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OHSU Drug Effectiveness Review Project Summary Report – Disease-Modifying Therapies for Multiple Sclerosis: Update

Date of Review: October 2024

Date of Last Review: October 2022
Literature Search: 01/01/2020 to 7/31/2023

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

Plain Language Summary:

- Multiple sclerosis (MS) is a condition where the body's immune system mistakenly attacks the brain and spinal cord. This damage can cause many symptoms including pain, blurred vision, and trouble with balance and walking. These symptoms can cause serious disability in people with MS.
- 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 about 20 medicines approved by the U.S. Food and Drug Administration to manage MS symptoms. Some medicines can be taken by mouth and other medicines are injected under the skin or given as an intravenous infusion.
- New medicines to manage relapsing-remitting forms of MS include injectable ofatumumab (KESIMPTA), injectable ublituximab (BRIUMVY), and oral ponesimod (PONVORY). Studies that compared these medicines to teriflunomide (AUBAGIO), an oral medicine also used to manage MS, found that these new medicines decreased the number of relapses more than teriflunomide in people with relapsing-remitting MS. The studies did not show that the safety of these medicines differ, but safety information will become clearer as people begin to be treated with these medicines.
- The Oregon Health Plan (OHP) fee-for-service (FFS) Preferred Drug List (PDL) pays for many medications for MS. The new medicines will require providers to submit documentation explaining why a person needs treatment with one of these medicines. This process is called prior authorization.

Drug Effectiveness Review Project Research Questions:

1. What is the effectiveness of disease modifying drugs (DMDs) for treating MS?
2. What is the effectiveness of DMDs for people with clinically isolated syndrome (CIS)?
3. Do DMDs differ in harms by indication (MS or CIS)?
4. Do the effectiveness and harms of DMDs vary by participant demographic characteristics, use of prior DMDs for MS, type of MS, presence of comorbidities, antibody status, or route of administration?

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Conclusions:

- The March 2024 drug class report on Disease Modifying Therapies for MS by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1]
- Since the 2020 DERP report on DMDs for MS, findings from the 11 previously reviewed head-to-head comparisons have not changed.[1] Six new head-to-head comparative randomized controlled trials (RCTs) conducted in adults with relapsing forms of MS are summarized in the 2024 DERP report.[1] Oral teriflunomide was the active comparator for 5 RCTs evaluating subcutaneous (SC) ofatumumab, oral ponesimod, and intravenous (IV) ublituximab.[1] One RCT compared oral fingolimod with SC glatiramer.[1]
- Compared with teriflunomide 14 mg once daily, ofatumumab 20 mg SC every 4 weeks reduced annualized relapse rates (ARR) at 30 months (mean difference [MD], -0.13; 95% confidence interval [CI], -0.16 to -0.09; p<0.001; 2 RCTs; moderate certainty of evidence [CoE]).[1] Summaries of many older studies provide an average figure of 0.4 to 0.6 relapses per year.[2] The risk of disability worsening was lower with ofatumumab compared to teriflunomide at 6 months as measured by an increase in Expanded Disability Scale Score (EDSS) (8.1% vs. 12%; hazard ratio (HR), 0.68; 95% CI, 0.50 to 0.92; p=0.01; moderate CoE).[1] The minimal important difference for the EDSS is an increase 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.[3] The proportion of study participants who experienced disability improvement at 6 months was not found to differ between ofatumumab and teriflunomide groups (11% vs. 8.1%; HR, 1.35; 95% CI 0.95 to 1.92; p=0.09; moderate CoE).[1]
- In one RCT, ponesimod reduced ARR at 108 weeks compared with teriflunomide 14 mg once daily (mean ARR, 0.20 vs. 0.29; rate ratio, 0.70; 99% CI, 0.54 to 0.90; p<0.001; moderate CoE).[1] No differences in changes in disability as measured by changes in the EDSS; very low CoE), rates of study discontinuation (low CoE), or rates of SAEs (low CoE) were observed between the two groups.[1]
- Two RCTs showed ublituximab 450 mg IV every 6 months reduced relapse rates at 96 weeks compared with teriflunomide 14 mg once daily (MD, -0.10; 95% CI -0.17 to -0.03; p=0.005; meta-analysis of 2 RCTs; moderate CoE).[1] Ublituximab was associated with a significantly higher number of reported SAEs compared with teriflunomide at 96 weeks (10.8% vs. 7.3%; p=0.04; low CoE).[1]
- Fingolimod 0.5 mg once daily reduced relapse rates compared with glatiramer 20 mg SC once daily at 12 months (ARR, 0.15 vs. 0.26; p=0.01; one RCT; moderate CoE).[1] Fingolimod 0.5 mg also improved functional disability at 12 months compared to glatiramer as assessed by the Multiple Sclerosis Functional Composite Score (MSFC) (MD, 0.09 vs. 0.03; p=0.05).[1] No difference was observed in ARR or change in function between fingolimod 0.25 mg and glatiramer (moderate CoE).[1]
- No new evidence was identified to evaluate the comparative effectiveness of DMDs for people with CIS.[1]
- Some information on variations by subgroup was provided in the RCTs. However, it was difficult to draw robust conclusions on differences due to age, previous treatment, baseline disease severity, neutralizing antibody status, body mass, number of prior relapses, gender, disease activity, subtype of MS or type of initial treatment for CIS due to inconsistent subgroup assessments across all the trials.[1]
- Several safety label updates for this class of drugs have been recently made by the FDA (see **Table 2**).[4]

Recommendations:

- Maintain ublituximab as non-preferred on the fee-for-service (FFS) Preferred Drug List (PDL).
- Add ublituximab to the prior authorization (PA) criteria for injectable MS medications.
- Revise PA criteria in Appendix 5 for injectable MS drugs, oral MS drugs, and natalizumab.
- After review of costs in executive session, additional PDL changes were made.

Summary of Prior Reviews and Current Policy

- Evidence for the comparative effectiveness of DMDs for MS was last reviewed by the Oregon Pharmacy & Therapeutic (P&T) Committee in October 2022. The Committee made the following recommendations:
    - Revise PA criteria for oral MS drugs to remove trial and failure of two drugs indicated for treatment of MS.
    - Consolidate PAs for injectable MS drugs ocrelizumab and ofatumumab into one document.
    - Make peginterferon preferred on the PDL.
- The PDL status of MS drugs is presented in **Appendix 1**. Interferons, peginterferon, and glatiramer are preferred on the PDL and do not require PA. All oral MS medications are non-preferred and require PA to ensure they are being used safely. Nonpreferred injectable medications including natalizumab, ocrelizumab, and ofatumumab are also non-preferred with specific PA criteria, which are presented in **Appendix 3**. Details about the DMDs used to manage MS symptoms are outlined in **Appendix 2**.
- During the second quarter of 2024 (April through June), 2 pharmacy claims were processed for diroximel fumarate. In the first quarter of 2024 (January through March), 12 claims were processed for interferon beta-1b, dimethyl fumarate, diroximel fumarate and teriflunomide. In the fourth quarter of 2023 (October through December), there were 3 claims for ocrelizumab, which is a physician-administered drug.

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.[5] Common neurological manifestations of MS include optic neuritis, diplopia, sensory loss, limb weakness, gait ataxia, loss of bladder control, and cognitive dysfunction.[5] The mean age of diagnosis is 32 years, with most patients presenting with periodic neurological relapses.[5,6] One to two decades after onset, many patients with MS enter a progressive phase of the disease.[5] 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).[6] In 2020, the estimated number of people with MS was estimated as 2.8 million.[6]

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.[7] The diagnosis of MS is defined by demonstration of MS disease characteristics in space and time.[7] Dissemination in space refers to the presence of lesions in distinct CNS locations.[7] Dissemination in time refers to the development of new lesions over time or multiple distinct clinical attacks.[7] Four distinct clinical courses of MS have been identified: CIS, Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS), and Primary Progressive MS (PPMS).[8] 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.[9] Secondary progressive MS begins as RRMS, but gradual worsening of neurologic symptoms is observed over time.[10] After 15 to 20 years, about 65% of RRMS patients enter the secondary progressive phase.[9] 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.[11] Primary progressive MS is distributed more equally between men and women than RRMS.[11] 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.[7] The EDSS was developed to provide a standardized measure of neurological impairment in MS.[12] 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.[12] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[13] 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.[12] 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.[3] 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.[14] The MSFC is a composite score that measures arm, leg, and cognitive function. Different clinical dimensions of function are evaluated including the 9-hole peg test (time to insert and remove 9 pegs), timed 25-foot walk, paced auditory serial addition test (number of correct additions), and cognition.[1] There is no defined range of scoring or minimal clinically important difference for this assessment.[1] Increased scores reflect better functioning.[1]

The ARR 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.[3] Understanding the role of MS relapses has been challenging, as they are not constant over time; they tend to be more common at the early stages of the disease and in younger female patients.[15] The most robust estimation of relapse incidence originates from clinical trials. Summaries of many older studies provided an average figure of 0.4 to 0.6 relapses per year.[2] In most of the clinical phase-3 placebo-controlled trials in MS, relapse incidence, measured by the ARR, is used as the primary or secondary efficacy outcome measure.[15] 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.[16] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[16] In addition to clinical measures, radiographic measures of disease progression include the development of new T2 lesions, enlarging T2 lesions, or both.[7]

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.[17] 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.[7] The FDA-approved DMDs for MS include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate (S1P) receptor modulators, fumarates, cladribine, and monoclonal antibodies. Subgroup analyses from phase 3 pivotal trials of alemtuzumab, fingolimod, and natalizumab showed a reduction in relapses and MRI measures in people with MS with highly active disease.[18] Compared with interferon therapy, treatment with these therapies resulted in more favorable outcomes in the subgroup of people with MS with highly active disease.[18] However, the risks and benefits of each treatment strategy need to be considered on a patient-by-patient basis.[18] The National Institute for Health and Care Excellence (NICE) has published medication-specific guidance for alemtuzumab, cladribine, natalizumab, diroximel fumarate, ponesimod, ozanimod, ofatumumab, siponimod, peginterferon, ocrelizumab, beta interferons, glatiramer, dimethyl fumarate, fingolimod, teriflunomide, and ublituximab for treating RRMS. Ocrelizumab guidance for treating PPMS is also available at the NICE website. The available evidence, based upon a limited number of RCTs, indirect cross-trial comparisons, observational studies, and clinical experience, suggests that the monoclonal antibodies (natalizumab, ocrelizumab, ofatumumab, and alemtuzumab) and (possibly) cladribine have the highest efficacy; S1PR modulators (e.g., fingolimod) and fumarates (e.g., dimethyl fumarate) have an intermediate efficacy; and teriflunomide and the older platform DMDs (interferons and glatiramer acetate) have the lowest efficacy to treat RRMS in adults.[19] More details about the DMDs approved for the treatment of MS are presented in **Appendix 2.**

The two primary treatment approaches for relapsing MS are based on balancing the risks and efficacy of DMDs.[7] The escalation approach starts with the least-potent medications with relatively few AEs, such as interferons or fumarates. If there is evidence of disease activity, treatment is escalated to a more potent medication.[7] This approach minimizes risks but may result in undertreatment, defined as breakthrough disease and accumulated disability.[7] An alternative option is to initiate a medication with higher potency, such as ocrelizumab or natalizumab, at the time of diagnosis.[7] The rationale for this treatment approach is to provide better relapse control and delay accumulation of disability.[7] A limitation of this strategy is that patients are exposed to higher risks of AEs and some patients may not require such intensive treatment.[7]

Methods:
The March 2024 drug class report on Disease Modifying Therapies for MS by the DERP at the Center for Evidence Based Policy at OHSU was used to inform recommendations for this drug class.[1]

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports. Literature was searched through July 31, 2023, for randomized controlled trials (RCTs) comparative cohort studies, and placebo-controlled trials that evaluated the effectiveness and harms of Food and Drug Administration (FDA)-approved DMDs for the treatment of MS and CIS. Outcomes of interest included measures of relapse and disease progression, functional capacity, SAEs, discontinuation, or treatment switches.

Summary Findings:
The 2024 MS DERP report on DMDs for MS reviewed new published evidence since the previous 2020 report.[1] Two treatments, mitoxantrone and natalizumab, were excluded from the 2020 report and remained excluded from the 2024 review.[1] The 2020 report found alemtuzumab, fingolimod, ocrelizumab, ozanimod and teriflunomide reduced relapses and were not associated with increased SAEs as reported in comparative RCTs of DMDs.[1] The 2024 update includes 38 RCTs (6 new and 32 carried over from the 2020 report) and 45 cohort studies (15 new and 30 carried over from the 2020 report).[1] Four new head-to-head DMD comparisons in MS were reported in 6 RCTs of moderate- to high-risk of bias (RoB).[1]

Four new DMDs received FDA approval since the previous DERP report: ofatumumab, ponesimod, ublituximab, and monomethyl fumarate. The P & T Committee reviewed evidence for the safety and efficacy of ofatumumab, ponesimod, and monomethyl fumarate in previous meetings. Ublituximab is the only DMD the P & T Committee has not yet reviewed. Key findings from new evidence in the DERP report are summarized below.

Fingolimod: One RCT (n=1,064) compared oral fingolimod 0.25 and 0.5 mg once daily with SC glatiramer acetate 20 mg once daily over 12 months in adults with RRMS who had experienced at least 1 relapse during the previous year or 2 relapses during the previous 2 years.[1] The RCT was graded with moderate RoB due to concerns about the small number of participants enrolled, lack of participant blinding, and author's conflicts of interest.[1] Data from this RCT reported:

- Lower relapse rates with fingolimod 0.5 mg compared with glatiramer at 12 months (ARR, 0.15 vs. 0.26; p=0.01; moderate CoE). No differences in relapse rates were observed with fingolimod 0.25 mg compared with glatiramer (ARR, 0.22 vs. 0.26; p=0.42; moderate CoE).[1]
- Fingolimod 0.5 mg improved functional disability more than glatiramer as measured by change from baseline in the MSFC score at 12 months (0.09 vs. 0.03; p=0.05; moderate CoE). No difference functional disability was observed between fingolimod 0.25 mg and glatiramer (0.03 vs. 0.03; p=0.52; moderate CoE).[1]

- Study completion was higher in the groups who received fingolimod 0.5 mg and 0.25 mg (85.2% and 84.1%) compared to those who received glatiramer (74.3%; p<0.001 for both comparisons with fingolimod; low CoE).[1]
- No differences in rates of SAEs were found with fingolimod 0.25 mg, fingolimod 0.5 mg, and glatiramer at 12 months (8.7%, 7.2%, 6.2% respectively; p-values not reported; low CoE).[1] Adverse events leading to study discontinuation of study drug were reported more often in the glatiramer group than the fingolimod groups (glatiramer, 13.9% vs. fingolimod 0.5 mg, 9.3% vs. fingolimod 0.25 mg, 7.4%; p-values not reported; low CoE).[1]

Ofatumumab: Two RCTs (n=1,882) compared SC ofatumumab 20 mg every 4 weeks with oral teriflunomide 14 mg once daily over 30 months in adults with RRMS or SPMS.[1] Trials were graded as moderate RoB because of concerns around author conflicts of interest and sponsor design in the study design and analysis.[1] The trials reported the following data:

- Ofatumumab reduced the adjusted ARR at 30 months compared to teriflunomide (MD, 0.13; 95% CI, -0.16 to -0.09; p<0.001; meta-analysis of 2 RCTs; moderate CoE).[1]
- Ofatumumab reduced the risk of disability worsening at 6 months compared with teriflunomide as assessed by the EDSS score change from baseline (12% vs. 8.1%; HR, 0.68; 95% CI, 0.50 to 0.92; p=0.01; pooled analysis of 2 RCTs; moderate CoE). No difference in confirmed disability improvement at 6 months was observed (11% ofatumumab vs. 8.1% teriflunomide; HR, 1.35; 95% CI, 0.95 to 1.92; p=0.09; pooled analysis of 2 RCTs; moderate CoE).[1]
- The risk of trial discontinuation favored the ofatumumab groups (risk ratio [RR], 1.05; 95% CI, 1.01 to 1.09; p=0.01; meta-analysis of 2 RCTs; moderate CoE).[1]
- No differences in rates of SAEs were found between teriflunomide and ofatumumab at 30 months (7.9% vs. 9.1%; p=0.36; pooled analysis of 2 RCTS; low CoE).[1] Rates of AEs (ofatumumab, 83.6% vs. teriflunomide, 84.2%; p-value not reported) and AEs leading to treatment discontinuation were also not reported to differ between groups (5.7% vs. 5.2%; p=0.65; low CoE).[1] The most commonly reported AEs included infections and nasopharyngitis.[1]

Ponesimod: One RCT (n=1,133) compared oral ponesimod 20 mg once daily to oral teriflunomide 14 mg once daily over 25 months in adults with RRMS or SPMS.[1] The RCT was graded as having a moderate RoB due to concerns around attrition, conflicts of interest, and sponsor involvement in all aspects of the study.[1] Results from the RCT included:

- Lower relapse rates with ponesimod versus teriflunomide at 108 weeks (ARR, 0.20 vs. 0.29; rate ratio, 0.70; 99% CI, 0.54 to 0.90; p<0.001; moderate CoE).[1]
- No difference in change in disability at 12 weeks was observed between ponesimod and teriflunomide groups as measured by the proportion of participants who experienced an increase in the EDSS score from baseline (defined as 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)[20] from baseline (10.1% vs. 12.4%; HR, 0.83; 95% CI, 0.58 to 1.18; p=0.29; very low CoE).[1]
- Study completion rates did not differ between ponesimod and teriflunomide (83.1% vs. 83.6%; p=0.82; low CoE).[1]
- Rates of SAEs did not differ between ponesimod and teriflunomide groups at 108 weeks (8.7% vs. 8.1%; p>0.05; low CoE).[1] The most commonly reported SAEs were nervous system disorders (1.6% ponesimod vs. 1.1% teriflunomide), infections (1.2% ponesimod vs. 0.7% teriflunomide), and gastrointestinal disorders (1.1% ponesimod vs. 0.7% teriflunomide).[1]

Ublituximab: Two RCTs (n=1,094) compared anIV infusion of ublituximab 150 mg on day 1 followed by 450 mg on day 15 and weeks 24, 48, and 72 with teriflunomide 14 mg once daily or placebo over 96 weeks in adults with RRMS and SPMS.[1] The RCTs were at high RoB due to author's financial conflicts of interest, and high level of sponsor involvement in study design, analysis, and publication.[1] The trials reported the following data:

- Ublituximab reduced the adjusted ARR at 96 weeks compared with teriflunomide (MD, -0.10; 95% CI, -0.17 to -0.03; p=0.005; meta-analysis of 2 RCTs (moderate CoE).[1]

- No differences between ublituximab and teriflunomide were observed in change in disability at 12 weeks as defined by an increase in EDSS score (5.2% vs. 5.9%; HR, 0.84; 95% CI 0.50 to 1.41; p=0.51; pooled analysis of 2 RCTs; low CoE).[1]
- Study completion rates did not differ between teriflunomide and ublituximab (RR 1.01; 95% CI 0.97 to 1.05; p=0.63; meta-analysis of 2 RCTs; low CoE).[1]
- Fewer SAEs were observed at 96 weeks in participants who received teriflunomide compared to those who received ublituximab (7.3% vs. 10.8%; RR, 1.48; 95% CI 1.01 to 2.18; p=0.04; meta-analysis of 2 RCTs; low CoE).[1] Participants who received ublituximab frequently reported infusion-related reactions (48%) and upper respiratory tract infections (45%).[1,21] The incidence of infusion reactions was highest with the first dose (43%) and decreased with subsequent infusions (10% with the second infusion and 8% with the third infusion).[21] The most commonly reported AEs with ublituximab were headache (34%), nasopharyngitis (18%), pyrexia (14%), and nausea (11%). Frequently reported AEs with teriflunomide included headache (27%), nasopharyngitis (18%), alopecia (15%), and diarrhea (11%).[1]
- Disability progression was not evaluated and change in function, as measured by MSFC, was reported as a tertiary endpoint from which no conclusions could be made.

In summary, data from RCTs that evaluated ofatumumab, ponesimod, or ublituximab versus teriflunomide all showed these newer DMDs reduced ARR relative to terflunomide.[1] When fingolimod was compared with glatiramer, fingolimod 0.5 mg reduced ARR more than glatiramer over 1 year.[1] Ublituximab was associated with more SAEs than teriflunomide but ofatumumab and ponesimod were not.[1]

Fifteen new cohort studies met inclusion criteria for the 2024 DERP report.[1] Most of the studies had moderate RoB due to concerns about investigator's conflicts of interest and industry funding.[1] Some studies were at high RoB due to concerns about adjustments for confounding.[1] Eleven new studies reported on treatment discontinuation or medication switches and 6 new studies reported on SAEs.[1] No direct comparison of harms by indication were identified.[1] Differences in risk of treatment discontinuation or medication switch for patients on oral DMDs versus those on injectable DMDs are uncertain, as not every FDA-approved DMD was included in the studies, and the reported outcomes are not generalizable to all categorically oral or injectable DMDs.[1] The association of DMDs and cancer risk remains uncertain.[1]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts.[4]

Drug Name	Brand Name	Date of Change	Location of Label Change	Description of Label Change
Ocrelizumab	Ocrevus	8/2022	Warnings and Precautions	**Progressive Multifocal Leukoencephalopathy (PML)** Cases of PML have been reported in patients with MS treated with OCREVUS in the post marketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in OCREVUS-treated patients who had not been treated previously with natalizumab (which has a known association with PML), were not taking any immunosuppressive or immunomodulatory medications associated with the risk of PML prior to or concomitantly with OCREVUS and did not have any known ongoing systemic medical conditions resulting in compromised immune system function.

				At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. 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. **Immune-Mediated Colitis** Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving OCREVUS in the post marketing setting. Some cases of colitis were serious, requiring hospitalization, with a few patients requiring surgical intervention. Systemic corticosteroids were required in many of these patients. The time from treatment initiation to onset of symptoms in these cases ranged from a few weeks to years. Monitor patients for immune-mediated colitis during OCREVUS treatment and evaluate promptly if signs and symptoms that may indicate immune-mediated colitis, such as new or persistent diarrhea or other gastrointestinal signs and symptoms, occur.
Ocrelizumab	Ocrevus	1/2024	Warnings and Precautions	**Serious Infections** Serious, including life-threatening or fatal, bacterial, viral, parasitic, and fungal infections have been reported in patients receiving OCREVUS. An increased risk of infections (including serious and fatal bacterial, fungal, and new or reactivated viral infections) has been observed in patients during and following completion of treatment with anti-CD20 B-cell depleting therapies.
Glatiramer Acetate	Copaxone	11/2023	Warnings and Precautions	**Medication Errors** Medication errors have occurred when glatiramer acetate products are administered with incompatible auto injectors. Some glatiramer acetate products can be administered by an optional compatible auto injector, should one be available; however, not all glatiramer acetate products have a marketed optional compatible auto injector for administration. If using an optional auto injector for administration, ensure the device is compatible for use with the specific glatiramer acetate product by referring to the auto injector labeling. The availability of compatible auto injectors for each glatiramer acetate product may change with time.
S1P Receptor Modulators Siponimod	Mayzent	8/2023	Warnings and Precautions	**Progressive Multifocal Leukoencephalopathy (PML)** Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptor modulators, who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often

Ozanimod Fingolimod Ponesimod	Zeposia Gilenya Ponvory			associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within a few months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.
Interferon Beta-1a Peginterferon Beta-1a	Avonex Betaseron Rebif Plegridy	7/2023	Warnings and Precautions	**Pulmonary Arterial Hypertension** Cases of pulmonary arterial hypertension (PAH) have been reported in patients treated with interferon beta products. PAH has occurred in patients treated with interferon beta products in the absence of other contributory factors. Many of the reported cases required hospitalization, including one case with interferon beta in which the patient underwent a lung transplant. PAH has developed at various time points after initiating therapy with interferon beta products and may occur several years after starting treatment. Patients who develop unexplained symptoms (e.g., dyspnea, new or increasing fatigue) should be assessed for PAH. If alternative etiologies have been ruled out and a diagnosis of PAH is confirmed, discontinue treatment, and manage as clinically indicated.
Natalizumab	Tysabri	4/2023	Warnings and Precautions	**REMs Update for the Tysabri Touch Prescribing Program:** Revised prescriber section to include a statement requiring the prescriber to review, complete, and sign the Prescriber Enrollment Form.
Fumarate Salts Dimethyl Fumarate Monomethyl Fumarate Diroximel Fumarate	 Tecfidera Bafiertam Vumerity	12/2023	Warnings and Precautions	**Serious Gastrointestinal Reactions** Serious gastrointestinal reactions, including perforation, ulceration, hemorrhage, and obstruction, some with fatal outcomes, have been reported in the post-marketing setting with the use of fumaric acid esters, with or without concomitant aspirin use. Most of these events have occurred within 6 months of fumaric acid ester treatment initiation. In controlled clinical trials, the incidence of serious gastrointestinal adverse events was 1% in patients treated with dimethyl fumarate; these events, none of which were fatal, included vomiting (0.3%) and abdominal pain (0.3%).

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Appendix 1: Current Preferred Drug List

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

glatiramer acetate	GLATOPA	SUBCUT	SYRINGE	N
interferon beta-1b	BETASERON	SUBCUT	VIAL	N
interferon beta-1b	EXTAVIA	SUBCUT	VIAL	N

Appendix 2: Disease-Modifying Drugs Approved for Management of Multiple Sclerosis

FDA-Approved Disease-Modifying Drugs used to manage Multiple Sclerosis.[22,23]

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, PML	Hepatitis B virus screening prior to starting therapy.
Ublituximab	BRIUMVI	450 mg via IV infusion every 6 months	CIS RRMS SPMS	No	Infusion reactions and infections, PML	Hepatitis B virus screening prior to starting therapy.
Others						
Mitoxantrone	NOVANTRONE	12 mg/m^2 IV infusion every 3 months – duration of therapy	RRMS SPMS	No	Black Box Warning: Dose-related Cardiotoxicity	ECG and LVEF before each infusion. CBC and LFTs every 6 months.

		limited to 2 years and cumulative dose of 140 mg/m^2			**Considered as last resort treatment for patients that have failed other therapies**	
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						

Multiple Sclerosis, Injectable 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.	
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

Approval Criteria		
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. Is the request for a drug with potential risks during pregnancy (e.g., ofatumumab, mitoxantrone, or ublituximab)?	**Yes**: Go to #8	**No**: Approve for up to 1 year
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to 1 year
9. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10
10. 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		
1. Has the patient's condition stabilized (i.e., reduced activity seen on magnetic resonance imaging (MRI), fewer relapses, and/or minimal or no disease progression) 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	
Ublituximab	BRIUMVI	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, completed screening for John Cunningham (JC) virus
Glatiramer acetate					
Interferon beta-1a	X	X	X		
Interferon beta-1b	X	X	X		
Mitoxantrone	X	X			ECG and LVEF, negative pregnancy test
Ocrelizumab				X	Serum immunoglobulins, up to date with all vaccinations, completed screening for John Cunningham (JC) virus
Ofatumumab				X	Serum immunoglobulins, up to date with all vaccinations, negative pregnancy test, completed screening for John Cunningham (JC) virus
Ublituximab				X	Serum immunoglobulins, up to date with all vaccinations, negative pregnancy test prior to each infusion,

					completed screening for John Cunningham (JC) virus

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: *10/24 (DM); 10/22 (DM)*
Implementation: *12/1/2024; 1/1/23*

Multiple Sclerosis, Oral 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 12 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.

Approval Criteria		
2. Is the request for ozanimod to treat moderate-to-severe ulcerative colitis?	**Yes:** Go to #3	**No:** Go to #4
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

Approval Criteria		
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.
10. Is the prescription for teriflunomide?	**Yes:** Go to #15	**No:** Go to #11
11. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #12	**No:** Go to #14
12. 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 #13	**No:** Go to #15
13. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for cladribine?	**Yes:** Go to # 15	**No:** Go to #17
15. Is the patient of childbearing potential?	**Yes:** Go to #16	**No:** Approve for up to 12 months
16. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #17
17. 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 stabilized (i.e reduced activity seen on magnetic resonance imaging (MRI), fewer relapses, and/or minimal or no disease progression) 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		Completed screening for John Cunningham (JC) virus

Ozanimod*	X	X	X	X	X		Completed screening for John Cunningham (JC) virus
Ponesimod*	X	X	X	X	X		Completed screening for John Cunningham (JC) virus
Siponimod*	X	X	X	X	X	X	Completed screening for John Cunningham (JC) virus
Teriflunomide	X (box warning)	X (box warning)	X				
Cladribine	X (box warning)	X	X (WNL)		X		TB; HBV; HIV; HCV; Completed screening for John Cunningham (JC) virus
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: *10/24 (DM); 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: *12/1/2024; 1/1/2023, 1/1/2022, 9/1/20; 1/1/18; 1/1/17; 1/1/14*

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

Approval Criteria		
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 ≤ 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:** 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: *10/24 (DM); 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*

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 #5
4. 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.
5. Does the patient have Crohn's Disease?	**Yes:** Go to #6	No: Pass to RPH; Deny for medical appropriateness.
6. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #7	**No:** Pass to RPH; Deny for medical appropriateness**.**

Approval Criteria		
7. 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: *10/24 (DM); 10/22 (DM); 6/21(DM); 10/20 (DM); 11/17*
Implementation: *12/1/24; 1/1/18*