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Drug Class Update: Multiple Sclerosis

Date of Review: October 2022

Date of Last Review: June 2021
Dates of Literature Search: 03/01/2021 – 06/23/2022

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

Plain Language Summary:

- Should the Oregon Health Authority change the current policy for multiple sclerosis (MS) medicines based on new available evidence?
- Multiple sclerosis (MS) is a condition where the body's immune system, which defends the body against disease and infection, mistakenly attacks the brain and spinal cord. This damage can cause many problems such as pins and needles pain, blurred vision, and trouble with balance and walking. These are called symptoms of MS. MS is a lifelong condition, and these symptoms can cause serious disability.
- There are several types of MS. Most people have “attacks” when new symptoms develop or existing symptoms worsen (called a relapse), followed by periods with no changes to their symptoms (called remittance). This type of MS is called relapsing-remitting MS. But some people’s symptoms may slowly and continually worsen. When symptoms change from occasional relapses to symptoms that continue to get worse over time, this is called secondary progressive MS. In primary progressive MS, people's symptoms gradually worsen over time.
- There are many medicines that the Food and Drug Administration has approved to treat MS. Medicines to treat MS include ocrelizumab, siponimod, ozanimod, and fingolimod. New evidence shows:
    - Ocrelizumab reduces the number and severity of relapses and slows the worsening of symptoms in relapsing-remitting MS and primary progressive MS. Evidence shows that ocrelizumab probably has the same side effects as interferon beta-1a. Interferon beta-1a is a medicine which is the standard treatment for MS.
    - It is not clear if siponimod is an effective treatment for people with relapsing-remitting MS, or if it causes serious side effects because the studies were pretty short. But studies of up to 6 months show that siponimod may reduce relapses and may help prevent disability of people with MS.
    - People taking siponimod, ozanimod, and fingolimod may have side effects such as a slow heart rate or high blood pressure compared to other medicines used to treat MS such as interferon beta, glatiramer acetate, or natalizumab. People taking fingolimod may also have an increased risk of unwanted infections.
- No changes are recommended for the current policy based on new evidence. Current policy is to prefer glatiramer and interferon products and not require prior authorization. Prior authorization is required for all oral medications used to treat MS, as well as ocrelizumab and natalizumab which are administered by a provider in a health care setting. Peginterferon and ofatumumab, which can be self-injected, also require prior authorization.

Purpose for Class Update:
Evidence for the comparative effectiveness of disease modifying drugs (DMDs) for MS was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in June 2021. This review examines new comparative evidence of DMDs for MS published since March 2021.

Research Questions:
1. What is the comparative effectiveness and efficacy of DMDs for management of different forms of MS?
2. Do DMDs for MS differ in harms?
3. Are there patients with MS, based on demographics characteristics (i.e., age, race, ethnicity, gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer adverse events?

Conclusions:
- Four high-quality systematic reviews,[1-4] four National Institute for Care and Excellence (NICE) guidelines,[5-8] and two Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[9,10] have been published since the previous P & T Committee review in 2021.
- A 2022 Cochrane review evaluated the benefits, harms, and tolerability of ocrelizumab in patients with relapsing-remitting MS (RRMS) and primary progressive (PPMS).[1] For patients with RRMS, ocrelizumab probably results in a large reduction in relapse rate and little to no difference in adverse events (AEs) when compared with interferon beta-1a at 96 weeks (based on moderate-certainty evidence).[1] Ocrelizumab may result in a large reduction in disability progression, treatment discontinuation caused by AEs, and may result in little to no difference in serious AEs (low-certainty evidence) in patients with RRMS.[1] For patients with PPMS, ocrelizumab probably results in a higher rate of AEs when compared with placebo for at least 120 weeks (moderate-certainty evidence).[1] Ocrelizumab may result in a reduction in disability progression and little to no difference in serious AEs and treatment discontinuation caused by AEs (based on low-certainty evidence).[1]
- A 2021 Cochrane review assessed the benefits and adverse effects of siponimod for patients diagnosed with MS.[2] There is low-certainty evidence to support use of siponimod 2 mg daily to reduce the annualized relapse and improve worsening of disability at 6 months versus placebo based on randomized controlled trials (RCTs).[2]
- A 2021 systematic review evaluated the risk of cardiovascular AEs in patients with MS treated with sphingosine-1-phosphate (S1P) receptor modulators.[3] A total of 8,157 were treated with S1P receptor modulators and 5,138 were treated with a placebo or other active DMD (interferon beta, glatiramer acetate, or natalizumab).[3] The overall rate of cardiovascular AEs was 10.9% in the S1P receptor modulator-treated group versus 4.8% in the control group (relative risk [RR] 2.21; 95% confidence interval [CI], 1.58–3.10; moderate quality evidence).[3]
- A 2021 systematic review sought to determine the risk of infection in patients with MS treated with fingolimod. Compared with the control (placebo, interferon beta, glatiramer, and natalizumab), fingolimod significantly increased the risk of infection (RR 1.16; 95% CI, 1.07 to 1.27; moderate quality evidence).[4] Fingolimod use was associated with a higher risk of lower respiratory and herpes virus infection.[4]
- There is insufficient evidence to identify subgroups of patients with MS based on specific demographic characteristics (i.e., age, race, ethnicity or gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer AEs.
- NICE recommends diroximel fumarate as a first-line DMD treatment option in adults with active RRMS (defined as 2 clinically significant relapses in the previous 2 years) if they do not have highly active or rapidly evolving severe RRMS.[5] Dimethyl fumarate is not recommended for people with highly active or rapidly evolving severe RRMS due to lack of evidence.[5]
- NICE recommends ponesimod for treating RRMS in adults with active disease defined by clinical or imaging features based on evidence that shows people who take ponesimod have fewer relapses than people who take teriflunomide.[6]

- NICE and CADTH do not recommend ozanimod for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations given the uncertainty of clinical effectiveness relative to other DMDs.[7],[10]
- NICE concluded that in people with RRMS, ofatumumab reduces the number of relapses and slows disease progression when compared with teriflunomide.[8] NICE recommends ofatumumab as an option for treating RRMS in adults with active disease defined by clinical or imaging features.[8]
- CADTH recommends ofatumumab in adults with RRMS if the patient has an Expanded Disability Status Scale (EDSS) score of less than 6 and evidence of active disease.[9]

Recommendations:
- No changes to the Preferred Drug List (PDL) based on clinical evidence are warranted.
- Revise PA criteria for oral MS drugs to remove trial and failure of two drugs indicated for treatment of MS.
- Consolidate PAs for peginterferon, ocrelizumab, and ofatumumab into one document.
- Retire PA criteria for peginterferon, ocrelizumab, and ofatumumab.
- After comparing medication costs in the executive session, make peginterferon preferred on the PDL.

Summary of Prior Reviews and Current Policy:
- At the June 2021 P&T Committee meeting, evidence for ofatumumab, ponesimod and other DMDs for MS was reviewed. Clinical prior authorization (PA) criteria was updated to include both medications.
- The PDL status of MS drugs is presented in **Appendix 1**. During the second quarter of 2022, 5 fee-for-service (FFS) patients had pharmacy claims processed for MS drugs. All of the claims were for the nonpreferred medications fingolimod (32%), dimethyl fumarate (11%), ofatumumab (21%), and peginterferon beta-1A (21%).

Background:
Multiple sclerosis is a chronic, immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination, and neuronal destruction which results in progressive, irreversible disability.[11] Common neurological manifestations of MS include optic neuritis, diplopia, sensory loss, limb weakness, gait ataxia, loss of bladder control, and cognitive dysfunction.[11] The mean age of diagnosis is 32 years, with most patients presenting with periodic neurological relapses.[11,12] One to two decades after onset, many patients with MS enter a progressive phase of the disease.[11] The prevalence of MS worldwide is approximately 36 per 100,000 people and more commonly impacts women (female to male sex distribution of nearly 2:1).[12] In 2020, the estimated number of people with MS was estimated as 2.8 million.[12] Greater sun exposure and higher vitamin D levels are postulated to protect against MS.[11] North Africa, sub-Saharan Africa, Latin America, Asia, Oceania, and the Middle East have the lowest incidence of MS.[11] The populations with the highest prevalence of MS are at higher latitudes including North America and Western Europe.[11]

Diagnosis of MS is based on a combination of history, examination, radiographic findings (e.g., MRI), and laboratory findings (e.g., cerebrospinal fluid–specific oligoclonal bands), which are components of the 2017 McDonald Criteria.[13] The diagnosis of MS is defined by demonstration of MS disease characteristics in space and time.[13] Dissemination in space refers to the presence of lesions in distinct CNS locations.[13] Dissemination in time refers to the development of new lesions over time or multiple distinct clinical attacks.[13] Four distinct MS clinical courses have been identified: Clinically Isolated Syndrome (CIS), Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS), and Primary Progressive MS (PPMS).[14] 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.[15] Secondary progressive MS begins as RRMS, but gradual worsening of neurologic symptoms is observed over time.[16] After 15 to 20 years, about 65% of RRMS patients enter the secondary progressive phase.[15] 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.[17] Primary progressive MS is distributed more equally between men and women than RRMS.[17] Most clinical evidence resides with 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, number of relapses, and MRI activity.[13] The Expanded Disability Status Scale (EDSS) was developed to provide a standardized measure of neurological impairment in MS.[18] 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.[18] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[19] 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.[18] 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 point when the score is between 0 and 5.5.[20] Trials with durations of at least 1 year and with 1-2 point changes in the EDSS scores may better identify patients with sustained disability.[21]

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 and which occur at least 30 days after the onset of a preceding event.[20] However, the probability of relapse is not a consistent function and often decreases over time. Patients who get enrolled in a clinical trial at the time of MS diagnosis have higher probability for relapse.[20] In order to have enough power to detect a significant reduction in relapses, clinical trials may need to evaluate efficacy date for at least 1 year. It is likely more meaningful when a trial evaluates the total number of relapses over a longer period of time.[22] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[22] In addition to clinical measures, radiographic measures of disease progression include the development of new T2 lesions, enlarging T2 lesions, or both.[13]

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 related to 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.[23] All DMDs modulate the immune system through various mechanisms that include sequestration of lymphocytes, interference with DNA synthesis in lymphocytes, depletion of immune cells, or changes in cytokine secretion pattern.[13] The FDA-approved DMDs for MS include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate (S1P) receptor modulators, fumarates, cladribine, and monoclonal antibodies. Efficacy rates of DMDs, defined by reduction in annualized relapse rates compared with placebo or active comparators, range from 29% to 68%.[13]

The two primary treatment approaches for relapsing MS are based on balancing the risks and efficacy of DMDs.[13] 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.[13] This approach minimizes risks but may result in undertreatment, defined as breakthrough disease and accumulated disability.[13] An alternative option is to initiate a medication with higher potency, such as ocrelizumab or natalizumab, at the time of diagnosis.[13] The rationale for this treatment

approach is to provide better relapse control and delay accumulation of disability.[13] 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.[13] The DMDs approved for the treatment of MS are presented in **Table 1**.

Table 1: FDA-Approved Disease-Modifying Drugs used to manage Multiple Sclerosis[24,25]

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 Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (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.

New Systematic Reviews

Cochrane Systematic Review: Ocrelizumab for Multiple Sclerosis

A 2022 Cochrane review evaluated the benefits, harms, and tolerability of ocrelizumab in people with RRMS and PPMS.[1] Literature was searched through October 2021 for RCTs involving adults diagnosed with RRMS or PPMS according to the McDonald criteria, comparing ocrelizumab alone or associated with other medications, at the approved dose of 600 mg every 24 weeks for any duration, versus placebo or any other active drug therapy.[1] Four RCTs met inclusion criteria.[1] The overall population included 2551 patients; 1370 treated with ocrelizumab 600 mg and 1181 treated with controls.[1] Among the controls, 298 patients received placebo and 883 received interferon beta-1a.[1] The treatment duration was 24 weeks in one study, 96 weeks in 2 studies, and at least 120 weeks in one study.[1] One study was at high risk of allocation concealment and blinding of participants and personnel; all 4 studies were at high risk of bias for incomplete outcome data.[1] Primary outcomes included the number of patients experiencing at least one relapse at one year, number of patients experiencing disability progression at 24 to 96 weeks, and the number of patients experiencing AEs, serious AEs, or treatment discontinuation caused by AEs.[1]

For RRMS, ocrelizumab was associated with a lower relapse rate versus interferon beta-1a (RR 0.61; 95% CI, 0.52 to 0.73; 2 studies, n=1656; moderate-certainty evidence) and a lower number of participants with disability progression (hazard ratio (HR) 0.60; 95% CI, 0.43 to 0.84; 2 studies, n=1656; low-certainty evidence).[1] No difference in AEs (RR 1.00; 95% CI, 0.96 to 1.04; 2 studies, n=1651; moderate-certainty evidence) or serious AE (RR 0.79; 95% CI 0.57 to 1.11; 2 studies, n=1651; low-certainty evidence) were found between the groups. A lower number of participants discontinued treatment from an AE with ocrelizumab therapy versus interferon beta-1a (RR 0.58; 95% CI, 0.37 to 0.91; 2 studies, n=1651; low-certainty evidence).[1]

For PPMS, ocrelizumab was associated with a lower number of participants with disability progression versus placebo (HR 0.75; 95% CI, 0.58 to 0.98; 1 study, n=731; low-certainty evidence).[26] A higher number of patients with any AEs were observed in patients receiving ocrelizumab versus placebo (RR 1.06; 95% CI, 1.01 to 1.11; 1 study, n=725; moderate-certainty evidence). No difference any serious AE (RR 0.92; 95% CI, 0.68 to 1.23; 1 study, n=725; low-certainty evidence) or the number of participants who discontinued treatment from an AE (RR 1.23; 95% CI, 0.55 to 2.75; 1 study, n=725; low-certainty evidence) were found for at least 120 weeks.[1] The most common AEs reported with ocrelizumab were infusion-related reactions, nasopharyngitis, urinary tract infections, and upper respiratory tract infections.[1]

In summary, ocrelizumab probably reduces the relapse rate with little difference in AEs versus interferon beta-1a for people with RRMS over 96 weeks (moderate-certainty evidence).[1] Ocrelizumab may reduce disability progression and result in less treatment discontinuation than interferon beta-1a in people with RRMS with little difference in serious AEs (low-certainty evidence).[1] In patients with PPMS, ocrelizumab may reduce disability progression, but it is associated with higher rates of AEs versus placebo over 120 weeks (moderate-certainty evidence) without much difference in serious AEs or treatment discontinuation from AEs (low-certainty evidence).[1]

Cochrane Systematic Review: Siponimod for Multiple Sclerosis

A 2021 Cochrane review assessed the benefits and AEs of siponimod for adults diagnosed with MS.[2] The literature search was completed through September 2021.[1] Any RCT that evaluated siponimod versus placebo or active comparator met selection critiera.[2] There were no restrictions on dose or administration frequency.[2] Two studies (n=1948) met selection criteria which compared siponimod with placebo in patients with SPMS (n=1651) and RRMS (n=297).[2] Both studies had a high risk of bias due to selective reporting and attrition.[2] Primary outcomes included the number of patients experiencing new relapses, the number of patients who experienced disability worsening as measured by the EDSS, and the number of patients who withdrew due to any AE.[2]

Only one RCT assessed the number of patients who experienced at least one relapse at 6 months.[2] Overall, the risk of new relapse in patients receiving 10 mg, 2 mg and 0.5 mg siponimod was 18%, 10.2% and 23.3% respectively.[2] To investigate the effect these doses, a subgroup analysis was performed which did not find

difference between 0.5 mg and 10 mg of siponimod (RR 0.87; 95% CI, 0.42 to 1.81 and RR 0.68; 95% CI, 0.31 to 1.45, respectively.[2] Siponimod 2 mg reduced disability progression at 6 months versus placebo (56 fewer people per 1000; RR 0.78; 95% CI, 0.65 to 0.94; 1 study, n=1641; low-certainty evidence) and reduced the annualized relapse rate (RR 0.43; 95% CI, 0.34 to 0.56; 2 studies, n=1739; low-certainty evidence) but it is unknown whether siponimod 2 mg reduced the number of patients with new relapse (166 fewer people per 1000; RR 0.38, 95% CI 0.15 to 1.00; 1 study, n=94; very low-certainty evidence).[2]

No difference in AEs were observed between siponimod and placebo (14 more people per 1000; RR 1.52, 95% CI 0.85 to 2.71; 2 studies, n=1739, low-certainty evidence).[2] Both studies had high attrition bias resulting from the unbalanced reasons for dropouts among groups and high risk of bias due to conflicts of interest.[2] No difference was observed between groups in the number of patients with at least one serious AE excluding relapses (113 more people per 1000; RR 1.80, 95% CI 0.37 to 8.77; 2 studies, n=1739; low-certainty evidence) at 6 months.[2] No data were available regarding serious cardiac adverse events.[2] In terms of safety profile, the most common AEs associated with siponimod were headache, back pain, bradycardia, dizziness, fatigue, influenza, urinary tract infection, lymphopenia, nausea, alanine amino transferase increase and upper respiratory tract infection.[2]

No difference was observed in the number of patients who withdrew due to AEs at 6 months between siponimod 0.5 mg (RR 2.62; 95% CI, 0.54 to 12.77) and 2 mg dosing (RR 1.52; 95% CI, 0.85 to 2.71) versus placebo.[2] The risk of discontinuing 10 mg of siponimod due to AEs was statistically significantly higher than placebo (RR 4.50; 95% CI, 1.04 to 19.45).[2] The AEs associated with siponimod have dose-related effects and rarely led to discontinuation of treatment.[2]

In summary, it is uncertain whether siponimod is beneficial for patients with MS.[2] There was low-certainty evidence to support siponimod 2 mg daily over 6 months to reduce the annualized relapse rate and the number of patients who experienced disability worsening.[2] The certainty of the evidence of siponimod to reduce the number of people with a relapse is very low.[2] The overall body of evidence for siponimod was low to very low due to serious study limitations, imprecision and indirectness.[2] More studies with robust methodology and longer follow-up are needed to evaluate the benefit of siponimod for the management of MS and to observe long-term adverse effects.[2] Head-to-head studies would help us compare siponimod to other available therapeutics.[2]

Risk for Cardiovascular Adverse Events Associated With Sphingosine-1-Phosphate Receptor Modulators

A 2021 systematic review with meta-analysis evaluated the risk of cardiovascular AEs in patients with MS treated with S1P receptor modulators.[3] Due to extensive S1P expression on cardiomyocytes and vascular endothelial cells, all S1P receptor modulators have some cardiovascular effect.[3] Literature was searched through January 2021 to identify RCTs that used S1P receptor modulator to treat patients with MS.[3] Outcomes evaluated were overall cardiovascular AEs (including general and serious cardiovascular AEs) and specific cardiovascular AEs (any arrhythmia, bradyarrhythmia, tachyarrhythmia, hypertension, hypotension, heart failure, coronary artery disease, acute coronary syndrome, and chronic coronary syndrome).[3] Serious cardiovascular AEs were defined as life-threatening or fatal AEs, or AEs that resulted in hospitalization (or extended hospital stay if already hospitalized).[3] Seventeen RCTs (12 for fingolimod; 3 for ozanimod; 2 for siponimod) met inclusion critiera.[3] A total of 13,295 patients were enrolled, among which 8,157 were treated with S1P receptor modulators and 5,138 were treated with a placebo or other active DMD (interferon beta, glatiramer acetate, or natalizumab).[3] Of the 17 trials, 12 (70.6%) had a low risk of bias, 4 had an unclear risk of bias due to unknown random sequence generation and incomplete outcome data, and 1 had a high risk of bias due to allocation concealment and blinding issues.[3]

The rate of cardiovascular AEs was 10.9% in the S1P receptor modulator group versus 4.8% in the control group (RR 2.21; 95% CI; 1.58–3.10; I^2 =75.6%).[3] The high-risk cardiovascular AEs associated with S1P receptor modulators were bradyarrhythmia (RR 2.92; 95% CI, 1.91–4.46; I^2 =30.8%) and hypertension (RR 2.00; 95% CI, 1.49–2.67; I^2 =56.5%).[3] Subgroup analyses were consistent with the primary analysis except that ozanimod was associated with a higher risk of hypertension (RR 1.76; 95% CI, 1.10-2.82; I^2 =0.0%) and siponimod was associated with higher risk of bradyarrhythmia (RR 2.75; 95% CI, 1.75-4.31; I^2 =0.0%).[3]

In summary, S1P receptor modulators increased risk of cardiovascular AEs by 1.21 times in MS patients, and the incidence for both general and serious cardiovascular AEs were increased significantly relative to control groups.[3] Patients treated with S1P receptor modulators were at 2.92- and 2.00-fold increased risk for bradyarrhythmia and hypertension, respectively.[3] The risk for bradyarrhythmia and hypertension may not differ between S1P receptor modulators or dose used.[3] Several limitations of this study were described by the authors. First, the incidence timing, duration and severity of cardiovascular AEs between patients treated with S1P receptor modulators versus control could not be compared due to limited data.[3] The limited number of ozanimod and siponimod trials studied prevent a robust comparative analysis of all S1P receptor modulators.[3] Third, analyses are based on the data from RCTs which have carefully selected participants who are usually be younger in age, which limits the ability to evaluate patients with late-onset MS whose cardiovascular AE risk might be higher.[3]

Incidence and Risk of Infection Associated With Fingolimod in Patients With Multiple Sclerosis

A 2021 systematic review and meta-analysis sought to determine the risk of infection in patients with MS treated with fingolimod.[4] Literature was searched through April 2020 to identify RCTs that reported the occurrence of infection associated with fingolimod treatment.[4] The primary outcome of this study was the overall infection rate. Secondary outcomes included general infection, serious infection, and other different types of infection.[4] Twelve RCTs conducted over 6 weeks to 24 months and including 8,448 patients met inclusion criteria.[4] Sixty-two percent of patients were treated with fingolimod and 38% of patients were treated with a placebo or first-generation DMD (interferon beta, glatiramer, or natalizumab).[4] Of these 12 trials, all studies (6,508 patients) involved fingolimod 0.5 mg daily and four studies (1,940 patients) involved fingolimod 1.25 mg daily.[4] Most trials had low risk of bias, but four trials were at high risk of bias due to selection, performance, attrition, and reporting biases.[4]

The overall rate of infection was 55.13% (56.78% vs. 52.20% for fingolimod and control groups, respectively).[4] Fingolimod was associated with increased risk of infection versus control (RR 1.16; 95% CI, 1.07 to 1.27; I^2 =81%), regardless of whether the infection was a general infection (RR 1.14; 95% CI, 1.05 to 1.25; I^2 =78%) or serious infection (RR 1.49; 95% CI, 1.06 to 2.10; I^2 =0%).[4] Analyses of subgroups found that fingolimod increased the risk of lower respiratory infection (RR 1.48; 95% CI, 1.19 to 1.85; I^2 =0%) and herpes virus infection (RR 1.34; 95% CI, 1.01 to 1.78; I^2 =9%).[4] No dose-dependent increase in risk of infection was observed with fingolimod (0.5 mg: RR 1.15; 95% CI, 1.07 to 1.25; I^2 =91% and 1.25 mg: RR 1.11; 95% CI, 0.97 to 1.28; I^2 =81%; p=0.66).[4] In summary, fingolimod increased the risk of overall infection by 16%, including both general and serious infections. Fingolimod was associated with higher risk of lower respiratory and herpes virus infection. The risk of infection did not appear to be dose-dependent.[4]

After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[27-32] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

National Institute For Health and Care Excellence: Diroximel fumarate for Treating RRMS

NICE published guidance for the use of diroximel fumarate for treatment of RRMS in June 2022.[5] Canadian regulatory approval for diroximel fumarate was granted because it has the same active metabolite as dimethyl fumarate and pharmacokinetic analyses have demonstrated bioequivalence.[5] The NICE concluded that diroximel fumarate and dimethyl fumarate are expected to be equally effective.[5] Results from the phase 3 RCT (EVOLVE-MS-2) suggest that diroximel fumarate is associated with fewer gastrointestinal side effects than dimethyl fumarate.[5]

- Diroximel fumarate is recommended as a first-line DMD option for treatment of active RRMS (defined as 2 clinically significant relapses in the previous 2 years) in adults if they do not have highly active or rapidly evolving severe RRMS.[5] Dimethyl fumarate is not recommended for people with highly active or rapidly evolving severe MS because of lack of evidence.[5]

National Institute For Health and Care Excellence: Ponesimod for Treating RRMS

NICE published guidance for the use of ponesimod for treatment of RRMS in February 2022.[6] Clinical trial evidence shows that people on ponesimod have fewer relapses than people who take teriflunomide.[6] The effect of ponesimod on disability progression is not clear.[6] Ponesimod cannot be compared with other DMDs due to the limitations in the clinical evidence.[6] Use in pregnancy is also an important area for research and ponesimod is not indicated for pregnant women.[6] NICE concluded that ponesimod may not be the most effective treatment, but individual risks and benefits should be considered.[6]

- Ponesimod is recommended as a treatment option for RRMS in adults with active disease defined by clinical or imaging features.[6]

National Institute For Health and Care Excellence: Ozanimod for Treating RRMS

NICE published guidance for the use of ozanimod in treatment of RRMS in June 2021.[7] Clinical trial evidence shows that ozanimod reduces the number of relapses and brain lesions compared with interferon beta-1a. The effect of ozanimod on progression of disability is unclear.[7]

- Ozanimod is not recommended for treating RRMS in adults with clinical or imaging features of active disease due to high cost of treatment (United Kingdom [UK] National Health Service [NHS] data).[7]

Canadian Agency for Drugs and Technologies in Health Drug Review: Ozanimod

The CADTH recommended that ozanimod should not be recommended for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations.[10] There is insufficient evidence to determine if ozanimod offers any meaningful clinical benefits compared with other DMDs for RRMS. Direct comparative evidence for ozanimod 1 mg with DMDs other than interferon beta-1a was not identified; however, interferon beta-1a is no longer a routinely used treatment option in current clinical practice, in part because of its modest efficacy, which limits the scope of the results obtained from RADIANCE Part B and SUNBEAM studies.[10] Furthermore, limitations associated with the indirect comparison provided by the manufacturer and reviewed by CADTH precluded any conclusions regarding the comparative efficacy and safety advantages of ozanimod with other DMDs for RRMS.[10] Given the uncertainty in the clinical effectiveness of ozanimod relative to other DMDs, the cost-effectiveness of ozanimod is highly uncertain (Canada, CADTH data).[10]

National Institute For Health and Care Excellence: Ofatumumab for Treating RRMS

NICE published guidance for the use of ofatumumab in treatment of RRMS in May 2021.[8] Clinical trial evidence shows that ofatumumab reduces the number of relapses and slows disease progression in people with RRMS when compared with teriflunomide.[8] The ASCLEPIOS trials showed that ofatumumab is more effective than teriflunomide for all main clinical outcomes and had no unexpected safety concerns.[8] There is no evidence directly comparing ofatumumab with the other treatments.[8] Ofatumumab is cost effective and is an acceptable use of NHS resources (UK, NHS data).[8]

- Ofatumumab is recommended as an option for treatment of RRMS in adults with active disease defined by clinical or imaging features.[8]

Canadian Agency for Drugs and Technologies in Health Drug Review: Ofatumumab

The CADTH based their recommendation for ofatumumab on 2 randomized, double-blind, active comparator–controlled trials (ASCLEPIOS I and ASCLEPIOS II) which demonstrated that ofatumumab was superior to teriflunomide in reducing the annualized relapse rate of MS based on annualized relapse rates (RR 0.50; 95% CI, 0.37 to 0.65; P < 0.001 in ASCLEPIOS I and RR 0.42; 95% CI, 0.31 to 0.56; P < 0.001 in ASCLEPIOS II).[9]

No deaths were reported in the ASCLEPIOS I and II trials.[9] Most patients reported at least one treatment-emergent AE (82.2% vs. 82.3% in ASCLEPIOS I and 85.0% vs. 86.1% in ASCLEPIOS II for the ofatumumab and teriflunomide groups, respectively).[9] The most commonly reported AEs were injection-related reactions, nasopharyngitis, headache, and upper respiratory tract infections.[9] In both studies, injection site reactions and a decrease in blood immunoglobulin M were

reported more in the ofatumumab groups.[9] In contrast, alopecia and diarrhea were more common in patients in the teriflunomide groups.[9] Specific to each trial, upper respiratory tract infections were reported more in patients on ofatumumab versus teriflunomide in the ASCLEPIOS I trial and injection-related reactions were reported more in patients on ofatumumab versus teriflunomide in the ASCLEPIOS II trial.[9]

Ofatumumab is recommended for the treatment of adults with RRMS if the following conditions are met:

Initiation Criteria

1. Patients must have all of the following characteristics at the time of initiating treatment with ofatumumab:
    - An Expanded Disability Status Scale (EDSS) score of less than 6; and
    - Evidence of active disease defined as at least 1 of the following:
        - One relapse during the previous year; or
        - Two relapses during the previous 2 years; or
        - A positive gadolinium (Gd)-enhancing magnetic resonance imaging (MRI) scan during the year before starting treatment with ofatumumab.[9]
2. Ofatumumab should not be used in combination with other DMDs to treat MS.[9]
3. Patients must be under the care of a specialist with experience in the diagnosis and management of MS.[9]

Renewal Criteria

1. Ofatumumab may only be renewed for patients who do not exhibit evidence of disease progression since the previous assessment.[9]
2. Patients should be assessed for response to ofatumumab every 12 months.[9]
3. Patients must not have experienced more than 1 relapse in the previous year.[9]

New Formulations:

A new formulation of fingolimod lauryl sulfate (TASCENSO ODT) received FDA approval in December 2021.[33] The orally disintegrating tablets are indicated for treatment of relapsing forms of MS including CIS, RRMS, and SPMS in pediatric patients aged 10 years of age and older and weighing less than or equal to 40 kg.[33] The recommended dose in this population is 0.25 mg orally once daily, with or without food.[33] TASCENSO ODT is not approved for use in any patients who weigh more than 40 kg.[33] Pediatric patients whose weight exceeds 40 mg after starting TASCENSO ODT should be switched another fingolimod product approved for use in this population.[33]

The capsule formulation of fingolimod (GILENYA) received FDA approval for use in pediatric patients 10 years of age and older with relapsing forms of MS in December 2019.[34] The recommended dose of GILENYA is 0.25 mg once a day in patients aged 10 years and above who weigh less than or equal to 40 kg.[34] In patients 10 years of age and older who weigh more than 40 kg, the FDA-approved dose is 0.5mg once daily.[34]

Safety and effectiveness of fingolimod for the treatment of relapsing forms of multiple sclerosis in pediatric patients 10 years to less than 18 years of age were established in one randomized, double-blind clinical study in 215 patients in which the 0.25 mg fingolimod dose was compared to intramuscular interferon beta-1a (fingolimod n = 107; intramuscular interferon beta-1a n = 108).[33] Median duration of exposure to study drug was 634 days in the fingolimod group and 547 days in the interferon beta-1a group.[33] In the fingolimod group, 6.5% of patients did not complete the study, compared to 18.5% in the interferon beta-1a group.[33] The primary endpoint was the annualized relapse rate. The annualized relapse rate was lower in patients treated with fingolimod than in patients who received interferon beta-1a (0.122 vs. 0.675 respectively; $p<0.001$).[33] The safety profile in pediatric patients (10 years to less than 18 years of age) receiving

fingolimod capsules daily was similar to that seen in adult patients.[33] In the pediatric study, cases of seizures were reported in 5.6% of fingolimod-treated patients and 0.9% of interferon beta-1a-treated patients.[33]

New FDA Safety Alerts:

The FDA issued an alert on 8/18/2022 regarding cross-compatibility issues with glatiramer acetate autoinjector devices.[35] Autoinjector devices that are optional for use with glatiramer acetate injection may not be compatible for use across FDA-approved glatiramer acetate injection drug products.[35] FDA has received reports that using an autoinjector that is not compatible with the patient's specific glatiramer acetate injection drug product has resulted in missed and partial doses.[35] Currently, there are 3 FDA-approved glatiramer acetate injection drug products on the market—all available in a single-dose prefilled syringe with an attached needle for subcutaneous administration.[35] Glatiramer acetate may be injected using only the syringe or by inserting the syringe into an autoinjector.[35] The autoinjectors are reusable, designed to facilitate injections in patients with limited dexterity, and are available by prescription separately.[35] FDA has requested that drug product manufacturers update their labeling to instruct users to confirm the autoinjector is compatible before using it to inject glatiramer acetate.[35] The FDA-approved glatiramer acetate injection drug products and their compatible autoinjector device are listed in **Table 1.** A description of additional new FDA safety alerts is presented in **Table 2**.

Table 1. Glatiramer Acetate Injection Products and Compatible Autoinjector Device (Optional for Use With Drug Product)[35]

Drug Product Name	Drug Manufacturer	Compatible Autoinjector Device
COPAXONE (glatiramer acetate)	Teva	Autoject 2
GLATOPA (glatiramer acetate)	Sandoz	Glatopa*ject*
Glatiramer acetate	Viatris/Mylan	*Whisper*JECT

Table 2. Description of new FDA Safety Alerts[36]

Generic Name	Brand Name	Month/Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Teriflunomide	AUBAGIO	4/2021	Warnings and Precautions	**Pancreatitis in Pediatric Patients** AUBAGIO is not approved for use in pediatric patients. Effectiveness of AUBAGIO for the treatment of relapsing form of multiple sclerosis in pediatric patients (10 to 17 years of age) was not established in an adequate and well-controlled clinical study in 166 patients (109 patients received once daily doses of AUBAGIO and 57 patients received placebo) for up to 96 weeks. In this pediatric clinical trial, cases of pancreatitis were observed in 1.8% (2/109) of patients receiving AUBAGIO; one of these cases was serious. If pancreatitis is suspected, discontinue teriflunomide and start an accelerated elimination procedure.
Ozanimod	ZEPOSIA	5/2021	Warnings and Precautions	**Bradyarrhythmia** In UC Study 1 and Study 3, bradycardia was reported on the day of treatment initiation in 1 patient (0.2%) treated with ZEPOSIA compared to none in patients who received placebo.

				After Day 1, bradycardia was reported in 1 patient (0.2%) treated with ZEPOSIA. In UC Study 2, bradycardia was not reported. **Liver Injury** In UC Study 1, elevations of ALT to 5-fold the ULN or greater occurred in 0.9% of patients treated with ZEPOSIA 0.92 mg and 0.5% of patients who received placebo, and in UC Study 2 elevations occurred in 0.9% of patients receiving ZEPOSIA and no patients receiving placebo. In UC Study 1, elevations of ALT to 3-fold the ULN or greater occurred in 2.6% of UC patients treated with ZEPOSIA 0.92 mg and 0.5% of patients who received placebo, and in UC Study 2 elevations occurred in 2.3% of patients and no patients, respectively. In controlled and uncontrolled UC studies, the majority (96%) of patients with ALT greater than 3-fold the ULN continued treatment with ZEPOSIA with values returning to less than 3-fold the ULN within approximately 2 to 4 weeks. Overall, the discontinuation rate because of elevations in hepatic enzymes was 0.4% in patients treated with ZEPOSIA 0.92 mg, and none in patients who received placebo in the controlled UC studies. Individuals with an AST or ALT greater than 1.5 times ULN were excluded from MS Study 1 and Study 2 and greater than 2 times the ULN for UC Study 1 and Study 3. There are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA. Use of ZEPOSIA in patients with hepatic impairment is not recommended. **Increased Blood Pressure** The mean increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in UC patients treated with ZEPOSIA is similar to patients with MS. In UC Study 1 and Study 3, the average increase from baseline in SBP was 3.7 mm Hg in patients treated with ZEPOSIA and 2.3 mm Hg in patients treated with placebo. In UC Study 2, the average increase from baseline in SBP was 5.1 mm Hg in patients treated with ZEPOSIA and 1.5 mm Hg in patients treated with placebo. There was no effect on DBP. Hypertension was reported as an adverse reaction in 1.2% of patients treated with ZEPOSIA 0.92 mg and none in patients treated with placebo in UC Study 1 and Study 3, and in 2.2% and 2.2% of patients in UC Study 2, respectively. Hypertensive crisis was reported in two patients receiving ZEPOSIA and one patient receiving placebo. **Respiratory Effects** In UC Study 1 the mean difference in decline in absolute FEV1 from baseline in patients treated with ZEPOSIA compared to patients who received placebo was 22 mL (95% CI: -84, 39) at 10 weeks. The mean difference in percent predicted normal (PPN) FEV1 at 10 weeks

				between patients treated with ZEPOSIA compared to those who received placebo was 0.8% (95% CI: -2.6, 1.0). The difference in reductions in FVC (absolute value and %-predicted) seen at Week 10 in UC Study 1, comparing patients who were treated with ZEPOSIA to those who received placebo was 44 mL, 95% CI (-114, 26); 0.5%, 95% CI (-2.3, 1.2), respectively. There is insufficient information to determine the reversibility of observed decreases in FEV1 or FVC after discontinuation of ZEPOSIA, or whether changes could be progressive with continued use.
Ozanimod	ZEPOSIA	5/2021	Warnings and Precautions	**Progressive Multifocal Leukoencephalopathy** Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. PML has been reported in patients treated with S1P receptor modulators, including ZEPOSIA, and other multiple sclerosis (MS) and UC therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation. If PML is confirmed, treatment with ZEPOSIA should be discontinued.
Peginterferon Beta-1A	PLEGRIDY	11/2021	Warnings and Precautions	**Injection Site Reactions Including Necrosis** Injection site abscesses and cellulitis have been reported in the post marketing setting with use of interferon beta. Some cases required treatment with hospitalization for surgical drainage and intravenous antibiotics. Periodically evaluate patient understanding and use of aseptic self-injection techniques and procedures, particularly if injection site necrosis has occurred.
Peginterferon Beta-1A	PLEGRIDY	03/2022	Warnings and Precautions	**Hepatic Injury** Cases of noninfectious hepatitis have been reported in the post marketing setting with use of PLEGRIDY.

Interferon Beta-1A	AVONEX	11/2021	Warnings and Precautions	**Injection Site Reactions Including Necrosis** Injection site reactions, including injection site necrosis, can occur with the use of interferon beta products, including AVONEX. In controlled clinical trials, injection site reactions (e.g., injection site pain, bruising or erythema) occurred in 18% of patients receiving AVONEX and 13% in the placebo group. These reactions included injection site inflammation (6%), injection site pain (8%), injection site mass (<1%), nonspecific reactions. Injection site abscesses and cellulitis and injection site necrosis have been reported in the post marketing setting with interferon beta products, including AVONEX. Some cases required treatment with hospitalization for surgical drainage and intravenous antibiotics. Periodically evaluate patient understanding and use of aseptic self-injection techniques and procedures, particularly if injection site necrosis has occurred. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with AVONEX after injection site necrosis has occurred, avoid administration of AVONEX into the affected area until it is fully healed. If multiple lesions occur, change injection site or discontinue therapy until healing occurs.
Alemtuzumab	LEMTRADA	01/2022	Warnings and Precautions	**Adults Onset Still's Disease** During post marketing use, Adult Onset Still's Disease (AOSD) has been reported in patients treated with LEMTRADA. AOSD is a rare inflammatory condition that requires urgent evaluation and treatment. Patients with AOSD may have a combination of the following signs and symptoms: fever, arthritis, rash, and leukocytosis in the absence of infections, malignancies, and other rheumatic conditions. Patients with manifestations of AOSD should be evaluated immediately and LEMTRADA should be discontinued if an alternate etiology for the signs or symptoms cannot be established.
Alemtuzumab	LEMTRADA	05/2022	Warnings and Precautions	**Autoimmune Encephalitis (AIE)** During post marketing use, cases of AIE have been reported in patients treated with LEMTRADA. AIE can present with a variety of clinical manifestations, including subacute onset of memory impairment, altered mental status, psychiatric symptoms, neurological findings, and seizures. LEMTRADA should be discontinued if AIE is confirmed by the presence of neural autoantibodies or an alternate etiology cannot be established.

Randomized Controlled Trials:

A total of 123 citations were manually reviewed from the initial literature search. After further review, 123 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).

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Appendix 1: Current Preferred Drug List

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

teriflunomide	AUBAGIO	ORAL	TABLET	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to June Week 3 2022, and , Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to June 23, 2022

1	exp Multiple Sclerosis/	50544
2	exp Glatiramer Acetate/	1459
3	exp Interferons/	106404
4	exp Alemtuzumab/	2201
5	exp Cladribine/	1365
6	dalfampridine.mp. or exp 4-Aminopyridine/	2612
7	exp Dimethyl Fumarate/	906
8	exp Fingolimod Hydrochloride/	2586
9	exp Fumarates/ or monomethyl fumarate.mp.	3610
10	ocrelizumab.mp.	544
11	ofatumumab.mp.	590
12	ozanimod.mp. or exp Sphingosine-1-Phosphate Receptors/	1012
13	peginterferon.mp.	6398
14	Sphingosine 1 Phosphate Receptor Modulators/ or ponesimod.mp.	190
15	siponimod.mp.	162
16	teriflunomide.mp.	694
17	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 or 16	121630
18	1 and 17	7516
19	limit 18 to (english language and humans and yr="2021 -Current")	639
20	limit 19 to (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 guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	123

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying drugs for multiple sclerosis or ulcerative colitis.
- 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 ozanimod to treat moderate-to-severe ulcerative colitis?	**Yes:** Go to #3	**No:** Go to #4

Approval Criteria		
3. Has the patient failed to respond or had an inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication these conventional therapies? AND • Has the patient tried and failed a 3-month trial of a Humira® product?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. 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 #6
6. Is the medication being prescribed by or in consultation with a neurologist or gastroenterologist (if the diagnosis is ulcerative colitis)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. 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 #8
8. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #9
9. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the prescription for teriflunomide?	**Yes:** Go to #11	**No:** Go to #14
11. Is the patient of childbearing potential?	**Yes:** Go to #12	**No:** Approve for up to 6 months.
12. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. 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 #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #15	**No:** Go to #18
15. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #16
16. 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 #17	**No:** Go to #21
17. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Go to #21	**No:** Pass to RPh. Deny; medical appropriateness.
18. Is the prescription for a fumarate product?	**Yes:** Go to # 19	**No:** Go to #20
19. 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.
20. Is the request for cladribine?	**Yes:** Go to #21	**No:** Go to #24
21. Is the patient of child bearing potential?	**Yes:** Go to #22	**No:** Go to #24
22. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #23

Approval Criteria		
23. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**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**	**Ulcerative Colitis**
Cladribine		X	X	
Fingolimod	X *(≥ 10 years)*	X *(≥ 10 years)*	X *(≥ 10 years)*	
Siponimod	X	X	X	
Ozanimod	X	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: *10/22 (DM); 10/21(DM); 8/21 (DM); 6/21 (DM); 8/20 (DM); 6/20; 11/17; 11/16; 9/15; 9/13; 5/13; 3/12*
Implementation: *1/1/2023, 1/1/2022, 9/1/20; 1/1/18; 1/1/17; 1/1/14; 6/21/2012*

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. Is a documented estimated glomerular filtration rate (eGFR) showing the product is not contraindicated? Note: Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl $\leq$ 50 mL/min)	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
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: *10/22 (DM); 6/21(DM); 8/20 (DM); 6/20; 11/17; 5/16; 3/12*
Implementation: *1/1/23, 8/16, 9/1/13*

~~Ocrelizumab (Ocrevus™) -~~ RETIRE

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		
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:** Go to #7
6. 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
7. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. 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: *10/22 (DM); 6/21(DM); 6/20; 11/17 (DM); 1/17*
Implementation: *TBD, 7/1/20; 1/1/18; 4/1/17*

~~Peginterferon Beta-1a (Plegridy®)~~ RETIRE

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.

Approval Criteria		
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: *10/22 (DM); 6/21(DM); 8/20 (DM); 6/20; 11/17; 9/23/14*
Implementation: *TBD, 10/15*

~~Ofatumumab (Kesimpta™)~~-RETIRE

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
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: *10/22 (DM); 6/21 (DM)*
Implementation: *7/1/2021*

Injectable Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of injectable or infused disease-modifying drugs for multiple sclerosis.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred injectable or infused multiple sclerosis pharmacy or physician administered claims.
- Note: Tysabri® (natalizumab) should be reviewed under separate Tysabri® PA criteria.
- Note: Requests for Arzerra™ (ofatumumab) 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.

Approval Criteria		
2. Is the request for an FDA-approved form of multiple sclerosis (see Table 1)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the drug 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., glatiramer, interferon, mitoxantrone, natalizumab, ofatumumab, ocrelizumab, or peginterferon) to treat MS?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient failed trials for at least 2 drugs indicated for the treatment of MS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the request for a drug with potential risks during pregnancy (e.g., ofatumumab or mitoxantrone)?	**Yes**: Go to #9	**No**: Approve for up to 1 year
9. Is the patient of childbearing potential?	**Yes:** Go to #10	**No:** Approve for up to 12 months
10. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11

Approval Criteria		
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:** Approve for up to 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
2. 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. FDA-Approved Indications for Injectable MS Drugs

Generic Name	Brand Name	FDA Indication			
		CIS	RRMS	SPMS	PPMS
Alemtuzumab	LEMTRADA		X	X	
Glatiramer acetate	GLATOPA, COPAXONE	X	X	X	
Interferon beta-1a	AVONEX, REBIF	X	X	X	
Interferon beta-1b	BETASERON, EXTAVIA	X	X	X	
Mitoxantrone	NOVANTRONE		X	X	
Ocrelizumab	OCREVUS	X	X	X	X
Ofatumumab	KESIMPTA	X	X	X	

Abbreviations: CIS = clinically isolated syndrome; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Table 2. FDA-recommended Baseline Safety Assessments

	LFTs	CBC	Thyroid Function Tests	Hepatitis B Virus Screening	Other Screening
Alemtuzumab	X	X	X		VZV and TB Screening, SCr, UA, up to date with all vaccinations
Glatiramer acetate					
Interferon beta-1a	X	X	X		
Interferon beta-1b	X	X	X		
Mitoxantrone	X	X			ECG and LVEF
Ocrelizumab				X	Serum immunoglobulins, up to date with all vaccinations
Ofatumumab				X	Serum immunoglobulins, up to date with all vaccinations

Abbreviations: CBC = complete blood count; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; JCV = John Cunningham Virus; LFTs = liver function tests; LVEF= left ventricular ejection fraction; PML = progressive multifocal leukoencephalopathy; Scr = serum creatinine; TB = tuberculosis; UA = urinalysis; VZV = varicella zoster virus

P&T / DUR Action: *10/22 (DM)*
Implementation: *1/1/23*

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®) pharmacy or physician administered claims

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.
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**.**

Approval Criteria		
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: *10/22 (DM); 6/21(DM); 10/20 (DM); 11/17*
Implementation: *1/1/18*