Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluations: Multiple Sclerosis

Date of Review: June 2021

Date of Last Review: August 2020
Dates of Literature Search: 02/03/2020 – 03/01/2021

Generic Name: Ofatumumab
Ponesimod

Brand Name (Manufacturer):
Kesimpta (Novartis)
Ponvory (Janssen)
Dossier Received: yes, for ofatumumab

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Evidence for the comparative effectiveness of disease modifying drugs (DMDs) for multiple sclerosis (MS) was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in August 2020 as summarized in a Drug Effectiveness Review Project (DERP) report. This review examines new comparative evidence of DMDs for MS published since 2020 and summarizes the evidence for 2 new DMDs, ofatumumab and ponesimod, approved to treat relapsing forms of MS.

Research Questions:
1. What is the comparative effectiveness and efficacy of DMDs for MS?
2. Do DMDs for MS differ in harms?
3. Are there subgroups of patients with MS based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer adverse events?
4. What is the evidence for efficacy and safety for use of ofatumumab in relapsing MS?
5. What is the evidence for efficacy and safety of ponesimod in relapsing MS ?

Author: Deanna Moretz, PharmD, BCPS

Conclusions:

Multiple Sclerosis Disease-Modifying Drugs

- No new evidence of comparative efficacy or effectiveness of DMDs approved to treat MS has been published since the last MS class review.
- A moderate-quality systemic review and meta-analysis evaluated the prevalence of alemtuzumab-induced autoimmune thyroid events (ATEs) in patients with MS.[1] A 33% prevalence of newly diagnosed ATEs was recorded in 1362 MS patients treated with alemtuzumab.[1] Among all ATEs, Graves' disease was the most represented (63% of cases), followed by Hashimoto thyroiditis (15% of cases).[1]
- The National Institute for Health and Clinical Excellence (NICE) updated guidelines for alemtuzumab in treatment of patients with relapsing-remitting multiple sclerosis (RRMS). The main disadvantages of alemtuzumab treatment are the possible serious adverse effects observed during the trials, including idiopathic thrombocytopenic purpura, kidney disease or failure, thyroid disease and death.[2] While alemtuzumab's marketing authorization permits its use as a first-line treatment, it is more likely to be offered to people for whom other disease-modifying treatments have not been effective.[2]
- NICE guidance recommends ocrelizumab as an option for treating early primary progressive multiple sclerosis (PPMS) with imaging features characteristic of inflammatory activity in adults.[3]
- NICE guidance for cladribine, peginterferon, and siponimod for treatment of RRMS was recently issued. Cladribine is recommended as an option for treating rapidly evolving severe RRMS in adults.[4] Peginterferon beta-1a is recommended as an option for treating RRMS in adults.[5] Siponimod is recommended as an option for treating Secondary Progressive Multiple Sclerosis (SPMS) with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults.[6]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends siponimod for the treatment of patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability, only if specific conditions are met.[7]
- There is insufficient evidence to address the role of DMDs in managing specific subpopulations of persons with MS.

Ofatumumab

- Ofatumumab (Kesimpta™) is a recombinant human monoclonal antibody that binds CD20 expressed on B lymphocytes. The safety and efficacy of ofatumumab in patients with relapsing forms of MS were evaluated in 2, identically designed, phase 3 trials; ASCLEPIOS I and ASCLEPIOS II.[8] The trials were multicenter, double-blind, randomized, active comparator-controlled studies conducted in parallel for up to 30 months.[8]
- In both trials, moderate-quality evidence showed ofatumumab significantly improved the adjusted annualized relapse rate compared with teriflunomide in ASCLEPIOS I (0.11 vs. 0.22, respectively; difference -0.11; 95% confidence interval [CI], -0.16 to -0.06; P<0.001) and in ASCLEPIOS II (0.10 vs. 0.25, respectively; difference -0.15; 95% CI, -0.20 to -0.09; P<0.001).[8] In pooled analysis of both trials, the percentage of patients with confirmed worsening disability was significantly reduced with ofatumumab compared with teriflunomide at 3 months based on moderate-quality evidence [10.9% ofatumumab vs. 15.0% teriflunomide; hazard ratio (HR) 0.66; P=0.002; number need to treat (NNT) 25]; and at 6 months (8.1% vs. 12.0%; HR 0.68; P=0.01; NNT 26).[8]
- Adverse events that occurred in at least 10% of patients treated with ofatumumab included injection-related reactions, nasopharyngitis, headache, injection-site reaction, upper respiratory tract infection, and urinary tract infection; events that occurred in at least 10% of those treated with teriflunomide included nasopharyngitis, injection-related reactions, alopecia, upper respiratory tract infection, headache, and diarrhea.[8] Ofatumumab is contraindicated in patients with active hepatitis B virus infection.[9]

Ponesimod

- Ponesimod is a selective, second-generation, sphingosine 1-phosphate receptor 1 ($S1PR_1$) modulator. The safety and efficacy of ponesimod in patients with relapsing MS were evaluated in a multicenter, double-blind, active-comparator, phase 3 superiority randomized controlled trial; OPTIMUM.[10]
- In the OPTIMUM trial, patients with RRMS or SPMS (n=1133) were randomized 1:1 to ponesimod 20 mg starting on day 15 or teriflunomide 14 mg once daily for 108 weeks. The primary endpoint was the annualized relapse rate. Impact on disability accumulation over 12 and 24 weeks were key secondary endpoints. Compared with teriflunomide, moderate-quality evidence showed ponesimod reduced the mean annualized relapse rate over 2 years (mean annualized relapse rate with teriflunomide, 0.290 vs. 0.202 with ponesimod; rate ratio, 0.695; 99% CI, 0.536-0.902; P<0.001).[10] Moderate-quality evidence showed the risk of 12-week confirmed disability accumulation was not statistically different between ponesimod and teriflunomide (10.1% vs. 12.4%; HR, 0.83; 95% CI, 0.58-1.18; P=0.29).[10] Similar results were observed in exploratory disability accumulation over 24 weeks (8.1% vs 9.9%; HR, 0.84; 95% CI, 0.57 to 1.24; P=0.37).[10]
- Overall, the proportion of patients who experienced at least 1 treatment-emergent adverse event (TEAE) was similar between the 2 treatment groups (ponesimod 88.8% versus teriflunomide 88.2%).[10] The most common TEAEs (≥ 10% in either group) were an increased alanine aminotransferase (ALT) level (19.5% vs. 9.4%), nasopharyngitis (19.3% vs. 16.8%), headache (11.5% vs. 72 12.7%), upper respiratory tract infection (10.6% vs. 10.4%), and alopecia (3.2% vs. 12.7%) in the ponesimod versus teriflunomide groups, respectively.[10]

Recommendations:

- Apply clinical prior authorization (PA) criteria to ofatumumab subcutaneous injection for both physician administered and point of sale pharmacy claims (**Appendix 5**). Limit use to:
    - Funded MS conditions
    - History of inadequate response to at least 2 DMDs approved for MS; and
    - Prescribed by a neurologist
- Add ponesimod tablets to the Oral MS Drug PA criteria (**Appendix 5**).
- No change in Preferred Drug List (PDL) status of ofatumumab and ponesimod was recommended after review of clinical evidence.
- After review of comparative drug costs in executive session, the PDL status for ofatumumab and ponesimod remained non-preferred.

Summary of Prior Reviews and Current Policy

At the June 2020 P & T Committee meeting, PA changes were proposed to accommodate expanded FDA-approved indications for MS treatments until a comprehensive evidence review could be completed. Several medications for MS, which were previously approved only for relapsing-remitting disease, received expanded indications in late 2019 for all forms of relapsing MS including Clinically Isolated Syndrome (CIS), RRMS, and active SPMS. In addition, it was recommended to remove daclizumab from the PA criteria as it was voluntarily recalled from the U.S. market due to safety concerns in 2018.

At the August 2020 P & T Committee Meeting, DMDs for MS were reviewed in detail based on a report compiled by the DERP at the Oregon Health & Science University (OHSU) Center for Evidence Based Policy.[11] Five new oral MS drugs were reviewed in the 2020 class update including: diroximel fumarate, monomethyl fumarate, ozanimod, cladribine, and siponimod. Prior authorization criteria for oral MS drugs were revised to include newly approved DMDs. In addition, safety monitoring metrics and renewal criteria were added to the oral MS drugs PA criteria. Finally, PA criteria for natalizumab were revised to reflect the expanded indication for all forms of relapsing MS.

The PDL status of MS drugs is presented in **Appendix 1**. During the first quarter of 2021, 5 fee-for-service (FFS) patients had pharmacy claims processed for MS drugs. Over half of the claims were for the nonpreferred oral medications dimethyl fumarate (40%) and fingolimod (40%). The rest of the claims were for the preferred injectable interferon beta-1a (20%).

Background:

Multiple sclerosis is a chronic, immune-mediated disease of the central nervous system characterized by inflammation, demyelination, and neuronal destruction. Common neurological manifestations of multiple sclerosis include optic neuritis, diplopia, sensory loss, limb weakness, gait ataxia, loss of bladder control, and cognitive dysfunction.[12] The mean age of diagnosis is approximately 30 years, with most patients presenting with periodic neurological relapses.[12] One to two decades after onset, many patients with multiple sclerosis enter a progressive phase of the disease.[12] In 2016, it was estimated that MS affects approximately 2.2 million individuals worldwide.[12] Prevalence of MS and disability-adjusted life-years (DALYs) associated with MS were significantly higher in women than in men, and there were significant gradients in prevalence and incidence across different regions of the world.[12] North Africa, sub-Saharan Africa, Latin America, Asia, Oceania, and the Middle East have the lowest incidence of MS.[12] The populations with the highest prevalence of MS include North America, Western Europe and Australia.[12] Greater sun exposure and higher vitamin D levels are postulated to protect against MS.[12] The 2010 prevalence for MS in the U.S. was estimated at 309 people per 100,000 individuals, representing an overall estimate of 727,350 patients in the U.S. diagnosed with MS.[13] This analysis was based on health claims data from Medicare, Medicaid, the Department of Veterans affairs, and 3 private insurance datasets (Optum, Truven Health, and Kaiser Permanente).[13]

Diagnosis of MS is based on a combination of signs and symptoms, radiographic findings (e.g., magnetic resonance imaging [MRI] T2 lesions), and laboratory findings (e.g., cerebrospinal fluid–specific oligoclonal bands), which are components of the 2017 McDonald Criteria.[14] Four distinct clinical courses have been identified for MS: CIS, RRMS, SPMS, and PPMS.[15] Clinically Isolated Syndrome is an acute demyelinating episode lasting greater than 24 hours and is the first onset of MS symptoms. Most patients who present with CIS are eventually diagnosed with MS. Patients with RRMS have clearly defined relapses lasting 3 to 6 months with full recovery and minimal disease progression between symptomatic episodes. Relapsing-remitting MS may be either characterized as active or not active. About 85% of patients with MS are initially diagnosed with RRMS.[16] Secondary progressive MS begins as RRMS, but gradual worsening of neurologic symptoms is observed over time.[17] After 15 to 20 years, about 65% of RRMS patients enter the secondary progressive phase.[16] Relapsing MS includes CIS, RRMS, and active SPMS in adults. Primary Progressive MS is characterized by a steady decline in neurologic function and progressive accumulation of disability without acute attacks or relapses. Approximately 10 to 15% of MS patients have PPMS, and in contrast to RRMS, symptoms typically begin in the patients' fifth or sixth decade, a later age of onset than RRMS.[18] PPMS is distributed more equally between men and women than RRMS. The majority of available direct evidence continues to reside in patients with relapsing forms of MS rather than progressing forms of MS.

Progression of MS is assessed by the amount of disability caused by the disease. The Expanded Disability Status Scale (EDSS) was developed to provide a standardized measure of neurological impairment in MS. The EDSS ranges from 0 (normal neurologic exam) to 5 (ambulatory without aid for 200 meters) to 10 (death due to MS), with lower scores indicating more mobility and activity by the patient.[19] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[20] In addition, it is nonlinear over its range in comparison with the actual level of function and it places a much greater emphasis on ambulation status than other neurologic functions.[19] Despite these limitations, the EDSS continues to be the standard disability measure for MS clinical research. Clinical trials have defined disability progression when assessed over 3 to 6 months as an increase in EDSS of 0.5 points when the score is between 5.6 to 8.5 and 1.0 point when the score is between 0 and 5.50.[21] Some researchers have proposed that longer trials (with duration of at least 1 year) with greater changes in the EDSS scores (greater than 1-2 points) may better identify patients with sustained disability.[22]

The annualized relapse rate is often included as an outcome measure for MS clinical trials because it is easy to quantify. Relapses are generally defined as neurologic symptoms lasting more than 24 hours which occur at least 30 days after the onset of a preceding event.[21] However, the probability of relapse is not a consistent function over time. Patients are usually enrolled in a trial at the time of MS diagnosis when the probability for relapses is high, and as time progresses, this probability decreases.[21] In order to have enough power to detect a significant reduction in relapses, research suggests a clinical trial needs to last at least 1 year, but this measure may also be less meaningful than evaluating the total number of relapses over a longer period of time.[23] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[23] In addition to clinical measures, radiographic measures of disease progression include the development of new T2 lesions, enlarging T2 lesions, or both.[14]

The FSIQ-RMS is a validated patient-reported outcome measure that was recently developed by Actelion Pharmaceuticals to evaluate fatigue-related symptoms and the impacts of those symptoms on the lives of people with relapsing MS.[24] An electronic questionnaire consisting of 7 items included in the fatigue-related symptom domains is administered daily over 7 days.[10] The total score for each domain is standardized onto a scale of 0 to 100 with higher scores indicating more fatigue.[10] A reduction of 6.3 points was considered a meaningful change threshold in the phase 3 ponesimod trial.[10]

Treatment of MS falls into three main categories: treatment of acute attacks, symptomatic therapy to improve the patient's quality of life, and treatment with DMDs to alter the natural course of the disease and reduce progressive disability over time. Acute relapses are treated with high-dose systemic corticosteroids for 3 to 5 days. Specific symptoms including spasticity, pain, bladder dysfunction, fatigue, and mood dysregulation are treated accordingly with appropriate agents. Early use of DMDs in patients with relapsing forms of MS has been shown to reduce the frequency of relapses, lessen severity of relapses, and slow progression of disability.[25] All DMDs modulate the immune system through various mechanisms that include sequestration of lymphocytes, interference with DNA synthesis in lymphocytes, depletion of immune cells, and/or changes in cytokine secretion pattern.[14] The FDA-approved DMDs for MS include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine, and 4 types of monoclonal antibodies. Efficacy rates of DMDs, defined by reduction in annualized relapse rates compared with placebo or active comparators, range from 29% to 68%.[14]

There are 2 main treatment approaches for relapsing MS that are based on evaluating the risks and efficacy of DMDs.[14] The escalation approach starts with the least-potent medications with relatively few adverse effects, such as interferons or fumarates, and if there is evidence of disease activity the treatment is escalated to a more potent medication.[14] This approach minimizes risks but may result in undertreatment, defined as breakthrough disease and accumulated disability.[14] An alternative option is to initiate a medication with higher potency, such as ocrelizumab or natalizumab, at the time of diagnosis.[14] The rationale for this treatment approach is to provide better relapse control and delay accumulation of disability.[14] A limitation of this approach is that patients are exposed to higher risks of adverse events and some patients may not require such intensive treatment.[14] Information about the DMDs that have been FDA-approved for the treatment of MS is presented in **Table 1**.

Table 1: FDA-Approved Disease-Modifying Drugs used to manage Multiple Sclerosis[26,27]

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication	REMS Program	Major Safety Concerns	Monitoring
ORAL AGENTS						
Sphingosine 1-Phosphate Receptor Modulators						
Fingolimod (Affects $S1PR_1$, $S1PR_3$, $S1PR_4$, & $S1PR_5$)	GILENYA	≥ 40 kg: 0.5 mg PO once daily < 40 kg: 0.25 mg PO once daily	CIS RRMS SPMS **Approved for patients ≥10 years of age**	No	Infections, PML, bradycardia with first dose, hepatotoxicity hypertension, teratogenicity, and macular edema	Cardiac monitoring with the first dose. Ophthalmic screening at baseline and 3-4 months after starting therapy. LFTs and CBC every 6 months.
Siponimod (Affects $S1PR_1$ & $S1PR_5$)	MAYZENT	2 mg PO once daily (maintenance) 1 mg PO once daily for patients with CYP2C9*1/*3 OR *2/*3 genotype	CIS RRMS SPMS	No	Infections, PML, bradycardia, AV conduction delays, hepatotoxicity, macular edema, hypertension, teratogenicity	CYP2C9 genotype determination before treatment initiation. CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Ozanimod (Affects $S1PR_1$ & $S1PR_5$)	ZEPOSIA	0.92 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, PML, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs at baseline and every 6 months. Ophthalmic screening and ECG at baseline.
Ponesimod (Affects $S1PR_1$)	PONVORY	20 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, PML, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Fumarates						
Dimethyl Fumarate	TECFIDERA	240 mg PO twice a day (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Monomethyl Fumarate	BAFIERTAM	190 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Diroximel Fumarate	VUMERITY	462 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Others						

Teriflunomide	AUBAGIO	7 mg or 14 mg PO once daily	CIS RRMS SPMS	No	Black Box Warnings: Hepatotoxicity and Teratogenicity Other Warnings: infections and hypertension	CBC, LFTs, and blood pressure every 6 months
Cladribine	MAVENCLAD	Cumulative dose of 3.5 mg/kg PO divided into 2 yearly treatment courses (1.75 mg/kg per treatment course).	RRMS SPMS	No	Black Box Warnings: Malignancies and Teratogenicity Other Warnings: Bone marrow suppression, PML, lymphopenia, infections, cardiac failure, and hepatoxicity **Due to its safety profile, cladribine is recommended for patients who have had an inadequate response to, or who are unable to tolerate an alternative MS treatment**	CBC with lymphocyte count and LFTs every 6 months
INJECTABLE AGENTS						
Interferons						
Interferon beta-1a	AVONEX	30 mcg IM once weekly (maintenance)	CIS RRMS SPMS	No	Hepatotoxicity, thrombocytopenia, increased risk of spontaneous abortion, depression, and suicidal ideation	Thyroid function, CBC and LFTs every 6 months
Interferon beta-1a	REBIF	22 or 44 mcg SC three times a week				
Peginterferon beta-1a	PLEGRIDY	125 mcg SC every 14 days				
Interferon beta-1b	BETASERON, EXTAVIA	250 mcg SC every other day				
Monoclonal Antibodies						
Alemtuzumab	LEMTRADA	Intravenous infusion for 2 treatment courses. First course: 12 mg IV over 4 hours once a day for 5 consecutive days (total 60 mg). Second course: 12 mg once a day for 3 days (total 36 mg). Begin 12 months after the first treatment course.	RRMS SPMS	Yes	Black Box Warnings: Autoimmunity, Infusion Reactions, Stroke, and Malignancies Other Warnings: Infections, PML, thyroid autoimmunity, glomerular nephropathies, thrombocytopenia, autoimmune hepatitis **Due to safety profile, reserve for patients who have inadequate response to 2 or more MS drugs**	Thyroid function every 3 months. CBC with differential, serum creatinine, and urinalysis every month. Baseline and yearly LFTs and skin exams.

Natalizumab	TYSABRI	300 mg via IV infusion every 4 weeks	CIS RRMS SPMS	Yes	Black Box Warnings: PML Other Warnings: infections, hypersensitivity, teratogenicity, thrombocytopenia, hepatotoxicity **consider risk of PML vs. benefit of therapy**	JCV antibody testing and brain MRI every 6 months. CBC and LFTs every 6 months
Ocrelizumab	OCREVUS	600 mg IV every 6 months (maintenance)	CIS RRMS SPMS PPMS	No	Infusion reactions, infections and PML	Hepatitis B virus screening prior to starting therapy
Ofatumumab	KESIMPTA	20 mg SC every 4 weeks	CIS RRMS SPMS	No	Infusion reactions and infections	Hepatitis B virus screening prior to starting therapy
Others						
Mitoxantrone	NOVANTRONE	12 mg/m^2 IV infusion every 3 months – duration of therapy limited to 2 years and cumulative dose of 140 mg/m^2	RRMS SPMS	No	Black Box Warning: Dose-related Cardiotoxicity **Considered as last resort treatment for patients that have failed other therapies**	ECG and LVEF before each infusion. CBC and LFTs every 6 months
Glatiramer Acetate	COPAXONE, GLATOPA	20 mg SC once daily; OR 40 mg SC three times a week	CIS RRMS SPMS	No	Transient post injection reactions (chest pain, dyspnea, tachycardia, anxiety, palpitations, flushing, urticaria) and hepatoxicity	None required

Abbreviations: AML = acute myeloid leukemia; CBC = complete blood count; CIS = clinically isolated syndrome; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; IM = Intramuscular; IV = Intravenous; JCV = John Cunningham Virus; LFTs = liver function tests; LVEF= left ventricular ejection fraction; MS = multiple sclerosis; MRI = magnetic resonance imaging; PO = Oral; PPMS = primary progressive multiple sclerosis; PML = progressive multifocal leukoencephalopathy; REMS = Restricted Evaluation and Mitigation Strategy; RRMS = relapsing-remitting multiple sclerosis; SC= Subcutaneous, S1PR = sphingosine 1-phosphate receptor; SPMS = secondary progressive multiple sclerosis

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU DERP, Agency for Healthcare Research and Quality (AHRQ), NICE, Department of Veterans Affairs, and the CADTH resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Alemtuzumab-Induced Thyroid Events in Multiple Sclerosis

The overall prevalence of ATEs after alemtuzumab is estimated to range from 34% to 41%, with Graves' disease appearing to be the leading thyroid event.[1] The purpose of a 2020 moderate-quality systemic review and meta-analysis was to evaluate evidence on prevalence of the spectrum of alemtuzumab-induced ATEs in patients with MS.[1] Literature on this topic was searched through July 2019. Studies that described alemtuzumab treatment in other disease states (e.g. chronic lymphocytic leukemia, rheumatoid arthritis, stem cell transplantation, and kidney transplantation) were excluded.[1] Case reports, reviews, editorials, letters, commentaries, and meeting abstracts were excluded from the analysis.[1] Seven studies reporting ATEs in MS patients treated with alemtuzumab were identfied.[1] Four RCTs, 2 observational studies, and 1 case series met inclusion criteria.[1] Overall, risk of bias for these studies was rated as low to unclear. Selection bias due to unclear allocation concealment and randomization contributed to unclear bias assessments for the RCTs.[1] Detection and reporting biases were rated as low risk of bias for all 7 studies.[1]

Among the overall pooled number of 1362 MS patients treated with alemtuzumab, a 33% prevalence of newly diagnosed ATEs was recorded.[1] Among all ATEs, Graves' disease was the most represented (63% of cases), followed by Hashimoto thyroiditis (15% of cases).[1] Of all patients with Grave's disease, 12% likely had spontaneous remission, 56% required only anti-thyroid drugs, 22% needed additional radioiodine, and 11% underwent definitive surgery.[1] The authors concluded among different categories of ATEs, Graves' hyperthyroidism was the most common thyroid dysfunction associated with alemtuzumab administration in MS patients, occurring in more than half of cases.[1]

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational),[28] comparator (e.g., no control or placebo-controlled),[29] or outcome studied (e.g., non-clinical).[30]

New Guidelines:

High Quality Guidelines:

National Institute for Health and Clinical Excellence

Since the last MS class review, NICE updated guidelines for alemtuzumab for treatment of RRMS. New guidance was also published for ocrelizumab for treatment of PPMS, and for cladribine, peginterferon, and siponimod for treatment of RRMS. NICE guidance for each of these drugs is summarized below.

Alemtuzumab for Treating Highly Active Relapsing-Remitting Multiple Sclerosis

In 2020, the NICE Appraisal Committee reviewed warnings and precautions associated with alemtuzumab based on a safety review from the European Medicine Agency (EMA). For people with active RRMS eligible for treatment under the Association for British Neurologists' guidelines, alemtuzumab should be considered as a first-line treatment option, alongside beta interferons or glatiramer acetate.[2] While alemtuzumab's United Kingdom marketing authorization permits its use as a first-line treatment, it is more likely to be offered to people for whom other DMDs have not been effective.[2] The primary disadvantages of alemtuzumab are possible serious adverse effects observed during the trials, including idiopathic thrombocytopenic purpura, kidney disease or failure, thyroid disease and death.[2] Thyroid disease is the most common complication, affecting one-third of patients with MS treated with alemtuzumab.[2] The primary advantages of alemtuzumab include high efficacy, lack of flu-like symptoms associated with beta interferons, and able to be used in pregnancy.[2] Alemtuzumab NICE guidance was updated in March 2020.

- Alemtuzumab is recommended as an option for treating highly active RRMS in adults with:
    - highly active disease despite a full and adequate course of treatment with at least 1 DMD; or

- rapidly-evolving severe RRMS defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.[2]

Ocrelizumab for Treating Primary Progressive Multiple Sclerosis

New NICE guidance for the use of ocrelizumab to treat PPMS was published June 2019. There are currently no DMDs available for PPMS.[3] Results of one clinical trial show that ocrelizumab can slow the worsening of disability in patients with PPMS, although the size and duration of this effect are uncertain.[3] Given the unmet clinical need, the most plausible cost-effectiveness estimates for ocrelizumab at the agreed price compared with best supportive care alone are within the range that NICE considers an acceptable use of National Health Service (NHS) resources.[3]

- Ocrelizumab is recommended as an option for treating early PPMS with imaging features characteristic of inflammatory activity in adults.[3]

Peginterferon Beta-1a for Treating Relapsing–Remitting Multiple Sclerosis

NICE issued updated guidance for the use of peginterferon for treatment of RRMS in February 2020. Clinical trials show that peginterferon beta-1a slows disease progression and reduces the frequency of relapses when compared with placebo in patients with RRMS.[5] There is also an indirect comparison suggesting that there are no differences in effectiveness when comparing peginterferon beta-1a with other beta interferons and glatiramer acetate. [5] However, it involves less frequent injections than other beta interferons, and offers an additional choice for people with RRMS.[5]

- Peginterferon beta-1a is recommended as an option for treating RRMS in adults.[5]

Cladribine for Treating Relapsing–Remitting Multiple Sclerosis

NICE issued new guidance for the use of cladribine in management of RRMS in December 2019. Highly active RRMS is currently treated with alemtuzumab, fingolimod or natalizumab.[4] Clinical trials show that cladribine tablets reduce relapses and slow the progression of disability compared with placebo for people with RRMS.[4] The effectiveness of cladribine for treating rapidly evolving, severe, or suboptimally treated RRMS is not proven, but it is likely to be more effective than placebo.[4] Based on indirect analyses, there is not enough evidence to determine whether cladribine is more or less effective than other treatments for people with rapidly evolving severe and suboptimally treated multiple sclerosis.[4] Because of this, cladribine and alternative treatments are considered equally effective by NICE.[4] Cladribine is less costly than other treatments and needs less frequent dosing and monitoring. It is cost effective compared with all other treatments, so it can be recommended for rapidly evolving, severe, and suboptimally treated RRMS.[4]

- Cladribine is recommended as an option for treating highly active MS in adults, only if the person has rapidly evolving severe RRMS, that is with at least:
  - 2 relapses in the previous year; and
  - 1 T1 gadolinium-enhancing lesion at baseline MRI or a significant increase in T2-lesion load compared with a previous MRI; or
  - RRMS that has responded inadequately to treatment Witham's, defined as 1 relapse in the previous year and MRI evidence of disease activity.[4]

Siponimod for Treating Secondary Progressive Multiple Sclerosis

NICE issued new guidance for the use of siponimod for treatment of SPMS in November 2020. Clinical trials show that siponimod reduces the number of relapses and slows disability progression in patients with SPMS compared with placebo.[6] It is uncertain how effective siponimod is compared with interferon beta-1b because there is no evidence directly comparing them.[6] The most plausible cost-effectiveness estimates for siponimod compared with interferon beta-1b are in the range that NICE normally considers an acceptable use of NHS resources.[6]

- Siponimod is recommended, as an option for treating SPMS with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults. [6]

Canadian Agency for Drugs and Technologies in Health (CADTH)

In September 2020, the CADTH published a clinical review of siponimod for treatment of SPMS.[7] Based on the data outlined in the report, the CADTH Canadian Drug Expert Committee recommends that siponimod be reimbursed for the treatment of patients with SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability, only if the following conditions are met:

- Patients who have all of the following characteristics:
  - History of RRMS and current active SPMS;
  - EDSS score of 3.0 to 6.5; and
  - Documented EDSS progression during the 2 years prior to initiating treatment with siponimod (≥ 1 point if EDSS < 6.0; ≥ 0.5 points if EDSS ≥ 6.0 at screening).[7]
- Siponimod should not be used in combination with other DMDs used to treat MS.

CADTH Renewal Criteria for Siponimod:

- Patients should be assessed for a response to siponimod every 6 months.
- Siponimod may be renewed for patients who do not exhibit evidence of disease progression since the previous assessment.
  - Disease progression is defined as an increase in the EDSS score of ≥ 1 point if the EDSS score was 3.0 to 5.0 at siponimod initiation, or an increase of ≥ 0.5 points if the EDSS score was 5.5 to 6.5 at siponimod initiation.[7]

CADTH Discontinuation Criteria for Siponimod:

- Treatment with siponimod should be discontinued in patients who exhibit either of the following:
  - Progression to an EDSS score of equal to or greater than 7.0 at any time during siponimod treatment; or
  - Confirmed worsening of at least 20% on the timed 25-foot walk since initiating siponimod treatment.[7]

Additional Guidelines for Clinical Context: After review, no guidelines were excluded due to poor quality.

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[31,32]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Natalizumab	TYSABRI	06/2020	Boxed Warning, Warnings and Precautions	Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified: • The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML. • Longer treatment duration, especially beyond 2 years. • Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).

				These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI.[31] Cases of thrombocytopenia, including immune thrombocytopenic purpura (ITP), have been reported with the use of TYSABRI in the post marketing setting. Symptoms of thrombocytopenia may include easy bruising, abnormal bleeding, and petechiae. Delay in the diagnosis and treatment of thrombocytopenia may lead to serious and life-threatening sequelae. If thrombocytopenia is suspected, TYSABRI should be discontinued.[31]
Glatiramer	COPAXONE GLATOPA	07/2020	Warnings and Precautions	Cases of hepatic injury, some severe, including liver failure and hepatitis with jaundice, have been reported with COPAXONE. Hepatic injury has occurred from days to years after initiating treatment with COPAXONE. If signs or symptoms of liver dysfunction occur, consider discontinuation of COPAXONE.[32]

Randomized Controlled Trials:

A total of 49 citations were manually reviewed from the initial literature search. After further review, 48 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in **Table 3** below. The full abstract is included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trial

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr><td>Cheshmavar M, et al.[33]

OL RCT</td><td>1. Rituximab 1 gm IV q6 months

2. Glatiramer 40 mg SC 3 times a week</td><td>Adults aged 18 to 55 years with SPMS with an EDSS 0 to 5

N=84</td><td>Comparison of EDSS between groups after 12 months of treatment</td><td>
<table>
<tr><th></th><th>Rituximab (n=43)</th><th>Glatiramer (n=41)</th><th>p-value (ITT analysis)</th></tr>
<tr><td>Baseline EDSS</td><td>3.09</td><td>3.22</td><td></td></tr>
<tr><td>EDSS at 12 months</td><td>4.02</td><td>4.60</td><td>0.179
Confidence Interval Not Reported</td></tr>
</table>
</td></tr>
<tr><td colspan="5">Abbreviations: EDSS=Expanded Disability Status Scale; ITT= Intention to Treat; IV=Intravenous; OL=open label; RCT=randomized clinical trial; SC=subcutaneous; SPMS=Secondary Progressive Multiple Sclerosis</td></tr>
</table>

NEW DRUG EVALUATION: Ofatumumab

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Ofatumumab (Kesimpta™) is a recombinant human monoclonal antibody that binds CD20 expressed on B lymphocytes, which results in antibody-dependent cellular cytolysis and complement-mediated lysis of B cells.[9] Ofatumumab received initial FDA approval in 2009 under the brand name Arzerra™ for treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.[34] In August 2020, ofatumumab received FDA-approval for the treatment of relapsing forms of MS (e.g., CIS, RRMS, SPMS).[9] Anti-CD20 monoclonal antibodies that induce B-cell depletion, such as rituximab and ocrelizumab, have been used as DMDs for MS.[8] These drugs are administered via intravenous infusion in a clinical setting. In contrast, ofatumumab can be administered subcutaneously (SC) by the patient at home after initial doses are given under medical supervision.[8]

The safety and efficacy of ofatumumab in patients with relapsing forms of MS were evaluated in 2 identically designed phase 3 trials: ASCLEPIOS I and ASCLEPIOS II.[8] Both trials were multicenter, randomized, double-blind, double-dummy, active comparator-controlled studies conducted in parallel for up to 30 months.[8] Adult patients with RRMS or active SPMS and an EDSS of 0 to 5.5 were recruited for both studies. A total of 1,882 patients were enrolled in ASCLEPIOS I (N=927) and ASCLEPIOS II (N=955).[8] Teriflunomide 14 mg was administered orally once daily as the active comparator. Teriflunomide, an oral inhibitor of pyrimidine synthesis, reduces T-cell and B-cell activation. Loading doses of ofatumumab 20 mg were administered SC once weekly at Week 0, 1, and 2. Maintenance doses of ofatumumab 20 mg were administered SC once monthly starting at Week 4. Oral placebo capsules and placebo injections were administered in the appropriate groups to maintain blinding to the study drug by patients and investigators.

The primary end point for both trials was the annualized relapse rate. The median time in each trial was 1.5 years in ASCLEPIOS I and 1.6 years in ASCLEPIOS II.[8] A relapse was defined as the appearance of a new neurological abnormality or worsening of a previously stable pre-existing neurological abnormality.[8] A confirmed relapse was defined as a relapse accompanied by a clinically relevant change in the EDSS performed by the independent EDSS rater (i.e., an increase of at least 0.5 points on the EDSS score, or an increase of 1.0 point on two functional scores compared to the previously available rating that did not occur during a relapse).[8] Key secondary end points included disability worsening confirmed at 3 months or 6 months, disability improvement confirmed at 6 months, the number of gadolinium-enhancing lesions per T1-weighted magnetic resonance imaging (MRI) scan, and the annualized rate of new or enlarging lesions on T2-weighted MRI.[8]

In both trials, ofatumumab improved the adjusted annualized relapse rate compared with teriflunomide in ASCLEPIOS I (0.11 vs. 0.22, respectively; difference -0.11; 95% CI, -0.16 to -0.06; P<0.001) and in ASCLEPIOS II (0.10 vs. 0.25, respectively; difference -0.15; 95% CI, -0.20 to -0.09; P<0.001).[8] In the pooled analysis, the percentage of patients with confirmed disability worsening was reduced with ofatumumab compared with teriflunomide at 3 months (10.9% ofatumumab vs. 15.0% teriflunomide; HR 0.66; P=0.002; 95% CI, 0.50 to 0.86); and 6 months (8.1% ofatumumab vs. 12.0% teriflunomide; HR 0.68; P=0.01; 95% CI, 0.50 to 0.92).[32] No significant difference between groups was observed on confirmed disability improvement at 6 months (11.0% ofatumumab vs. 8.1% teriflunomide; HR 1.35; P=0.09; 95% CI, 0.95 to 1.92).[8]

Ofatumumab was also superior to teriflunomide in suppressing lesion activity on MRI.[8] In ASCLEPIOS I, the number of gadolinium-enhancing lesions per T1-weighted MRI scan was significantly lower with ofatumumab compared with teriflunomide [0.01 ofatumumab and 0.45 teriflunomide (97% lower number of

lesions ofatumumab, P<0.001)]; in ASCLEPIOS II, the corresponding numbers were 0.03 and 0.51, respectively (94% lower ofatumumab, P<0.001).[8] The annualized rate of lesions on T2-weighted MRI was also significantly lower with ofatumumab compared with teriflunomide in ASCLEPIOS I [0.72 ofatumumab and 4.00 teriflunomide (82% lower number of lesions ofatumumab, P<0.001)]; corresponding values in ASCLEPIOS II were 0.64 and 4.15, respectively (85% lower ofatumumab, P<0.001).[8] Both trials are described in further detail in **Table 4** (Comparative Evidence Summary).

Trial Limitations

Lesion counts on MRI in the teriflunomide groups were higher than those previously reported in one phase 3 trial of teriflunomide as compared with placebo, which suggests either a population with more disease activity overall in the ASCLEPIOS trials, differences in the assessment methods used at the MRI analysis centers, or both.[8] In ASCLEPIOS I, more patients withdrew from the teriflunomide arm compared to ofatumumab (19% versus 10%, respectively).[8] Reasons for study withdrawal were primarily due to patient decision [n=42; (52%) in the teriflunomide arm versus n=16; (33%) in the ofatumumab arm].[8] Discontinuations due to adverse events, loss to follow up, physician decision, and protocol deviation were similar in both treatment arms. In ASCLEPIOS II, the discontinuation rate from ofatumumab and teriflunomide was similar throughout the entire trial.[8] Larger and longer trials are required to determine the long-term effect and risks of ofatumumab as compared with other DMDs, including other anti-CD20 monoclonal antibodies.[8]

Clinical Safety:

Adverse events that occurred in at least 10% of the patients treated with ofatumumab were injection-related systemic reactions, nasopharyngitis, headache, injection-site local reactions, upper respiratory tract infection, and urinary tract infection. Events that occurred in at least 10% of those treated with teriflunomide were nasopharyngitis, injection-related systemic reactions, alopecia, upper respiratory tract infection, headache, and diarrhea.[8] Serious adverse events were reported in 9.1% of the patients treated with ofatumumab and 7.9% of those treated with teriflunomide. One death occurred in the teriflunomide group (aortic dissection) during the post-treatment follow-up period.[8] Injection-related systemic reactions occurred in 21% in the ofatumumab group and in 15.0% in the teriflunomide group (placebo injections).[8] Serious infections occurred in 2.5% of patients in the ofatumumab group and 1.8% of patients in the teriflunomide group.[8]

A summary of reported adverse reactions observed with ofatumumab compared with teriflunomide is presented in **Table 2**. Animal data suggests a risk of fetal harm with ofatumumab administration.[9] The prescribing information recommends use of an effective method of contraception during ofatumumab treatment and for 6 months after discontinuation.[9]

Table 2. Adverse Reactions Observed In Patients With RMS With Ofatumumab And Teriflunomide[9]

Adverse Reactions	Ofatumumab N=946	Teriflunomide N=936
Upper Respiratory Tract Infections	39%	38%
Injection-Related Systemic Reactions (fever, headache, nausea, chills, pruitus)	21%	15%
Headache	13%	12%
Injection-Site Local Reactions	11%	6%
Urinary Tract Infection	10%	8%
Back Pain	8%	6%
Blood Immunoglobulin M Decrease	6%	2%

Look-alike / Sound-alike Error Risk Potential: No other drugs identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Disability Worsening at 3 and 6 months
2) Disability Improvement at 6 months
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Annualized Relapse Rate

Table 3. Pharmacology and Pharmacokinetic Properties.[9]

Parameter	
Mechanism of Action	CD20 binding on B lymphocytes
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 5.42 L; Protein Binding not reported
Elimination	Ofatumumab is eliminated in two ways: 1) Target-independent route as with other IgG molecules and 2) Target-mediated route that is related to binding to B-cells
Half-Life	16 days
Metabolism	Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes.

Abbreviations: IgG = Immunoglobulin G; L = liters; N/A = Not Applicable

Table 4. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Hauser SL et al.[8] ASCLEPIOS I DB, AC, MC Phase 3 RCT	1. Ofatumumab 20 mg SC on days 0, 7, 14 and 28, followed by 20 mg SC every 4 weeks (plus teriflunomide-matching placebo capsule orally once daily) 2. Teriflunomide 14 mg orally once daily (plus ofatumumab-matching SC placebo injection at frequency of group 1) Duration: Variable based on when end of study criteria was met. Median Duration: 1.5 years Maximum duration: 30 months	Demographics: -Mean Age: 38 yo -Female: 69% -White: 89% -Median EDSS score: 3.0 -Type of MS RRMS: 94% SPMS: 6% -No previous DMD treatment: 40% -Previous DMD: Interferon beta: 40% Glatiramer: 25% Dimethyl fumarate: 8% Teriflunomide: 1.5% Natalizumab: 6% Key Inclusion Criteria: -Age 18-55 y -RRMS or active SPMS -EDSS 0 to 5.5 - ≥ 1 relapse in year prior to study enrollment OR 2 relapses in 2 years prior to study enrollment OR presence of a T1 Gd-enhancing lesion within year prior to study enrollment. -Neurologically stable in month prior to study enrollment. Key Exclusion Criteria: -Use of previous MS DMDs within specified time frames prior to study enrollment -	ITT: 1.465 2.462 PP: 1.416 2.376 Attrition: 1.48 (10%) 2.81 (19%)	Primary Endpoint: Adjusted annualized relapse rate at median follow up of 1.5 years 1. 0.11 2. 0.22 Difference: -0.11; 95% CI, -0.16 to -0.06; P<0.001 Secondary Endpoints: 1. Percentage of patients with worsening disability at 3 months (Kaplan-Meier estimate) 1. 11.3% 2. 15.4% HR, 0.65; 95% CI, 0.45 to 0.96; p-value NR 2. Percentage of patients with worsening disability at 6 months (Kaplan-Meier estimate) 1. 8.2% 2. 13% HR 0.61; 95% CI 0.40 to 0.93; P-value NR 3. Percentage of patients with disability improvement at 6 months (Kaplan-Meier estimate) 1. 9.7% 2. 8.2% HR 1.19; 95% CI 0.71 to 1.98 p-value NR 4. Mean number of new or enlarging lesions on MRI per year	NA 4.1%/25 4.8%/21 NS NA	Any Adverse Event 1. 382 (82.2%) 2. 380 (82.3%) Early Discontinuation due to Adverse Event 1. 27 (5.8%) 2. 24 (5.2%) Serious Adverse Events 1. 48 (10.3%) 2. 38 (8.2%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IRT. Stratified by geographic region (Western Europe, Eastern Europe, North America & Australia, and Others) and by MS subtype (RRMS vs. SPMS). Baseline demographics were similar in both arms. Performance Bias: Low. Laboratory assessments that could lead to unblinding were not revealed to staff or sponsor study team. Matching oral and SC placebos were used to maintain treatment blinding. Detection Bias: Low. The investigators, the sponsor, and the steering committee were unaware of treatment assignment. MRI scans independently analyzed by staff blinded to treatment assignments. EDSS assessments completed by an independent clinician. Attrition Bias: High. More patients withdrew from the teriflunomide arm compared to ofatumumab. Reasons for study withdrawal were primarily due to patient decision. Reporting Bias: Low. Protocol available on-line. All prespecified outcomes reported. Other Bias: High. Sponsored by the manufacturer, Novartis. Data collected by investigators was analyzed by Novartis. The manuscript was drafted with medical writing assistance funded by the sponsor. Several investigators reported grant support from Novartis. **Applicability**: Patient: Patients were representative of MS population with EDSS scores ≤ 5.5, indicating patients were ambulatory and active. 40% of patients had not had previous DMD treatment and may have benefited from interferon or fumarate therapy. Intervention: Selected dose for ofatumumab in MS patients was proven to be the lowest, maximally effective dose in a Phase II trial.

		(Dimethyl fumarate: 1 month; Fingolimod: 2 months; Daclizumab: 4 months; Teriflunomide: 3.5 months; Rituximab, Ocrelizumab: 2 years) -PPMS -SPMS without disease activity -Disease duration > 10 years with EDSS score ≤ 2 -PML		1. 0.72 2. 4.0 Rate Ratio: 0.18 95% CI 0.15 to 0.22 P<0.001				Comparator: Teriflunomide, an IST with proven efficacy in reducing relapses, selected as an active comparator at recommended dosing. Outcomes: Annualized relapse rate used as primary outcome, similar to other DMD trials in MS. Setting: Both trials were conducted at 385 sites in 37 countries Europe, North America, South America, Australia, Asia, and Africa. 120 sites (31%) were located in the United States.
2. Hauser SL et al.[8] ASCLEPIOS II DB, AC, MC Phase 3 RCT	1. Ofatumumab 20 mg SC on days 0, 7, 14 and 28 followed by 20 mg SC every 4 weeks (plus teriflunomide-matching placebo capsule orally once daily) 2. Teriflunomide 14 mg orally once daily (plus ofatumumab-matching SC placebo injection) Duration: Variable based on when end of study criteria was met. Median Duration: 1.6 years Maximum duration: 30 months	Demographics: -Age: 38 y -Female: 67% -White: 87% -Median baseline EDSS score: 2.5 -No previous DMD treatment: 39% Key Inclusion Criteria: see ASCLEPIOS I Key Exclusion Criteria: see ASCLEPIOS I	ITT: 1. 481 2. 474 PP: 1. 398 2. 390 Attrition: 1.83 (17%) 2.84 (18%)	Primary Endpoint: Adjusted annualized relapse rate at median follow up of 1.6 years 1. 0.10 2. 0.25 Difference: -0.15; 95% CI -0.20 to -0.09; P<0.001 Secondary Endpoints: 1.Percentage of patients with worsening disability at 3 months (Kaplan-Meier estimate) 1. 10.5% 2. 14.6% HR 0.66; 95% CI 0.45 to 0.97 P-value NR 2. Percentage of patients with worsening disability at 6 months (Kaplan-Meier estimate) 1. 8.0% 2. 10.9% HR 0.76; 95% CI 0.49 to 1.17 p-value NR 3. Percentage of patients with disability	NA 4.1%/25 2.9%/35	Any Adverse Event 1. 409 (85%) 2. 408 (86.1%) Early Discontinuation due to Adverse Event 1. 27 (5.6%) 2. 25 (5.3%) Serious Adverse Event 1. 38 (7.9%) 2. 36 (7.6%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: see ASCLEPIOS I Performance Bias: see ASCLEPIOS I Detection Bias: see ASCLEPIOS I Attrition Bias: Low. Attrition rates were similar in both groups. Reporting Bias: see ASCLEPIOS I Other Bias: see ASCLEPIOIS I **Applicability**: Patient: see ASCLEPIOS I Intervention: see ASCLEPIOS I Comparator: see ASCLEPIOS I Outcomes: see ASCLEPIOS I Setting: see ASCLEPIOS I

				improvement at 6 months (Kaplan-Meier estimate) 1. 12.3% 2. 8.1% HR 1.52; 95% CI 0.93 to 2.47 p-value NR 4. Mean number of new or enlarging lesions on MRI per year 1. 0.64 2. 4.15 RR 0.15; 95% CI 0.13 to 0.19; P<0.001	NS NA			

Abbreviations: AC = active comparator; ARR = absolute risk reduction; CI = confidence interval; DMD = disease-modifying drug; DB = double blind; EDSS = Expanded Disability Status Scale; Gd = gadolinium; HR = hazard ratio; IRT = Interactive Response Technology; IST = Immunosuppressive Therapy; ITT = intention to treat; MC = multi-center; MRI = magnetic resonance imaging; MS = multiple sclerosis; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PP = per protocol; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; y = years

NEW DRUG EVALUATION: Ponesimod

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Ponesimod is a selective, second-generation, $S1PR_1$ modulator. Other sphingosine 1-phosphate (S1P) receptor modulators include fingolimod, siponimod, and ozanimod. Ponesimod induces a rapid, dose-dependent, and reversible reduction of peripheral blood lymphocyte counts by blocking the egress of lymphocytes from lymphoid organs.[10] In contrast to fingolimod, which has a half-life of 6 to 9 days and slow elimination, ponesimod is eliminated within 1 week of discontinuation due to a half-life of 33 hours, and its pharmacologic effects can be rapidly reversed. Rapid elimination of ponesimod and the reversibility of its effects on lymphocyte levels allows the rapid return of normal immune system function, which may be beneficial in terms of safety for pregnancy planning, serious infections, or vaccinations.[10] Fingolimod, a first-generation, non-selective, S1P receptor modulator, can cause adverse events due to its pharmacologic effect on other S1P receptors expressed in diverse tissues, including cardiac myocytes. The specificity of ponesimod for subtype 1 of the S1P receptors is theorized to minimize undesirable effects related to interaction with other S1P receptor subtypes. Ponesimod received FDA approval March 2021 for treatment of relapsing forms of MS, including CIS, RRMS, and SPMS.[35] The FDA-approved dosing initiates ponesimod with a 14-day titration starting with 2 mg once daily and slowly increasing to the recommended maintenance dose of 20 mg orally once daily.[35] Ponesimod was evaluated in clinical trials as a treatment option for plaque psoriasis in adults, but has not been FDA-approved for this indication.

Clinical Efficacy:
Results from the Oral Ponesimod Versus Teriflunomide in Relapsing Multiple Sclerosis (OPTIMUM) trial contribute to the efficacy data for the use of ponesimod in relapsing MS, which are described and evaluated below in **Table 7.** The OPTIMUM trial was a multicenter, double-blind, active-comparator, phase 3 superiority RCT.[10] Patients with relapsing MS (n=1133) were randomized 1:1 to ponesimod 20 mg starting on day 15 or teriflunomide 14 mg once daily for 108 weeks. Ponesimod was slowly titrated upwards over 14 days, starting with 2 mg once daily to mitigate first-dose cardiac effects associated with S1P modulators. One hundred sixty two sites randomized patients across 28 countries in North America, Europe, Israel, and Turkey.[10] The primary endpoint was the annualized relapse rate based on the number of confirmed relapses per patient-year over 108 weeks. A relapse was defined as new, worsening or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, and that lasted at least 24 hours, in the absence of fever or infection.[10] The new, worsening or recurrent neurological symptoms were to be evaluated by the treating neurologist and, if all the elements of the above definition had been verified, and in the absence of another, better explanation of the patient's symptoms, the event was considered as a relapse.[10] A relapse was confirmed by the treating neurologist only when the patients' symptoms were accompanied by an increase in EDSS scores or functional system scores from a previous clinical assessment.[10] Secondary endpoints included changes in fatigue-related symptoms evaluated via the FSIQ–RMS score at week 108 and an assessment of 12-week and 24-week confirmed disability accumulation based on changes in the EDSS score. An increase of at least 1.5 with a baseline EDSS score of 0.0, at least 1.0 with baseline EDSS score of 1.0 to 5.0, or at least 0.5 with a baseline EDSS score of 5.5 or more was considered confirmed change.[10] Cumulative number of combined unique active lesions (CUALs) on MRI from baseline to week 108 (defined as new Gd+ T1 lesions plus new or enlarging T2 lesions) was an additional secondary endpoint.[10]

In total, there were 242 confirmed relapses reported for ponesimod compared with 344 for teriflunomide over the 108-week study period.[10] Ponesimod reduced annualized relapse rate by 30.5% at week 108 compared with teriflunomide (mean annualized relapse rate, 0.202 vs 0.290; rate ratio, 0.695; 99% CI, 0.536-0.902; P<0.001).[10] The change in FSIQ-RMS weekly symptom score from baseline to week 108 was lower (where higher scores indicate more fatigue) for fatigue symptoms in the ponesimod group than the teriflunomide group.[10] The least-square means were 0.01 (ponesimod) versus 3.56 (teriflunomide); mean difference, −3.57; 95% CI, −5.83 to −1.32; P=0.002.[10] The risk of 12-week confirmed disability accumulation was not statistically different between ponesimod and teriflunomide (10.1% vs. 12.4% respectively; HR, 0.83; 95% CI, 0.58-1.18; P=0.29).[10] Similar results were observed in exploratory disability accumulation over 24 weeks (8.1% vs 9.9%; HR, 0.84; 95% CI, 0.57 to 1.24; P=0.37).[10] For the secondary efficacy outcome of cumulative number of (CUALs) per year from baseline to week 108, ponesimod reduced the number of new inflammatory lesions on brain MRI scans by 56% compared to teriflunomide (1.405 vs.3.164; rate ratio, 0.44; 95% CI, 0.36 to 0.54; P<0.001).[10]

Trial Limitations:
Baseline EDSS scores (mean, 2.6) and the proportion of patients with EDSS scores of 3.5 or less (83.5%) are indicative of a relatively low level of disability, and few 12-week confirmed disability accumulation were observed in both the ponesimod and teriflunomide groups, leading to a limitation in the ability to detect significant differences between treatment groups.[10] The low rate of confirmed disability accumulation in both arms and the fact that teriflunomide demonstrated a significant benefit on 12-week confirmed disability progression in 2 separate trials in subjects with relapsing MS[36,37] suggests that OPTIMUM was underpowered to detect a difference within the 2-year treatment period.[10] Although the investigators limited the percentage of patients with SPMS to 15%, there were a very limited number of patients with SPMS (2.5%) enrolled in the trial. Finally, the patient reported outcome used to evaluate changes in fatigue related to relapsing MS was recently developed by the manufacturer of ponesimod. Although the FSIQ-RMS tool has been validated, it has only been used in clinical trials evaluating the efficacy of ponesimod.[24] A reduction of 6.3 points in the FSIQ-RMS symptom scale was considered a meaningful change threshold.[10]

The reported overall improvement for ponesimod compared to teriflunomide in FSIQ-RMS symptom score was 3.57 on a 100 point score, which raises some uncertainty regarding the clinical significance for improved fatigue symptoms.

Clinical Safety:
Overall, the proportion of patients who experienced at least 1 TEAE was similar between the 2 groups (ponesimod 88.8% vs. teriflunomide 88.2%).[10] The most common TEAEs (≥10% in either group) were an increased ALT level (19.5% vs. 9.4%), nasopharyngitis (19.3% vs. 16.8%), headache (11.5% vs. 12.7%), upper respiratory tract infection (10.6% vs. 10.4%), and alopecia (3.2% vs. 12.7%) in the ponesimod versus teriflunomide groups, respectively.[10] Two patients in the teriflunomide group died: 1 of coronary artery insufficiency and 1 of MS (adjudicated as sudden cardiac death).[10] Both deaths were considered by the investigators to be not associated with the study drug. Overall, TEAEs leading to treatment discontinuation were more frequent in the ponesimod group (8.7% vs. 6.0%]; dyspnea, an increased ALT level, an increased aspartate aminotransferase level, and macular edema were the most commonly reported reasons.[10] The overall incidence of first-dose heart rate and rhythm adverse effects on day 1 (at a 2 mg dose) of up-titration or treatment reinitiation was 2.1% in the ponesimod group (n = 12) compared with 0.4% (n = 2) in the teriflunomide group, with none reported as serious or leading to treatment discontinuation.[10] No second-degree or higher-degree atrioventricular blocks occurred.[10]

Table 5. Adverse Reactions Reported In The OPTIMUM Study Occurring In At Least 5% Of Ponesimod-Treated Patients And At A Higher Rate Than Teriflunomide-Treated Patients[35]

Adverse Reaction	Ponesimod (n=565)	Teriflunomide (n=566)
Upper respiratory infection	37%	34%
Hepatic transaminase elevation	23%	12%
Hypertension	10%	9%
Urinary trat infection	6%	5%
Dyspnea	5%	1%
Dizziness	5%	3%

Look-alike / Sound-alike Error Risk Potential: No other drugs identified

Comparative Endpoints:
Clinically Meaningful Endpoints:
1) Number of Relapses
2) Worsening Fatigue at 108 weeks
3) Disability Accumulation over 3 and 6 months
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Annualized Relapse Rate

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Sphingosine 1-phosphate receptor 1 modulator – reduces peripheral blood lymphocyte counts by blocking the egress of lymphocytes from lymphoid organs
Oral Bioavailability	84% (10 mg dose)
Distribution and Protein Binding	Volume of Distribution: 160 Liters; Protein Binding: > 99%
Elimination	Renal: 10 to 18% unchanged: Hepatic: 57 to 80% (16% as unchanged drug); Total Body Clearance: 3.8 Liters/hour
Half-Life	33 hours
Metabolism	Extensively metabolized to inactive metabolites by hepatic enzymes

Table 7. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Kappos L, et al.[10] Phase 3 MC, DB, AC, RCT	1. Ponesimod 20 mg PO once daily 2. Teriflunomide 14 mg PO once daily	Demographics: 1. Mean age: 36.8 yo 2. Women: 64.9% 3. White: 97.4% 4. Mean baseline EDSS score: 2.6 5. RRMS: 97.5% SPMS: 2.5% 6.Disease modifying drugs received within 2 years prior to study enrollment: 39.5% Key Inclusion Criteria: 1.Adults aged 18 to 55 yo with RRMS or SPMS 2. 1 or more MS relapses 12 months prior to study enrollment or 2 or more MS relapses 24 months prior to enrollment 2. Ambulatory with an EDSS score ≤ 5.5 3. Subjects could be treatment-naïve or previously treated with interferon, glatiramer acetate, dimethyl fumarate or natalizumab. Key Exclusion Criteria:	ITT: 1. 567 2. 566 PP: 1. 471 2. 473 Attrition: 1.96 (16.9%) 2.93 (16.4%)	Primary Endpoint: Mean Annualized Relapse Rate 1. 0.202 2. 0.290 Rate Ratio: 0.695 99% CI, 0.536 to 0.902 P<0.001 Secondary Endpoints: A. Least squares mean FSIQ-RMS weekly symptoms score change 1. -0.01 2. 3.56 Mean Difference: -3.57 95% CI -5.83 to -1.32 P=0.002 B. Patients with confirmed 12-	NA NA NA NS	TEAEs: 1. 502 (88.8%) 2. 499 (88.2%) TEAEs leading to treatment discontinuation: 1. 49 (8.7%) 2. 34 (6.0%) Serious Adverse Events 1. 49 (8.7%) 2. 46 (8.1%) 95% CI and p-values NR Fatal TEAEs 1. 0 2. 2 (0.4%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 to ponesimod or teriflunomide via IRT. Patients were stratified by prior use of MS DMD (yes/no) and baseline EDSS (≤ 3.5 vs. >3.5). Baseline characteristics were similar between groups. Performance Bias: Low. Patients received ponesimod & matching placebo tablet OR teriflunomide & matching placebo capsule during the first 14 days of the study. First doses were observed by a first-dose administrator as potential adverse effects of ponesimod (effects on heart rate and AV conduction) could have resulted in unblinding. Access to information regarding adverse effects observed with the first dose was not permitted for all members of the study team. At day 15, subjects were switched to receiving 1 capsule containing either ponesimod or teriflunomide. Investigators, study staff, and subjects were all blinded to treatment arm. Detection Bias: Low. EDSS scores were assessed by independent evaluators. Treating neurologists evaluated symptoms indicative of relapse. Attrition Bias: Low. Attrition rates were similar between groups. However, there were fewer treatment discontinuations due to efficacy in the ponesimod arm compared to teriflunomide (1.9% vs. 4.3%) and more treatment discontinuations in the ponesimod arm due to adverse effects compared with teriflunomide (6.5% vs. 2.4%). Reporting Bias: Low. Protocol available on-line. All prespecified outcomes reported.

		1.Patient with contraindications to magnetic resonance imaging. 2.Treatment with beta-blockers, verapamil, digoxin or any other anti-arrhythmic or heart rate lowering medication within 15 days of randomization 3. Subjects with progressive forms of MS 4.Treatment with alemtuzumab, mitoxantrone, fingolimod, or other investigational S1P1 modulators 5. Treatment with systemic corticosteroids and ACTH within 30 days of randomization except for treatment of MS relapses. 6. Subjects with significant medical conditions or therapies for such conditions (e.g., cardiovascular, pulmonary, immunological, hepatic, ophthalmological, ocular) or lactating or pregnant women are not eligible to enter the study.		week disability accumulation 1. 57 (10.1) 2. 70 (12.4%) HR: 0.83 95% CI 0.58 to 1.18 P=0.29 C. Cumulative number of combined active lesions per year 1. 1.405 2. 3.164 Rate Ratio: 0.444 95% CI 0.36 to 0.54 P<0.001	NA			Other Bias: Unclear. Funding was provided by Janssen Research & Development LLC, and the OPTIMUM study was supported by Actelion Pharmaceuticals, part of Janssen Pharmaceutical Companies. Janssen employees were responsible for the design and conduct of the study and collection, management, analysis, and interpretation of the data. Several study investigators received substantial grant funding from Actelion or Janssen. **Applicability**: Patient: Patients enrolled in the study had relatively low levels of disability (mean baseline EDSS score: 2.6). Most of the patients had RRMS (97.5%). Only 2.5% of patients had SPMS. Most patients (62.5%) were naïve to MS disease modifying treatment. Intervention: Safety and efficacy of ponesimod 20 mg once daily dosing was evaluated in a Phase 2 trial. Comparator: Teriflunomide is an oral MS drug with proven efficacy in RRMS and SPMS. Fingolimod may have been a better active comparator, since it has a similar mechanism of action as ponesimod. Outcomes: Annualized relapse rate used as primary outcome, similar to other DMD trials in MS. Setting: 162 centers across 28 countries in North America, Europe, Mexico, Israel, and Turkey.

Abbreviations: AC = active comparator; ACTH = adrenocorticotropin hormone; ARR = absolute risk reduction; CI = confidence interval; DMD = disease-modifying drug; DB = double blind; EDSS = Expanded Disability Status Scale; Gd = gadolinium; HR = hazard ratio; IRT = Interactive Response Technology; IST = Immunosuppressive Therapy; ITT = intention to treat; MC = multi-center; MRI = magnetic resonance imaging; MS = multiple sclerosis; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PP = per protocol; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; TEAEs = treatment-emergent adverse events: y = years

References:

1. Scappaticcio L, Castellana M, Virili C, et al. Alemtuzumab-induced thyroid events in multiple sclerosis: a systematic review and meta-analysis. *Journal of Endocrinological Investigation.* 2020;43(2):219-229.
2. National Institute for Health and Care Excellence (NICE) Alemtuzumab for treating highly active relapsing-remitting multiple sclerosis. March 2020 https://www.nice.org.uk/Guidance/TA312 Accessed March 4, 2021.
3. National Institute for Health and Care Excellence (NICE) Ocrelizumab for treating primary progressive multiple sclerosis. June 2019. https://www.nice.org.uk/guidance/ta585 Accessed March 4, 2021.
4. National Institute for Health and Care Excellence (NICE) Cladribine for treating relapsing–remitting multiple sclerosis. December 2019. https://www.nice.org.uk/guidance/ta616. Accessed March 4, 2021.
5. National Institute for Health and Care Excellence (NICE) Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis. February 2020. https://www.nice.org.uk/guidance/ta624. Accessed March 4, 2021.
6. National Institute for Health and Care Excellence (NICE) Siponimod for treating secondary progressive multiple sclerosis. November 2020. https://www.nice.org.uk/guidance/ta656/resources. Accessed March 4, 2021.
7. Canadian Agency for Drugs and Technologies in Health (CADTH) Canadian Drug Expert Committee Recommendation. Siponimod Clinical Review Report. September 2020. https://www.cadth.ca/siponimod. Accessed March 4, 2021.
8. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. *N Engl J Med.* 2020;383(6):546-557.
9. KESIMPTA (ofatumumab) Injection Prescribing Information East Hanover, NJ; Novartis Pharmaceuticals 8/2020.
10. Kappos L, Fox RJ, Burcklen M, 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.
11. Shaw B CS, Kelly R, Vintro A, Anderson R, Harrod C. Disease-modifying drugs for multiple sclerosis. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2020.
12. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology.* 2019;18(3):269-285.
13. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology.* 2019;92(10):e1029-e1040.
14. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *Jama.* 2021;325(8):765-779.
15. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014;83(3):278-286.
16. Harrison DM. In the clinic. Multiple sclerosis. *Annals of internal medicine.* 2014;160(7):ITC4-2-ITC4-18; quiz ITC14-16.
17. Inojosa H, Proschmann U, Akgün K, Ziemssen T. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *J Neurol.* 2019.
18. Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. *Handb Clin Neurol.* 2014;122:231-266.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis. *An expanded disability status scale (EDSS).* 1983;33(11):1444-1444.
20. Amato MP, Portaccio E. Clinical outcome measures in multiple sclerosis. *J Neurol Sci.* 2007;259(1-2):118-122.
21. Lavery AM, Verhey LH, Waldman AT. Outcome measures in relapsing-remitting multiple sclerosis: capturing disability and disease progression in clinical trials. *Multiple sclerosis international.* 2014;2014:262350.

22. Ebers GC, Heigenhauser L, Daumer M, Lederer C, Noseworthy JH. Disability as an outcome in MS clinical trials. *Neurology.* 2008;71(9):624-631.
23. Sormani MP, Signori A, Siri P, De Stefano N. Time to first relapse as an endpoint in multiple sclerosis clinical trials. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2013;19(4):466-474.
24. Hudgens S, Schüler R, Stokes J, Eremenco S, Hunsche E, Leist TP. Development and Validation of the FSIQ-RMS: A New Patient-Reported Questionnaire to Assess Symptoms and Impacts of Fatigue in Relapsing Multiple Sclerosis. *Value Health.* 2019;22(4):453-466.
25. Olek MJ. Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults. Gonazlez-Scarano F. ed. UpToDate. Waltham MUIhwucAJ.
26. Lexicomp® Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Accessed March 8, 2021.
27. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. 2020 Available at: https://www-micromedexsolutions-com.liboff.ohsu.edu Accessed March 8, 2021.
28. Nicholas JA, Edwards NC, Edwards RA, Dellarole A, Grosso M, Phillips AL. Real-world adherence to, and persistence with, once- and twice-daily oral disease-modifying drugs in patients with multiple sclerosis: a systematic review and meta-analysis. *BMC neurology.* 2020;20(1):281.
29. Landmeyer NC, Burkner PC, Wiendl H, et al. Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis: A meta-analysis. *Neurology.* 2020;94(22):e2373-e2383.
30. Sellner J, Rommer PS. Immunological consequences of "immune reconstitution therapy" in multiple sclerosis: A systematic review. *Autoimmunity Reviews.* 2020;19(4):102492.
31. TYSABRI (natalizuamb) Intravenous Injection Prescribing Information Cambridge, MA; Biogen Inc. June 2020.
32. COPAXONE (glatiramer) Subcutaneous Injection Prescribing Information Parsippany, NJ; Teva Pharmaceuticdals USA, Inc. July 2020.
33. Cheshmavar M, Mirmosayyeb O, Badihian N, Badihian S, Shaygannejad V. Rituximab and glatiramer acetate in secondary progressive multiple sclerosis: A randomized clinical trial. *Acta Neurologica Scandinavica.* 2021;143(2):178-187.
34. ARZERRA (ofatumumab) Intravenous Injection Prescribing Information Research Triangle Park, NC; GlaxoSmith Kline 10/2009.
35. PONVORY (ponesimod) Tablet Prescribing Information. Titusville, NJ; Janssen Pharmaceutical Companies. March 2021.
36. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Neurology.* 2014;13(3):247-256.
37. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* 2011;365(14):1293-1303.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
glatiramer acetate	COPAXONE	SUB-Q	SYRINGE	Y
interferon beta-1a	AVONEX PEN	INTRAMUSC	PEN IJ KIT	Y
interferon beta-1a	AVONEX	INTRAMUSC	SYRINGEKIT	Y
interferon beta-1a/albumin	AVONEX	INTRAMUSC	KIT	Y
interferon beta-1a/albumin	REBIF REBIDOSE	SUB-Q	PEN INJCTR	Y
interferon beta-1a/albumin	REBIF	SUB-Q	SYRINGE	Y
interferon beta-1b	BETASERON	SUB-Q	KIT	Y
interferon beta-1b	EXTAVIA	SUB-Q	KIT	Y
alemtuzumab	LEMTRADA	INTRAVEN	VIAL	N
cladribine	MAVENCLAD	ORAL	TABLET	N
dalfampridine	AMPYRA	ORAL	TAB ER 12H	N
dalfampridine	DALFAMPRIDINE ER	ORAL	TAB ER 12H	N
dimethyl fumarate	DIMETHYL FUMARATE	ORAL	CAPSULE DR	N
dimethyl fumarate	TECFIDERA	ORAL	CAPSULE DR	N
diroximel fumarate	VUMERITY	ORAL	CAPSULE DR	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	N
glatiramer acetate	COPAXONE	SUB-Q	SYRINGE	N
glatiramer acetate	GLATIRAMER ACETATE	SUB-Q	SYRINGE	N
glatiramer acetate	GLATOPA	SUB-Q	SYRINGE	N
interferon beta-1b	BETASERON	SUB-Q	VIAL	N
interferon beta-1b	EXTAVIA	SUB-Q	VIAL	N
monomethyl fumarate	BAFIERTAM	ORAL	CAPSULE DR	N
ocrelizumab	OCREVUS	INTRAVEN	VIAL	N
ofatumumab	KESIMPTA PEN	SUB-Q	PEN INJCTR	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAP DS PK	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAPSULE	N
peginterferon beta-1a	PLEGRIDY PEN	SUB-Q	PEN INJCTR	N
peginterferon beta-1a	PLEGRIDY	SUB-Q	SYRINGE	N
siponimod	MAYZENT	ORAL	TAB DS PK	N
siponimod	MAYZENT	ORAL	TABLET	N
teriflunomide	AUBAGIO	ORAL	TABLET	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	
Ponesimod	PONVORY	ORAL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Cheshmavar M, Mirmosayyeb O, Badihian N, Badihian S, Shaygannejad V.

Rituximab and glatiramer acetate in secondary progressive multiple sclerosis: randomized clinical trial. *Acta Neurologica Scandinavica.* 2021;143(2):178-187.[33]

BACKGROUND: Treatment options for secondary progressive multiple sclerosis (SPMS) are limitedly investigated. We aimed to compare the efficacy of rituximab (RTX) and glatiramer acetate (GA) in SPMS patients.

METHOD: This open, randomized clinical trial was conducted on 84 SPMS patients, assigned to receive RTX or GA for 12 months. In RTX group, patients received 1 g intravenous RTX primarily and then every 6-months. In GA group, patients received 40 mg of GA 3-times/week subcutaneously. We measured EDSS as the primary outcome and neuroimaging findings, relapse rate (RR), and side effects as the secondary outcomes.

RESULTS: Seventy-three patients completed the study (37 and 36 in RTX and GA groups, respectively). The mean EDSS increased from 3.05 +/- 1.01 to 4.14 +/- 0.91 in RTX group ($p < 0.001$) and from 3.22 +/- 1.20 to 4.60 +/- 0.67 in GA group ($p < 0.001$). No statistically significant difference was observed in EDSS between two groups ($F(1, 67) = 3.377$; $p = 0.071$). The number of active lesions in brain and cervical spine decreased with no difference between groups ($p > 0.05$). Also, RR decreased in both groups without significant difference between them ($F(1, 67) = 0.390$; $p = 0.534$). Non-serious complications were observed in both groups.

CONCLUSION: Neither RTX nor GA affects EDSS in SPMS patients. They are equally effective in the relapse control of these patients.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 3 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to February 26, 2021

1 exp Glatiramer Acetate/	1359
2 exp Interferon-beta/	8808
3 alemtuzumab.mp.	2925
4 exp Fingolimod Hydrochloride/	2248
5 ocrelizumab.mp.	349
6 peginterferon beta.mp.	59
7 teriflunomide.mp.	453
8 exp cladribine	1241
9 Dimethyl Fumarate/or diroximel fumarate.mp or Fumarates	3241
10 dalfampridine.mp or 4-aminopyridine	2523
11 monomethyl fumarate.mp	72
12 ofatumumab.mp	532
13 ozanimod.mp or Sphingosine 1 Phosphate Receptor Modulators/	120
14 siponimod.mp	109
15 teriflunomide.mp	453
16 exp Multiple Sclerosis	44227
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	22333
18 17 and 16	5956
19 limit 18 to (humans and yr="2020 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	49

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KESIMPTA safely and effectively. See full prescribing information for KESIMPTA.

KESIMPTA® (ofatumumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
KESIMPTA is a CD20-directed cytolytic antibody indicated 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. (1)

----------DOSAGE AND ADMINISTRATION----------
- Hepatitis B virus (HBV) and quantitative serum immunoglobulins screening are required before the first dose. (2.1)
- Administer KESIMPTA by subcutaneous injection only. (2.2, 2.3)
- Initial Dosing: 20 mg administered at Week 0, 1, and 2. (2.2)
- Subsequent Dosing: 20 mg administered monthly starting at Week 4. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 20 mg/0.4 mL solution in a single-dose prefilled Sensoready® pen (3)
- Injection: 20 mg/0.4 mL solution in a single-dose prefilled syringe (3)

----------CONTRAINDICATIONS----------
- Active HBV infection. (4)

----------WARNINGS AND PRECAUTIONS----------
- Infections: Delay KESIMPTA administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with KESIMPTA and after discontinuation, until B-cell repletion. (5.1)
- Injection-Related Reactions: Management for injection-related reactions depends on the type and severity of the reaction. (5.2)
- Reduction in Immunoglobulins: Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with KESIMPTA until B-cell repletion. Consider discontinuing KESIMPTA if a patient develops a serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise. (5.3)
- Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping KESIMPTA. (5.4, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than 10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PONVORY safely and effectively. See full prescribing information for PONVORY.

PONVORY™ (ponesimod) tablets, for oral use
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------

PONVORY is a sphingosine 1-phosphate receptor modulator indicated 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. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assessments are required prior to initiating PONVORY (2.1)
- Titration is required for treatment initiation (2.2)
- The recommended maintenance dosage is 20 mg taken orally once daily (2.2)
- First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg (3)

----------CONTRAINDICATIONS----------

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure (4)
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: PONVORY may increase the risk of infections. Obtain a complete blood count (CBC) before initiating treatment. Monitor for infection during treatment and for 1-2 weeks after discontinuation. Do not start PONVORY in patients with active infection. (5.1)
- Bradyarrhythmia and Atrioventricular Conduction Delays: PONVORY may result in a transient decrease in heart rate; titration is required for treatment initiation. Check an electrocardiogram (ECG) to assess for preexisting cardiac conduction abnormalities before starting PONVORY. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate. (5.2, 7.2, 7.3)
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated. (5.3)
- Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating PONVORY. (5.4)
- Increased Blood Pressure (BP): Monitor BP during treatment. (5.5)
- Cutaneous Malignancies: Periodic skin examination is recommended. (5.6)
- Fetal Risk: Women of childbearing potential should use effective contraception during and for 1 week after stopping PONVORY. (5.7)
- Macular Edema: An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking PONVORY. Diabetes mellitus and uveitis increase the risk. (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence at least 10%) are upper respiratory tract infection, hepatic transaminase elevation, and hypertension. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Vaccines: Avoid live *attenuated* vaccines during and for up to 1-2 weeks after treatment with PONVORY (7.4)
- Strong CYP3A4 and UGT1A1 Inducers: Coadministration with PONVORY is not recommended. (7.5)

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment: PONVORY is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2021

Ofatumumab (Kesimpta™)

Goal(s):

- Restrict drug use to patient populations in which the drug has been shown to be effective and safe.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Kesimpta™ (ofatumumab) pharmacy or physician administered claims
- Requests for Arzerra™ should be reviewed under the Oncology PA.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication FDA-approved or compendia-supported for the requested indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient of childbearing potential?	**Yes:** Go to #7	**No:** Go to #9

Approval Criteria		
7. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Has the patient failed trials for at least 2 drugs indicated for the treatment of relapsing multiple sclerosis?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the drug prescribed by or in consultation with a neurologist?	**Yes**: Approve ofatumumab 20 mg SC at week 0, 1 and 2 followed by 20 mg once monthly starting at week 4 for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *6/21 (DM)*
Implementation: *7/1/2021*

Dalfampridine

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization:

- Up to 12 months

Requires PA:

Dalfampridine

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Multiple Sclerosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy previously approved by the FFS program (patient has completed 2-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Does the patient have moderate or severe renal impairment (est. GFR <50 mL/min)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7

Approval Criteria		
7. Is the patient ambulatory with a walking disability requiring use of a walking aid **OR;** have moderate ambulatory dysfunction and does not require a walking aid AND able to complete the baseline timed 25-foot walk test between 8 and 45 seconds?	**Yes:** Approve initial fill for 2-month trial.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking dalfampridine for ≥2 months with documented improvement in walking speed while on dalfampridine (≥20% improvement in timed 25-foot walk test)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Clinical Notes:

- Because fewer than 50% of MS patients respond to therapy and therapy has risks, a trial of therapy should be used prior to beginning ongoing therapy.
- The patient should be evaluated prior to therapy and then 4 weeks to determine whether objective improvements which justify continued therapy are present (i.e. at least a 20% improvement from baseline in timed walking speed).
- Dalfampridine is contraindicated in patients with moderate to severe renal impairment.
- Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.

P&T Review: *6/21(DM); 8/20 (DM); 6/20; 11/17; 5/16; 3/12*
Implementation: *8/16, 9/1/13*

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying multiple sclerosis drugs
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 6 months

Requires PA:
- All oral MS therapy including:
  - Sphingosine 1-phosphate receptor modulators (e.g. fingolimod, ozanimod, ponesimod, siponimod, etc.)
  - Teriflunomide
  - Fumarate salts (e.g., dimethyl fumarate, monomethyl fumarate, diroximel fumarate, etc.)
  - Cladribine

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1b, glatiramer acetate, interferon beta-1a, natalizumab, ofatumumab, ocrelizumab, or mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #7
7. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the prescription for teriflunomide?	**Yes:** Go to #9	**No:** Go to #12
9. Is the patient of childbearing potential?	**Yes:** Go to #10	**No:** Approve for up to 6 months.
10. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #13	**No:** Go to #16

Approval Criteria		
13. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #14
14. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #15	**No:** Go to #19
15. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Go to #19	**No:** Pass to RPh. Deny; medical appropriateness.
16. Is the prescription for a fumarate product?	**Yes:** Go to # 17	**No:** Go to #18
17. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
18. Is the request for cladribine?	**Yes:** Go to #19	**No:** Go to #22
19. Is the patient of child bearing potential?	**Yes:** Go to #20	**No:** Go to #22
20. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #21
21. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.
22. Has the patient had an inadequate response to or they are unable to tolerate alternative MS treatment?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1. Dosing And FDA-Approved Indications for Oral MS Drugs

Generic Name	**FDA Indication (Adults unless otherwise indicated)**		
	CIS	**RRMS**	**SPMS**
Cladribine		X	X
Fingolimod	X *(≥ 10 years)*	X *(≥ 10 years)*	X *(≥ 10 years)*
Siponimod	X	X	X
Ozanimod	X	X	X
Ponesimod	X	X	X
Teriflunomide	X	X	X
Dimethyl Fumarate	X	X	X
Monomethyl Fumarate	X	X	X
Diroximel Fumarate	X	X	X
Abbreviations: CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis			

Table 2. FDA-recommended Baseline Safety Assessments (see clinical notes for details)

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Varicella Zoster Antibodies	CYP2C9 genotype	Other Screening
Fumarate salts		X	X (>500)				
Fingolimod*	X	X	X	X	X		
Ozanimod*	X	X	X	X	X		
Ponesimod	X	X	X	X	X		

Siponimod*	X	X	X	X	X	X	
Teriflunomide	X (box warning)	X (box warning)	X				
Cladribine	X (box warning)	X	X (WNL)		X		TB; HBV; HIV; HCV; MRI for PML
Abbreviations: HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; WNL = within normal limits							

* sphingosine 1-phosphate receptor modulators

Sphingosine 1-Phosphate Receptor Modulators (fingolimod, ozanimod, ponesimod, siponimod) Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for 4 to 6 hours after initial dose in a clinically appropriate area (fingolimod, ponesimod, siponimod).
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod, ozanimod, ponesimod, or siponimod with caution. A cardiology evaluation should be performed before considering treatment.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod, ozanimod, ponesimod, or siponimod initiation with subsequent evaluations based on clinical symptoms.
- Patients starting on siponimod therapy must be tested for CYP2C9 variants to determine CYP2C9 genotype before starting siponimod. Siponimod is contraindicated in patients with a CYP2C9*3/*3 genotype. The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg. The recommended maintenance dosage in all other patients is 2 mg.

Teriflunomide Clinical Notes:

- Before starting teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in individuals of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting teriflunomide, monitor ALT levels at least monthly for 6 months. Consider additional ALT monitoring when teriflunomide is given with other potentially hepatotoxic drugs. Consider stopping teriflunomide if serum transaminase levels increase (>3-times the upper limit of normal). Monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue teriflunomide and start accelerated elimination in those with suspected teriflunomide-induced liver injury and monitor liver tests weekly until normalized. Check blood pressure periodically and manage hypertension. Check serum potassium level in teriflunomide-treated patients with hyperkalemia symptoms or acute renal failure. Monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from teriflunomide to another agent with a known potential for hematologic suppression because systemic exposure to both agents will overlap.

Fumarate Salts (Dimethyl Fumarate, Monomethyl Fumarate, Diroximel Fumarate) Clinical Notes:

- Fumarate salts may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. There was no increased incidence of serious infections observed in patients

with lymphocyte counts <0.8 $x10^3$ cells/mm^3 (equivalent to <0.8 cells/µL). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Fumarate salts should be held if the WBC falls below 2 $x10^3$ cells/mm^3 or the lymphocyte count is below 0.5 $x10^3$ cells/mm^3 (cells/µL) and permanently discontinued if the WBC did not increase to over 2 $x10^3$ cells/mm^3 or lymphocyte count increased to over 0.5 $x10^3$ cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored every 6 to 12 months.

Cladribine Clinical Notes:
- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Prior to initiating cladribine follow standard cancer screening guidelines because of the risk of malignancies.
- Obtain a CBC with differential including lymphocyte count. Lymphocytes must be: within normal limits before initiating the first treatment course and at least 800 cells per microliter before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with cladribine.
- Infection screening: exclude HIV infection, perform TB and hepatitis screening. Evaluate for active infection; consider a delay in cladribine treatment until any acute infection is fully controlled.
- Administer all immunizations according to immunization guidelines prior to starting cladribine. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting cladribine.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

P&T/DUR Review: *6/21 (DM); 8/20 (DM); 6/20; 11/17; 11/16; 9/15; 9/13; 5/13; 3/12*
Implementation: *9/1/20; 1/1/18; 1/1/17; 1/1/14; 6/21/2012*

Ocrelizumab (Ocrevus™)

Goal(s):

- Restrict use of ocrelizumab in patients with relapsing-remitting multiple sclerosis (RRMS) to those who have failed multiple drugs for the treatment of RRMS.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Ocrevus™ (ocrelizumab) pharmacy or physician administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
12. What diagnosis is being treated?	Record ICD10 code.	
13. Is the medication FDA-approved or compendia-supported for the requested indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
14. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
15. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
16. Is the patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis?	**Yes:** Go to #6	**No:** Go to #7

Approval Criteria		
17. Has the patient failed trials for at least 2 drugs indicated for the treatment of relapsing multiple sclerosis?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
18. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
19. Is the drug prescribed by or in consultation with a neurologist who regularly treats multiple sclerosis?	**Yes**: Approve ocrelizumab 300 mg every 2 weeks x 2 doses followed by 600mg IV every 6 months for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1.Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *6/21(DM); 6/20; 11/17 (DM); 1/17*
Implementation: *7/1/20; 1/1/18; 4/1/17*

Peginterferon Beta-1a (Plegridy®)

Goal(s):

- Approve therapy for covered diagnosis that are supported by the medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.
3. Will the prescriber consider a change to a Preferred MS product?	**Yes:** Inform provider of covered alternatives in the class.	**No:** Go to #4.
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny for medical appropriateness.
5. Does the patient have any of the following: • Adherence issues necessitating less frequent administration • Dexterity issues limiting ability to administer subcutaneous injections	**Yes:** Approve for up to one year.	**No:** Pass to RPH; Deny for medical appropriateness.

P&T / DUR Action: *6/21(DM); 8/20 (DM); 6/20; 11/17; 9/23/14*
Implementation: *10/15*

Author: Moretz Date: June 2021

Natalizumab (Tysabri®)

Goal(s):

- Approve therapy for covered diagnosis which are supported by the medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Natalizumab (Tysabri®)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Has the patient been screened for John Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness
3. Does the patient have a diagnosis of relapsing multiple sclerosis (CIS, RRMS, or SPMS)?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny for medical appropriateness.
6. Does the patient have Crohn's Disease?	**Yes:** Go to #7	No: Pass to RPH; Deny for medical appropriateness.
7. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #8	**No:** Pass to RPH; Deny for medical appropriateness**.**
8. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • Has the patient tried and failed a 3 month trial of Humira?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.

P&T / DUR Action: *6/21(DM); 10/20 (DM); 11/17*
Implementation: *1/1/18*