions
Aubagio (Teriflunomide) 2012	Relapsing forms of MS	orally once daily	black box warnings for hepatotoxicity and teratogenicity	Labeling – Boxed Warning
Tecfidera (Dimethyl fumarate) 2013	Relapsing forms of MS	orally twice daily	Lymphopenia, PML	Labeling – Warnings and Precautions
Plegridy (PEGylated Interferon Beta) 2014	Relapsing forms of MS	subcutaneous every 2 weeks	None	Labeling – Warnings and Precautions
Lemtrada (Alemtuzumab) 2015	Relapsing forms of MS after inadequate response to ≥ 2 MS treatments	2 intravenous courses 12 months apart	black box warnings for serious/fatal autoimmune conditions; serious and life-threatening infusion reactions, stroke, and increased risk of	REMS with communication plan and elements for safe use; Labeling – Boxed Warning

			malignancies	
Ocrevus (Ocrelizumab) 2016	Relapsing forms of MS and Primary Progressive MS (PPMS)	IV every 2 weeks x 2 then IV x1 every 6 months	infusion reactions, increased risk of breast cancer	Labeling – Warnings and Precautions
Mayzent (Siponimod) 2019	Relapsing forms of MS	Oral once daily	1st dose bradycardia, macular edema, fetal risk	Labeling – Warnings and Precautions
Mavenclad (Cladribine) 2019	Relapsing forms of MS	2 oral courses one year apart	Malignancy, teratogenicity, infections, lymphopenia, liver injury	Labeling – Boxed Warning
Vumerity (Diroximel fumarate) 2019	Relapsing forms of MS	orally twice daily	Lymphopenia, PML	Labeling – Warnings and Precautions

10.2 REFERENCES

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[18] Pratt RG. Food and Drug Administration. Division of Risk Management. NDA 022527. Gilenya (fingolimod) - REMS Review. November 9, 2016.

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