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OHSU Drug Effectiveness Review Project Summary Report – Disease-Modifying Drugs for Multiple Sclerosis

Date of Review: August 2020

Date of Last Review: November 2017
Literature Search: 01/01/16 - 2/3/2020

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

Purpose for Class Update:
This review examines new comparative evidence of disease modifying drugs (DMDs) for multiple sclerosis (MS) published since 2017 and summarizes the evidence for 3 new DMDs approved to treat MS; cladribine, ozanimod, and siponimod, as presented in a 2020 Drug Effectiveness Review Project (DERP) systematic review focused on MS.

Research Questions:
1. What is the comparative effectiveness of DMDs for MS?
2. What is the comparative effectiveness of DMDs for clinically isolated syndrome (CIS)?
3. Do DMDs for MS or CIS differ in harms?
4. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer adverse events?

Conclusions:
- Since the last review, 5 new oral MS drugs have received Food and Drug Administration (FDA) approval: diroximel fumarate, monomethyl fumarate, ozanimod, cladribine, and siponimod. Dimethyl fumarate is a prodrug of an diroximel fumarate FDA approval was based upon clinical trials of dimethyl fumarate.
- When comparing the DMDs directly, alemtuzumab, fingolimod, ocrelizumab, and teriflunomide significantly reduce relapses and are not associated with increased serious adverse events (AEs) compared with other DMDs assessed in the eligible trials.[1]
- The newer drugs with FDA approval, cladribine and siponimod, are significantly more effective than placebo for MS, although cladribine is highlighted as having some safety concerns including a black box warning related to malignancies and teratogenicity.[1]
- For CIS, cladribine, glatiramer acetate, interferon beta-1a, interferon beta-1b, and teriflunomide significantly reduced conversion to MS compared with placebo and did not appear to be associated with more serious adverse events.[1]
- No eligible RCTs were identified to compare diroximel fumarate with placebo.[1] The FDA approval in 2019 was based on bioavailability studies comparing oral dimethyl fumarate delayed release capsules to diroximel fumarate delayed-release capsules and 2 placebo-controlled trials of dimethyl fumarate.[1]
- Compared to other DMDs, the risk of infection was lower with interferon beta and glatiramer acetate.[1]

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- Overall, the risk of specific adverse events is higher with some DMDs compared to other DMDs:
  - The risk of liver injury was higher for alemtuzumab, teriflunomide, and fingolimod.[1]
  - The risk of PML was higher with fingolimod and dimethyl fumarate.[1]
- Subgroup analyses are not reported consistently across studies, but there is some evidence that women may benefit more than men with glatiramer acetate and interferon beta-1a for CIS compared to other DMDS.[1]

Recommendations:
- Revise prior authorization (PA) criteria to include newly approved DMDs (monomethyl fumarate, diroximel fumarate, ozanimod, cladribine, and siponimod), add safety monitoring metrics, and renewal criteria.
- Revise natalizuamb PA criteria to reflect expanded indication for all forms of relapsing MS.
- No changes to the preferred drug list (PDL) are recommended for MS therapies based on efficacy or safety data, and no PDL changes were recommended after evaluation of costs in executive session.

Summary of Prior Reviews and Current Policy
Evidence for the comparative effectiveness of DMDs for management of MS was reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in November 2017. Ocrelizumab, a new biologic approved to treat MS, was also reviewed at this meeting. Prior authorization criteria for ocrelizumab were approved by the P and T Committee to insure use in funded MS conditions. Clinical PA criteria for natalizumab were created separately from the biologic medications. In addition, PA criteria for oral multiple sclerosis drugs were amended to remove the requirement of failure of a trial of interferon beta-1a, interferon beta-1b, and glatiramer prior to approval.

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

The PDL status of MS drugs is presented in **Appendix 1**. Preferred MS drugs on the PDL include: glatiramer acetate, interferon beta-1a, and interferon beta-1b. Non-preferred agents include: alemtuzumab, cladribine, dalfampridine, dimethyl fumarate, diroximel fumarate, fingolimod, ocrelizumab, ozanimod, peginterferon beta-1a, siponimod, and teriflunomide. During the first quarter of 2020, less than 10 fee-for-service (FFS) patients had claims processed for MS drugs. Most of the claims were for 2 of the non-preferred oral drugs, dimethyl fumarate (44%) and fingolimod (22%) followed by the preferred injectable agent, interferon beta-1a (33%).

Methods:
The May 2020 drug class report on DMDs for MS by 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]

The original report is available to Oregon P and T Committee members upon request. An executive summary report is publicly available in the agenda packet and on the DURM website.

The purpose of 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.

Background:

Four distinct clinical courses have been identified for MS: CIS, RRMS, secondary progressive (SPMS), and PPMS.[2] 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. RRMS may be either characterized as active or not active. About 85% of patients with MS are initially diagnosed with RRMS.[3] Secondary progressive MS begins as relapsing-remitting MS, but gradual worsening of neurologic symptoms is observed over time.[4] Approximately 65% of RRMS patients will enter the secondary progressive phase.[3] 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 10-15% of MS patients have PPMS, and in contrast to RRMS, symptoms typically begin in the patients' fifth or sixth decade, a later age of onset than RRMS.[5] PPMS is distributed more equally between men and women than RRMS. The majority of available direct evidence continues to reside in patients with relapsing forms of MS rather than progressing forms of MS.

Treatment of MS falls into three main categories: symptomatic therapy to improve the patient's quality of life, treatment of acute attacks, and treatment with DMDs to alter the natural course of the disease and reduce progressive disability over time. Acute relapses are treated with corticosteroids and symptoms are treated accordingly with appropriate agents. DMDs are broadly categorized into 3 routes of administration: injectable, oral, and infusion therapies. Early use of DMDs in patients with RRMS has been shown to reduce the annualized relapse rate (ARR), lessen severity of relapses, and slow progression of disability.[6] Interferons have proven efficacy in managing MS and do not require substantial clinical monitoring, so they are considered first-line agents for treating MS.[6] Around 25% of patients discontinue interferon therapy within 1 to 2 years due to difficulty adhering to daily or weekly injection regimens. Patient preference and tolerance should be considered when evaluating oral versus injectable treatment options.

Ocrelizumab received FDA approval for treatment of adult patients with RRMS or PPMS in March 2017. Ocrelizumab is the only FDA-approved treatment for PPMS and provides another treatment option for RRMS patients. The efficacy of rituximab to treat PPMS has also been studied, but use is limited due to poor efficacy and serious adverse effects associated with its administration.[7] Four new oral options are available for management of MS to increase time to disability progression: monomethyl fumarate, ozanimod, siponimod and cladribine. Disease-modifying drugs that have been FDA-approved for the treatment of MS are presented in **Table 1**.

Table 1: FDA-Approved Disease-Modifying Drugs used to manage MS[8,9]

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication	REMS Program	Major Safety Concerns	Monitoring
ORAL AGENTS						
Fingolimod	GILENYA	≥ 40 kg: 0.5 mg PO once daily < 40 kg: 0.25 mg PO once daily	CIS RRMS SPMS	No	Infections, PML, bradycardia with first dose, hepatotoxicity hypertension, teratogenicity, and macular edema	Cardiac monitoring with the first dose. Ophthalmic screening at baseline

			Approved for patients ≥ 10 years of age			and 3-4 months after starting therapy. LFTs and CBC every 6 months.
Siponimod	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, 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	ZEPOSIA	0.92 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
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
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
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*	CBC with lymphocyte count and LFTs every 6 months

					*had an inadequate response to, or who are unable to tolerate an alternative MS treatment**	
INJECTABLE AGENTS						
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)	None required
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	CBC and LFTs every 6 months
Interferon beta-1a	REBIF	22 or 44 mcg SC three times a week				
Interferon beta-1b	BETASERON, EXTAVIA	250 mcg SC every other day				
Peginterferon beta-1a	PLEGRIDY	125 mcg SC every 14 days				
Monoclonal Antibodies						
Alemtuzumab	LEMTRADA	Intravenous infusion for 2 or more 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	JCV antibody testing and brain MRI every 6 months. CBC and LFTs every 6 months

					consider risk of PML vs. benefit of therapy	
Ocrelizumab	OCREVUS	600mg IV every 6 months (maintenance)	CIS RRMS SPMS PPMS	No	Infusion reactions, infections and PML	Hepatitis B virus screening prior to starting therapy
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, SPMS = secondary progressive multiple sclerosis						

Progression of MS is assessed by the amount of disability caused by the disease. The Expanded Disability Status Scale (EDSS) was developed to provide a standardized measure of neurological impairment in MS. The EDSS ranges from 0 (normal neurologic exam) to 5 (ambulatory without aid for 200 meters) to 10 (death due to MS), with lower scores indicating more mobility and activity by the patient.[10] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[11] 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.[10] Despite these limitations, the EDSS continues to be the standard disability measure for MS clinical research. Clinical trials have defined disability progression when assessed over 3 to 6 months as an increase in EDSS of 0.5 points when the score is between 5.6 to 8.5 and 1.0 point when the score is between 0 and 5.5.[12] Some researchers have proposed that longer trials (with duration of at least 1 year) with greater changes in the EDSS scores (greater than 1-2 points) may better identify patients with sustained disability.[13] Because of the limitations of the EDSS, the National MS Society task force developed the Multiple Sclerosis Functional Composite (MSFC) score. This score is a composite measure of walking speed, upper-limb movements, and cognition. There is no defined range for the MSFC score; negative values indicate worsening and positive values indicate improvement. Similar to the EDSS, researchers have had difficulty quantifying a meaningful change in MSFC scores. Individual components of the test may change over time which may not be reflected in composite scores.[12]

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 which occur at least 30 days after the onset of a preceding event.[12] However, the probability of relapse is not a consistent function over time. Patients are usually enrolled in a trial at the time of MS diagnosis when the probability for relapses is high, and as time progresses, this probability decreases due to the regression to the mean phenomenon.[12] In order to have enough power to detect a significant reduction in relapses, research suggests a clinical trial needs to last at least 1 year, but this measure may also be less meaningful than evaluating the total number of relapses over a longer period of time.[14] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[14] MRI lesion counts may assist clinicians in tool to assess disease progression. However, there is a poor correlation between MRI activity, a surrogate endpoint for CNS disease, and relapse rate as the appearance of new MRI lesions often outnumber clinical relapses.[14] This paradox in MS became apparent when MRI was first used in MS and attempts to correlate T2 lesions with EDSS revealed a dissociation between the two measures.[15]

DERP Summary Findings:

The 2020 DERP drug class review on DMDs for MS was the fourth update of the original 2007 report. The DERP authors searched Ovid MEDLINE and the Cochrane Library from January 1, 2016 up to October 15, 2019, and several other websites to identify eligible studies.[1] For new drugs not included in the previous DERP reports, the authors searched from database inception.[1] The Ovid MEDLINE search was rerun on February 3, 2020 to capture any studies published since the initial search in October 2019. Fourteen new RCTs were identified for the 2020 update.[1] Overall, the DERP MS summary includes 42 RCTs and 30 observational studies. All the RCTs were assessed as being fair- or poor-quality using the GRADE methodology.[1] DERP used the following health outcomes to assess efficacy: disability, clinical exacerbation/relapse, quality of life, functional outcomes (wheelchair use, time lost from work), and persistence (drug discontinuation rates). Harms associated with drug therapy were assessed using the incidence of overall AEs, serious AEs, withdrawals due to AEs, and specific AEs such as hepatoxicity.

1. Effectiveness and Harms of DMDs for MS

A. When compared directly, the following therapies were significantly more effective in reducing relapses than the active comparator.[1]

Alemtuzumab vs. Interferon Beta-1a 44 mcg (Meta-Analysis of 3 RCTs; 1472 participants)

Three RCTs compared alemtuzumab 12 mg infusion with interferon beta-1a 44 mcg subcutaneous (SC) injection over 24 to 36 months in adults with RRMS.[1] The fair-quality trials had some risk of bias due to lack of blinding, high loss to follow-up, author conflicts of interest, and funding by industry.[1] The following data is derived from a meta-analysis of the 3 RCTs, unless stated otherwise. Compared to interferon beta-1a, alemtuzumab significantly reduced the proportion of relapses at 24 months (risk ratio [RR] 0.65; 95% CI, 0.48 to 0.88) and at 36 months (RR 0.52; 95% CI, 0.34 to 0.80; moderate quality of evidence [QoE]).[1] Alemtuzumab significantly reduced the proportion of disability progression at 24 months (RR 0.73; 95% CI, 0.54 to 0.99) and at 36 months (RR 0.33; 95% CI, 0.15 to 0.70; low QoE).[1] Alemtuzumab improved disability, as measured by the EDSS, at 36 months (mean difference [MD] -0.07; 95% CI, -1.04 to -0.36), but not at 24 months (MD -0.20; 95% CI, -0.60 to 0.20; low QoE).[1] However, the changes in EDSS were small and are unlikely to be clinically meaningful.[1] Alemtuzumab improved function compared to interferon, as measured by the MSFC at 24 months, but the clinical importance of the improvement is not clear as the MSFC changes were small (MD 0.10; 95% CI, 0.05 to 0.16; meta-analysis 2 RCTs; moderate QoE).[1] Participants in the alemtuzumab groups had higher levels of study completion compared to interferon beta-1a at 36 months (RR 1.37; 95% CI, 1.15 to 1.63), but not at 24 months (RR 1.16; 95% CI, 0.98 to 1.37; low QoE).[1]

The 3 RCTs reported the same AEs with both medications. For alemtuzumab, patients reported headache (43% to 61%), nausea (14% to 24%), rash (39% to 91%), and fever related to the infusion (16% to 37%).[1] In the alemtuzumab group, patients also reported nasopharyngitis (20% to 29%), urinary tract infections (11% to 21%), herpes viral infections (8% to 16%), and upper respiratory tract infections (15% to 59%).[1] In the interferon beta-1a group, patients reported influenza-like illness (8% to 27%), injection-site erythema (25%), headache (19% to 63%), and relapse (33% to 39%).[1] No significant differences in serious AEs at 24 months or 36 months were reported between the 2 medications (very low QoE).[1]

Fingolimod vs. Interferon Beta-1b 250 mcg (1 RCT; 157 participants)

One poor-quality RCT conducted over 18 months compared oral fingolimod with SC interferon beta-1b 250 mcg in adults with RRMS.[1] Lack of reporting of key trial components (including randomization), high losses to follow-up, and author conflicts of interest contributed to the high risk of bias for this trial.[1] The authors designed the trial to provide evidence for the effect of fingolimod and interferon beta-1b on cognitive, MRI and clinical outcomes.[1] A direct comparison between fingolimod and interferon beta-1b was not a prespecified objective. Fingolimod reduced relapse rates numerically compared to interferon beta-1b, but the statistical significance is not clear (ARR 0.12 vs. 0.39; P value between groups not reported; low QoE).[1] No significant difference in disability as measured by

the EDSS was observed (mean increase of 0.12 fingolimod vs. 0.19 interferon; P value not reported; low QoE).[1] Disability progression and changes in function (MSFC) were not evaluated. Overall, significantly more participants randomized to fingolimod completed the 18-month trial compared with those randomized to interferon beta-1b (91.5% vs. 58.8%; RR 1.56; 95% CI, 1.23 to 1.97; P <0.001; moderate QoE).[1]

Overall, patients in the fingolimod groups reported more adverse events than patients in the interferon beta-1b group (79.81% vs. 59.57%; P=0.009; low QoE).[1] The most commonly reported adverse events in the fingolimod group were infections and infestations (28%, primarily nasopharyngitis and influenza) and changes in liver function tests (25%, primarily alanine aminotransferase, cholesterol and transaminase increases).[1] In the interferon beta-1b group, the most commonly reported adverse events were nervous system disorders (26%, primarily MS relapses) or general disorders and administration-site conditions (21%, primarily fever, fatigue and influenza-like illnesses).[1] No significant difference in serious AEs was noted between fingolimod and interferon beta-1b (8.65% vs. 2.13%; P=0.14; low QoE).[1]

Fingolimod vs. Interferon Beta-1a 30 mcg (1 RCT; 1292 participants)

One fair-quality RCT conducted over 12 months compared oral fingolimod 0.5 mg and 1.25 mg with intramuscular (IM) interferon beta-1a 30 mcg in adults with RRMS.[1] Concerns about the potential for unblinding because of adverse events, author conflicts of interest, and funding by industry downgraded the quality assessment of this RCT.[1] Fingolimod significantly reduced relapse rates compared to interferon beta-1a (ARR 0.16 vs. 0.33; P<0.001; low QoE).[1] At 12 months, levels of disability for patients in the fingolimod and in the interferon beta-1a group remained relatively stable, and there was no significant difference between the groups (p=0.06; low QoE).[1] No significant differences in disability progression, function as measured by the MSFC, or disability as measured by the EDSS were noted at 12 months (low QoE).[1] No difference between fingolimod and interferon beta-1a was observed in study persistence (moderate QoE). No significant differences in serious AEs related to increased liver enzymes, macular edema or infections were associated with either drug (low QoE).[1]

Ocrelizumab vs. Interferon Beta-1a (3 RCTs; 1876 participants)

Three RCTs compared ocrelizumab infusion and IM or SC interferon beta-1a over 6 to 24 months in adults with RRMS.[1] The smaller trial (n=220) was assessed as poor-quality due to concerns about lack of blinding, the shorter length of follow-up, author conflict of interests, and funding by industry.[1] The two larger, 24-month trials (n=821 and n=835) are fair-quality; however, some risk of bias was identified due to author conflict of interests and funding by industry.[1] Ocrelizumab significantly reduced relapse rates compared to interferon beta-1a (ARR 0.13 vs. 0.36; P=0.03 and ARR 0.16 vs. 0.29; P<0.001; 1 RCT and pooled analysis of 2 RCTs; n=1876; low QoE).[1] Ocrelizumab significantly reduced disability progression compared to interferon beta-1a (hazard ratio [HR] 0.60; 95% CI, 0.45 to 0.81; pooled analysis of 2 RCTs; n=1656; low QoE;).[1] Compared to interferon beta-1a, ocrelizumab improved functioning (MD 0.07; 95% CI, 0.02 to 0.13), as measured by the MSFC, but the clinical importance of the small difference is not clear (meta-analysis of 2 RCTs; n=1656; moderate QoE:).[1] Change in disability (EDSS) was not evaluated. Ocrelizumab significantly increased persistence compared to interferon beta-1a at 24 months (RR 1.10; 95% CI, 1.05 to 1.15; meta-analysis 3 RCTs; n=1656; low QoE), but not at 6 months (1 RCT; n=220; low QoE).[1] No significant difference in serious AEs was observed between ocrelizumab and interferon beta-1a (RR 0.79; 95% CI, 0.56 to 1.09; meta-analysis of 3 RCTs; n=1876; low QoE).[1]

Ozanimod 0.5 mg and 1 mg vs. Interferon Beta-1a 30 mcg (2 RCTs; 2666 participants)

Two fair-quality RCTs compared oral ozanimod 0.5 mg and 1 mg once daily with IM interferon beta-1a 30 mcg once weekly over 12 to 24 months in adults with relapsing MS.[1] Risk of bias included concerns about author conflict of interests and funding by industry.[1] Ozanimod significantly reduced relapse rates (ARR 0.24, ozanimod 0.5 mg; ARR 0.18, ozanimod 1 mg) compared to interferon beta-1a (ARR 0.35) for at least 12 months (rate ratio, ozanimod 0.5 mg vs. interferon beta-1a, 0.69; 95% CI, 0.55 to 0.86; rate ratio, ozanimod 1 mg vs. interferon beta-1a, 0.52; 95% CI, 0.41 to 0.66; 2 RCTs; low QoE).[1] No significant difference between each of the 3 treatment groups was observed in disability rate progression at 24 months (9.3% ozanimod 0.5 mg, vs. 12.5% vs. ozanimod 1 mg, vs. 11.3%

interferon beta-1a; P>0.05; 2 RCTs; low QoE).[1] Over 24 months ozanimod 0.5 mg significantly improved function as measured by the MSFC compared to interferon beta-1a (MD 0.10; 95% CI, 0.01 to 0.19), but no difference was noted with ozanimod 1 mg (MD 0.06; 95% CI, -0.03 to 0.15; 1 RCT; n=1320; very low QoE).[1] However, the clinical importance of the nominal difference is not clear.[1] Change in disability (EDSS) was not evaluated. No significant difference in persistence was observed at 24 months (RR 1.03; 95% CI, 0.97 to 1.08; 1 RCTs; n=1320; very low QoE).[1]

The most frequently reported adverse events in the ozanimod groups were nasopharyngitis (13% to 16%), alanine aminotransferase increases (6% to 7%), hypertension (5% to 6%), γ-glutamyltransferase increase (4% to 6%), pharyngitis (4% to 6%), and urinary tract infection in the ozanimod groups (4% to 5%).[1] The most frequent adverse events in the interferon beta-1a group were influenza-like illness (incidence not reported), headache (incidence not reported), nasopharyngitis (11%), upper respiratory tract infection (incidence not reported), fever (incidence not reported), and orthostatic hypotension (incidence not reported).[1] No significant difference in serious AEs was noted at 24 months (RR 1.06; 95% CI, 0.69 to 1.64; 1 RCT; n=1320; very low QoE).[1]

Teriflunomide 7 mg and 14 mg vs. Interferon Beta-1a (1 RCT; 324 participants)

One fair-quality RCT compared oral teriflunomide 7 mg and 14 mg once daily with SC interferon beta-1a 44 mcg three times a week for up to 12 months in adults with relapsing MS.[1] Risk of bias included concerns about high and differential loss to follow-up, author conflicts of interest, and funding by industry.[1] Teriflunomide 7 mg significantly reduced relapse rates compared to interferon beta-1a (ARR 0.41 vs. 0.22; P=0.03), but no significant differences were observed with teriflunomide 14 mg (RR 0.26 vs. 0.22; P=0.59; low QoE).[1] Disability progression, changes in disability (EDSS), and changes in function (MSFC) were not evaluated. Teriflunomide 7 mg significantly increased persistence (RR 1.20; 95% CI, 1.02 to 1.40), but the difference was only marginal with teriflunomide 14 mg (RR 1.17; 95% CI, 1.00 to 1.38; very low QoE).[1]

Patients in the 2 teriflunomide groups reported higher rates of nasopharyngitis than did patients in the interferon beta-1a group (20% to 26% vs. 18%), as well as higher rates of diarrhea (21% to 23% vs. 8%), hair thinning (6% to 20% vs. 1%), paresthesia (10% to 13% vs. 8.0%), and back pain (10% vs. 8%).[1] Patients in the interferon beta-1a group reported influenza-like symptoms (54% vs. 3% to 4%), alanine aminotransferase increases (31% vs. 10% to 11%), and headache (26% vs. 16% to 21%) more frequently than patients in the teriflunomide groups.[1] Teriflunomide 7 mg increased the number of serious AEs compared to placebo, but the difference was not significant (RR 1.57; 95% CI, 0.64 to 3.84), and no significant differences were noted between placebo and teriflunomide 14 mg (very low QoE).[1]

Cladribine in combination with Interferon Beta (various formulations) vs. Interferon Beta (various formulations) Monotherapy (1 RCT; 172 participants)

One poor-quality RCT compared cladribine (3.5 mg/kg) plus existing of interferon-beta therapy to existing interferon-beta therapy plus a placebo in adults with relapsing MS over a 24-month study period.[1] The trial was designed to evaluate a 5.25 mg/kg dosage of cladribine, but was discontinued because of an association with lymphopenia.[1] Risk of bias included concerns about high and differential loss to follow-up, author conflicts of interest, and funding by industry.[1] Cladribine plus interferon beta significantly reduced relapse rate compared to interferon beta alone (ARR 0.12 vs. 0.32; RR 0.37; 95% CI, 0.22 to 0.63; moderate QoE).[1] No significant difference in disability progression was observed (15.3% vs. 12.5%; P value not reported; low QoE).[1] Changes in disability (EDSS) and function (MSFC) were not evaluated. Overall, 64.5% (80 of 124) of participants in the combination therapy group completed the 96-week trial compared with 81.3% (39 of 48) of participants in the interferon beta group, with persistence being significantly lower in the combination therapy (P value not reported; low QoE).[1]

The most commonly reported adverse events in the cladribine plus interferon beta group were lymphopenia (40%), headache (25%), and nasopharyngitis (23%).[1] In the placebo plus interferon beta group, patients commonly reported headache (21%), nasopharyngitis (17%), and upper respiratory tract infection (17%).[1] In

the cladribine plus interferon beta group, 3.2% of participants had serious infections or infestations, compared with no participants in the placebo plus interferon beta group.[1] Participants in the cladribine plus interferon beta group also had higher rates of neoplasms, including 1 report of squamous cell carcinoma, than participants in the placebo plus interferon beta group (4.0% vs. 0%).[1] Elevated levels of alanine transaminase and aspartate transaminase were seen in 2 participants in the cladribine plus interferon beta group and 1 patient in the placebo plus interferon beta group (1.6% vs. 2.1%).[1] No significant difference in serious AEs was observed between treatment groups (P value not reported; low QoE).[1]

Glatiramer Acetate in combination with Interferon Beta-1a vs. Interferon Beta-1a Monotherapy (1 RCT; 1008 participants)

One fair-quality RCT compared the combination of SC glatiramer acetate and IM interferon beta-1a versus interferon beta-1a monotherapy over 36 months in adults with RRMS.[1] Concerns about high loss to follow-up and author conflicts of interest contributed to the fair-quality assessment of this RCT.[1] Glatiramer acetate plus interferon beta-1a reduced relapse rates compared with interferon beta-1a alone (ARR, 0.12 vs. 0.16; P=0.02; 95% CI not reported; low QoE).[1] No significant difference in disability progression was observed between the combination therapy and monotherapy (23.9% vs. 21.6%; P>0.05; low QoE).[1] Patients experienced similar improvements in function (MSFC) in the 2 treatment groups (0.1 interferon beta-1a vs. 0.1 combination; P>0.05; low QoE).[1] Change in disability (EDSS) was not evaluated. The completion rates at 36 months for each treatment group were similar in the combination group (79.6%) and in the interferon beta-1a group (77.6%; low QoE).[1] No significant difference in serious AEs was observed with interferon beta-1a alone or glatiramer acetate in combination with interferon beta-1a (low QoE).[1]

B. When compared directly, the following therapies were not significantly different for relapse.[1]
Dimethyl Fumarate vs. Glatiramer Acetate (1 RCT; 1430 participants)

One poor-quality RCT compared oral dimethyl fumarate with SC glatiramer acetate over 24 months in adults with RRMS.[1] Concerns about author conflicts of interest, funding by industry, and the potential for unblinding in the dimethyl fumarate groups (a flushing reaction is known to be an adverse effect associated with dimethyl fumarate) resulted in downgrading the quality assessment of this RCT.[1] Different doses of dimethyl fumarate were compared to placebo. The RCT was not designed to test the superiority or noninferiority of dimethyl fumarate compared with glatiramer acetate.[1] A post hoc evaluation was conducted to provide direct comparison of dimethyl fumarate with glatiramer acetate.[1] The statistical testing for this direct comparison should be considered exploratory, and not definitive.[1] No significant difference in disability progression between dimethyl fumarate and glatiramer acetate was observed (HR 0.85; 95% CI, 0.56 to 1.29 very low QoE).[1] No significant difference in disability was seen for dimethyl fumarate compared with glatiramer acetate (P=0.37; very low QoE).[1] In the direct post hoc comparison, participants in the dimethyl fumarate and glatiramer acetate groups had similar ARRs at 2 years (rate ratio, 0.78; 95% CI, 0.59 to 1.05; very low QoE).[1] When compared directly, similar number of participants in the dimethyl fumarate and glatiramer acetate groups relapsed at 2 years (HR, 0.92; 95% CI, 0.70 to 1.22; very low QoE).[1] No significant difference between dimethyl fumarate and glatiramer acetate was observed in study persistence (no P value reported; moderate QoE).[1] Changes in disability (EDSS) and function (MSFC) were not evaluated.[1] No significant differences in serious AEs were noted between dimethyl fumarate and glatiramer acetate (no P value reported; low QoE).[1]

Glatiramer Acetate vs. Interferon Beta-1b 250 mcg (2 RCTs; 2319 participants)

Two RCTs compared SC glatiramer acetate 20 mg with SC interferon beta-1b 250 mcg over 2 to 3.5 years in adults with RRMS and CIS.[1] The smaller trial (n=75) conducted over 2 years, was rated as poor quality due to the lack of blinding, small sample size, author conflict of interests, and funding by industry.[1] The second, longer duration trial (n=2244) was of fair quality, but risks of bias were identified due to the method of analysis (per-protocol), author conflict of interests, and funding by industry.[1] No significant difference in relapse rates between glatiramer acetate and interferon beta-1b was noted (2 RCTs; low QoE).[1] No significant difference in disability progression was observed between glatiramer acetate and interferon beta-1b (20% vs. 21%; P=0.68; 1 RCT; low QoE).[1]

Changes in disability (EDSS) and function (MSFC) were not evaluated. No significant difference in persistence was observed (meta-analysis of 2 RCTs; moderate QoE).[1] No significant difference in serious AEs was observed (P value not reported; 1 RCT; low QoE).[1]

Glatiramer Acetate vs. Interferon Beta-1a 30 mcg or 44 mcg (3 RCTs; 1937 participants)

Three RCTs compared glatiramer acetate and interferon beta-1a over 24 to 36 months in adults with RRMS.[1] One trial (n=1008) was assessed as fair-quality due to concerns about high loss to follow-up and author conflicts of interest.[1] The other 2 trials (n=165 and n=764) were of poor methodological quality because of concerns about randomization and blinding, high loss to follow-up, author conflicts of interest, and funding by industry.[1] No significant difference in relapse rates between glatiramer acetate and interferon beta-1a at 24 or 36 months were observed, although the proportion was numerically lower with glatiramer acetate at 36 months (20% vs. 26%; 2 RCTs; n=1772; low QoE).[1] No significant difference in disability progression was observed between either drug (2 RCTs; n=1772; very low QoE).[1] Glatiramer acetate significantly increased persistence at 24 months (RR, 1.08; 95% CI, 1.02 to 1.15) and at 36 months (RR, 1.08; 95% CI, 1.01 to 1.16; meta-analysis of 3 RCTs; n=1687; low QoE).[1] No significant difference in disability as measured by the EDSS was noted (1 RCT; n=165; low QoE).[1] No significant difference in function as measured by the MSFC was reported (1 RCT; n=1008; Low QoE).[1] No significant difference in serious AEs between glatiramer acetate and interferon beta-1a was observed (RR 0.84; 95% CI, 0.60 to 1.17; meta-analysis of 2 RCTs; n=1772; very low QoE).[1]

Interferon Beta-1b 250 mcg vs. Interferon Beta-1a 30 mcg and 44 mcg (4 RCTs; 648 participants)

Four fair- to low-quality RCTs compared interferon beta-1b and interferon beta-1a over 12 to 24 months in adults with RRMS and CIS. Risks of bias included lack of blinding, method of analysis (per-protocol rather than intention-to-treat), no randomization details, and lack of reporting of author conflicts of interest.[1] No significant difference in relapse was observed between interferon beta-1b and interferon beta-1a at 24 months (RR 0.85; 95% CI, 0.59 to 1.21; meta-analysis of 4 RCTs; n=648; very low QoE).[1] No significant difference in disability progression was noted between interferons at 24 months (RR 0.63; 95% CI, 0.34 to 1.16; meta-analysis of 2 RCTs; n=489; very low QoE).[1] There was no significant difference in disability, as measured by the EDSS, at 12 or 24 months (meta-analysis of 4 RCTs; n=648; very low QoE).[1] No significant difference in persistence was noted at 24 months (meta-analysis of 4 RCTs; n=648; very low QoE).[1] Serious AEs were not evaluated.

C. When compared with placebo, the following therapies were significantly more effective in reducing relapse.[1]

Cladribine vs. Placebo (1 RCT; 1326 participants)

One fair-quality RCT compared oral cladribine and placebo over 24 months in adults with RRMS.[1] Participants were randomized to 3.5 mg/kg of cladribine, 5.25 mg/kg of cladribine, or placebo. Concerns about baseline differences between treatment groups and funding by industry downgraded the quality assessment of this trial.[1] The FDA-approved cladribine dosage is a cumulative dose of 3.5 mg/kg. Cladribine is only indicated for the treatment of adults with RRMS and active SPMS. Cladribine is serious safety concerns and the manufacturer's label contains a black box warning related to malignancies and teratogenicity. Because of its adverse effect profile, cladribine is generally reserved for patients who do not tolerate or have inadequate response to other drugs for MS. Compared to placebo, cladribine 3.5 mg/kg significantly reduced relapse rates over 24 months (ARR 0.33 vs. 0.14; P<0.001; low QoE).[1] Similar results were seen in the non-FDA-approved dose group of 5.25 mg/kg.[1] Cladribine 3.5 mg/kg significantly reduced disability progression compared to placebo (HR 0.67; 95% CI, 0.48 to 0.93; low QoE).[1] Similar results were seen in the non-FDA-approved dose group of 5.25 mg/kg.[1] Changes in disability (EDSS) and function (MSFC) were not evaluated.[1] Persistence was significantly higher in the cladribine 3.5 mg/kg group compared with placebo (91.9% vs. 87%; P value not reported; low QoE).[1] In the non-FDA approved dose group, 89.0% of participants in the 5.25 mg/kg completed the study.[1]

The most common adverse events reported by participants were headache (17% to 24%), lymphocytopenia (22% to 32% in the cladribine groups, vs. 2% in the placebo group), nasopharyngitis (13% to 14%), upper respiratory tract infection (10% to 13%), and nausea (9% to 11%).[1] In addition, 2.3% of participants in the

cladribine 3.5 mg/kg group reported infections and infestations compared to 1.6% of those on placebo.[1] Neoplasms (benign, malignant, and unspecified) were diagnosed in 1.4% of participants in the cladribine 3.5 mg/kg group.[1] No neoplasms were reported in the placebo group.[1] There were 3 cases of cancer in the cladribine 3.5 mg/kg group (1 melanoma, 1 pancreatic cancer, and 1 ovarian cancer).[1] In addition, 20 patients in the cladribine groups (8 patients at 3.5 mg/kg vs. 12 patients at 5.25 mg/kg) developed herpes zoster infections.[1] No significant difference in serious AEs between cladribine and placebo were reported (P value note reported; low QoE).[1]

Peginterferon beta-1a vs. Placebo (1 RCT; 1012 participants)

One fair-quality RCT compared SC peginterferon beta-1a 125 mcg every 2 weeks with placebo over 48 weeks in adults with RRMS.[1] Concerns about differential loss to follow-up, author conflicts of interest, and funding by industry contributed to the fair-quality assessment of this trial.[1] Peginterferon beta-1a significantly reduced relapse rates compared to placebo (ARR 0.26 vs. 0.40; rate ratio 0.64; 95% CI, 0.50 to 0.83; low QoE).[1] Compared to placebo, peginterferon beta-1a significantly reduced disability progression (HR 0.62; 95% CI, 0.40 to 0.97; moderate QoE).[1] Changes in disability (EDSS) and function (MSFC) were not evaluated.[1] Overall, 85.5% of participants in the peginterferon beta-1a group completed the 48-week trial compared with 91.2% of participants in the placebo group, with lower persistence in the peginterferon group (P value not reported; moderate QoE).[1] No significant difference in serious AEs between peginterferon beta-1a and placebo was reported (low QoE).[1]

Siponimod vs. Placebo (2 RCTs; 1756 participants)

Two fair-quality RCTs that compared siponimod to placebo were identified for inclusion in the DERP report.[1] Concerns about author conflict of interest and funding by industry were the 2 issues that impacted quality assessment for these RCTs.[1] In the larger trial, 1651 adults with SPMS were randomized to oral siponimod 2 mg once daily or placebo for up to 3 years.[1] In the smaller trial, 188 adults with RRMS were randomized to 1 of 4 groups; siponimod 10 mg, siponimod 2 mg, siponimod 0.5 mg, or placebo once daily for 6 months.[1] The FDA-recommended maintenance dose for siponimod is 2 mg for adults with relapsing MS and 1 mg for adults with a CYP2C9*1/*3 or *2/*3 genotype.[1] Siponimod 2 mg significantly reduced relapse in RRMS (ARR ratio 0.45; 95% CI, 0.34 to 0.59) and in SPMS (ARR 0.20 vs. 0.58; P=0.04; 2 RCTs; moderate QoE) compared to placebo.[1] Siponimod 2 mg significantly reduced disability progression in adults with SPMS (HR 0.79; 95% CI, 0.65 to 0.95; 1 RCT; low QoE;).[1] No significant difference in function was observed between siponimod 2 mg and placebo, as measured by the MSFC in patients with SPMS (p=0.08; 1 RCT; very low QoE).[1] In the larger trial, 81.7% of participants with SPMS in the siponimod 2 mg group completed the trial compared with 77.7% in the placebo group, with a maximum trial duration of 3.5 years (P=0.06; low QoE).[1] Change in disability (EDSS) was not evaluated.

In the siponimod 2 mg groups, the most commonly reported adverse events were headache (31%), nasopharyngitis (12%), vertigo (12%), infections and infestations (49%), and hypertension (12%).[1] In the placebo groups, the most commonly reported adverse events were infections and infestations (49%), dizziness (9% to 13%), nasopharyngitis (11% to 19%), and upper respiratory tract infections (0% to 16%).[1] Serious adverse events in the siponimod groups included second-degree atrioventricular block (6%), intentional overdose (2%), and urinary tract infection (1%).[1] Serious adverse events in the placebo groups included urinary tract infection (1%), suicide attempt (1%), gait disturbance (1%), and paraparesis (i.e., partial paralysis of the legs; 1%).[1] Overall, 2 patients (1 in the siponimod group and 1 in the placebo group) were diagnosed with a basal cell carcinoma.[1] Participants in the siponimod groups and in the placebo groups had raised alanine aminotransferase levels (1% vs. <1% in SPMS; 8% vs. 0 in RRMS) and raised aspartate aminotransferase levels (<1% vs. <1% in RRMS; results in SPMS patients not reported).[1] No significant differences in serious AEs were identified between siponimod 2 mg and placebo in patients with SPMS or RRMS (RR 11.16; 95% CI 0.62 to 202.40 in adults with RRMS and RR 1.18; 95% CI 0.93 to 1.49 in adults with SPMS; 2 RCTs; very low QoE).[1]

Ozanimod 0.5 mg and 1 mg vs. Placebo (1 RCT; 258 participants)

One poor-quality, phase 2 RCT compared ozanimod 0.5 mg or 1 mg with placebo in adults with relapsing MS over 24 weeks.[1] Risk of bias included concerns about baseline differences, short duration of follow-up, author conflict of interest, and funding by industry.[1] No significant difference in relapse rates with ozanimod compared to placebo was reported (ARR 0.35 0.5 mg, vs. 0.50 placebo; OR, 0.69; 95% CI, 0.36 to 1.34; ARR 0.24 1 mg, vs. 0.50 placebo; OR, 0.47; 95% CI, 0.22 to 1.01; low QoE).[1] Participants in both ozanimod groups were more likely to be relapse-free at 24 weeks than participants in the placebo group, but this difference was not formally statistically tested (83% ozanimod 0.5 mg, vs. 89% ozanimod 1 mg, vs. 77% placebo; *P* value not reported).[1] No significant difference in persistence between groups was observed (97.7% ozanimod 0.5 mg; 98.8% ozanimod 1 mg; 96.6% placebo; moderate QoE).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated.

The most commonly reported adverse events in the ozanimod groups were nasopharyngitis (6% to 13%), headache (4% to 6%), and urinary tract infection (2% to 7%).[1] Participants in the placebo groups also experienced these adverse events, with the proportions of headache (9%) and nasopharyngitis (14%) numerically higher in the placebo group compared with the ozanimod groups.[1] In the ozanimod 0.5 mg group, 3 serious treatment-emergent adverse events occurred (3%) and were assessed as being unrelated to treatment (optic neuritis, somatoform autonomic dysfunction, and uterine cervical squamous metaplasia).[1] Increased alanine aminotransferase greater than 3 times the upper limit of normal occurred in 3 participants in the ozanimod groups.[1] No significant difference in serious AEs was noted (very low QoE).[1]

Diroximel Fumarate vs. Placebo

No eligible studies were identified to compare diroximel fumarate with placebo. The FDA approval in 2019 was based on bioavailability studies comparing oral dimethyl fumarate delayed release capsules to diroximel fumarate delayed-release capsules and 2 placebo-controlled trials of dimethyl fumarate.[1] Since FDA-approval, 1 ongoing study and 1 published RCT evaluating the efficacy and safety of diroximel fumarate were published; however, neither study met DERP inclusion criteria for this report.[1]

2. Effectiveness and Harms of DMDs for CIS

Cladribine vs. Placebo (1 RCT; 412 participants)

One poor-quality RCT compared cladribine 3.5 mg/kg and placebo over 24 months in adults with a first clinical demyelinating event.[1] Risks of bias included high and differential loss to follow-up, early termination, author conflict of interest, and funding by industry.[1] This trial was terminated early because the sponsor suspended the development of cladribine. Cladribine is not FDA-approved for use in people with CIS because of concerns about safety.[1] Cladribine significantly reduced conversion to MS compared to placebo (HR 33; 95% CI, 0.21 to 0.51; moderate QoE).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated. Compared to placebo, cladribine significantly reduced persistence (RR 0.90; 95% CI, 0.82 to 0.99; low QoE).[1]

The most commonly reported adverse events in the cladribine and placebo groups were headache (31% vs. 28%) and nasopharyngitis (17% vs. 18%).[1] Participants in the cladribine group contracted herpes virus infections at a higher rate than participants in the placebo group (8% vs. 1%).[1] Overall, 3 patients in the cladribine group and 6 patients in the placebo group were diagnosed with neoplasms.[1] Of these, 2 patients in the cladribine 3.5 mg/kg group were diagnosed with cancer; 1 with papillary thyroid cancer and 1 with squamous cell carcinoma.[1] No significant difference between cladribine and placebo in serious adverse events was observed (11% vs. 10%; p value not reported; low QoE).[1]

Glatiramer Acetate 20 mg vs. Placebo (1 RCT; 481 participants)

One fair-quality RCT compared SC glatiramer acetate to placebo over 36 months in people with CIS.[1] Concerns about early termination of the study due to benefit observed with glatiramer, author conflict of interest, and funding by industry contributed to the quality assessment of this RCT.[1] Compared to placebo, glatiramer acetate reduced conversion to MS (HR, 0.55; 95% CI, 0.40 to 0.77; moderate QoE).[1] Patients in the glatiramer acetate group also had a lower risk of a second attack (24.7% vs. 42.9%; OR 0.41; 95% CI, 0.28 to 0.62).[1] The time to conversion to MS was also longer in the glatiramer acetate group compared with the placebo group (722 days vs. 336 days; P=0.004).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated. No significant difference in persistence between glatiramer acetate and placebo was noted (84.8% vs. 91.2%; p value not reported; low QoE).[1] No significant difference in serious adverse events was observed (8% glatiramer acetate vs. 5% placebo; P value not reported; low QoE).[1]

Interferon Beta-1b 250 mcg vs. Placebo (1 RCT; 487 participants)

One fair-quality RCT compared SC interferon beta-1b with placebo over 24 months in adults with a first clinical demyelinating event.[1] Risks of bias included concerns about author conflict of interest and funding by industry.[1] Compared to placebo, interferon beta-1b significantly reduced conversion to MS (HR 0.50; 95% CI, 0.36 to 0.70; moderate QoE).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated. No significant difference in persistence was noted between the interferon (78.7%) and placebo groups (84.6%; p value not reported; low QoE).[1] No significant difference in serious adverse events between groups was observed (very low QoE).[1]

Interferon Beta-1a (various doses) vs. Placebo (4 RCTs; 1411 participants)

Four RCTS compared interferon beta-1a SC and IM dosing regimens with placebo over 2 to 3 years in adults with a first episode suggestive of MS, including a first clinical demyelinating event.[1] Three trials were assessed as fair-quality due concerns about lack of reporting on randomization, author conflict of interest, and funding by industry.[1] One trial (n=217) was evaluated as poor-quality due to lack of reporting on key study components (including randomization and blinding), intent-to-treat analysis not being conducted, and no information on author conflicts of interest or study funding.[1] Compared to placebo, interferon beta-1a significantly reduced conversion to MS at 2 years (RR 0.80; 95% CI, 0.68 to 0.95) and at 3 years (RR 0.62; 95% CI, 0.50 to 0.78; meta-analysis of 4 RCTs; low QoE).[1] No significant difference in disability, as measured by the EDSS was reported (1 RCT; low QoE).[1] Disability progression and change in function (MSFC) were not evaluated. At 2 years, similar numbers of participants in the interferon beta-1a groups and placebo groups completed the trials (RR 1.03; 95% CI, 0.98 to 1.09; 2 RCTs; moderate QoE).[1] Rates of serious adverse events were similar in the interferon beta-1a and placebo groups (RR 0.80; 95% CI, 0.52 to 1.25; meta-analysis of 4 RCTs very low QoE).[1]

Teriflunomide 7 mg and 14 mg vs. Placebo (1 RCT; 618 participants)

One fair-quality RCT compared teriflunomide 7 mg and 14 mg with placebo over 27 months in adults with a first clinical episode suggestive of MS.[1] Concerns about high loss to follow-up, author conflict of interest, and funding by industry contributed to the fair-quality assessement.[1] This trial was stopped early because of changes in the diagnostic criteria.[1] Teriflunomide significantly reduced conversion to MS (HR, 0.63; 95% CI, 0.42 to 0.95 for teriflunomide 7 mg; HR, 0.57; 95% CI, 0.38 to 0.87 for teriflunomide 14 mg; low QoE).[1] Patients in the teriflunomide groups and patients in the placebo group had similar rates of disability progression (10% for teriflunomide 7 mg [HR 0.98; 95% CI, 0.52 to 1.83 vs. placebo] vs. 7% for teriflunomide 14 mg [HR 0.70; 95% CI, 0.36 to 1.37 vs. placebo] vs. 10% placebo (very low QoE).[1] Teriflunomide significantly improved disability compared to placebo, as measured by the EDSS (mean change, -0.25 teriflunomide 7 mg vs. -0.27 teriflunomide 14 mg vs. -0.06 placebo; mean difference of -0.26 for teriflunomide 7 mg vs. placebo; mean difference of -0.23 for teriflunomide 14 mg vs. placebo; $P < .05$ for both comparisons; low QoE).[1] No significant difference in function, as measured by the MSFC was observed (low

QoE).[1] Overall, 73.2% of participants in the teriflunomide 7 mg group, 75.5% in the teriflunomide 14 mg group, and 71.6% in the placebo group completed the study. Persistence was not significantly different between groups (low QoE).[1] No significant difference in serious adverse events was noted (low QoE).[1]

3. Comparative Harms from Cohort Studies

Twenty-four cohort studies compared treatment discontinuation or treatment switch by disease-modifying therapy.[1] No studies compared treatment discontinuation or treatment switch by DMD for alemtuzumab, cladribine, diroximel fumarate, ocrelizumab, ozanimod, peginterferon beta-1a, or siponimod. Data from these cohort studies are summarized in **Table 2.**

Table 2: Summary of Comparative Harms with DMD's

Outcome	Comparison	Results
Overall Discontinuation	DMF vs. interferons or glatiramer acetate (2 studies)	Favors DMF
	DMF vs. fingolimod (4 studies)	Favors fingolimod
	DMF vs. teriflunomide (1 study)	Favors teriflunomide
	DMF vs. interferons, glatiramer or fingolimod (1 study)	No difference vs. DMF
	DMF vs. interferons (1 study)	Favors DMF
	Fingolimod vs. interferons (1 study)	Favors fingolimod
	Fingolimod vs. teriflunomide (2 studies)	Favors fingolimod
	Fingolimod vs. teriflunomide (1 study)	No difference
	Glatiramer vs. interferon beta-1b (2 studies) or interferon beta-1a (1 study)	No difference
	Glatiramer vs. interferons (1 study)	Favors interferons
Discontinuation due to AEs	DMF vs. fingolimod (1 study)	Favors fingolimod
	DMF vs. teriflunomide (1 study)	No difference
	DMF vs. teriflunomide (1 study)	Favors teriflunomide
	Glatiramer vs. interferon beta-1a (1 study)	Favors glatiramer
Discontinuation due to lack of efficacy	DMF vs. teriflunomide (1 study)	Favors DMF
	Fingolimod vs. interferons (2 studies)	Favors fingolimod
Time to discontinuation	DMF vs. interferon beta, glatiramer or teriflunomide (1 study)	No difference vs. DMF
	DMF vs. fingolimod (1 study)	Favors fingolimod
	Fingolimod vs. teriflunomide (1 study)	Favors fingolimod
	Glatiramer vs. interferon beta-1b (1 study)	No difference

Abbreviations: AE = adverse reaction; DMD = disease modifying drug; DMF = Dimethyl Fumarate

Serious Adverse Events

One cohort study found that the risk of liver injury was increased with MS therapies, including interferons and newer therapies, specifically alemtuzumab, teriflunomide, and fingolimod.[1] One cohort study evaluated the risk of PML and the analysis found that fingolimod and dimethyl fumarate were associated with an increased risk of PML.[1] Two studies evaluated infection risk. In 1 study, the rate of infections was lowest with interferon beta and glatiramer acetate.[1] Compared to no DMT, exposure to any second-generation DMT (fingolimod, dimethyl fumarate, or natalizumab) was associated with a significantly increased risk of an infection-related physician claim.[1] When assessed individually, the association was not significant for fingolimod and dimethyl fumarate.[1] One cohort

study evaluating the risk of cancer found that women with MS who are treated with glatiramer acetate had an increased risk of breast cancer, though the increase was not statistically significant.[1] All individuals with MS who were treated with interferon beta showed an increased risk of non-breast cancers. The increase was not statistically significant, although the effect was large.[1] However, the evidence is from only 1 retrospective study in Israeli patients, and may not be generalizable to the U.S. Medicaid population.[1] When comparing the DMTs directly, alemtuzumab, fingolimod, ocrelizumab, and teriflunomide significantly reduce relapses and are not associated with increased serious adverse events, compared with other disease-modifying therapies assessed in the eligible trials.[1]

New Safety Alerts:

1. Thirteen worldwide cases of stroke (ischemic and hemorrhagic) or arterial dissection, occurring shortly after the patient received alemtuzumab, have been reported to the FDA since its approval in 2014 to treat relapsing forms of MS.[16] Twelve of these cases reported symptoms within 1 day of receiving alemtuzumab.[16] As a result, the FDA added a new warning about this risk in the *Warnings and Precautions* section of the prescribing information in the drug label as of November 2108.[16] The risk of stroke was also added to the existing *Boxed Warning*, the FDA's most prominent warning.[16]

2. Thirty-five cases of severely increased disability accompanied by the presence of multiple new lesions on MRI that occurred 2 to 24 weeks after fingolimod was stopped were reported to the FDA since its September 2010 approval.[16] Most patients experienced this worsening in the first 12 weeks after stopping fingolimod.[16] The severe increase in disability in these patients was more severe than typical MS relapses, and in cases where baseline disability was known, appeared unrelated to the patients' prior disease state.[16] Several patients who were able to walk without assistance prior to discontinuing fingolimod progressed to needing wheelchairs or becoming totally bedbound.[16] In patients experiencing worsening of disability after stopping fingolimod, recovery varied. Seventeen patients had partial recovery, 8 experienced permanent disability or no recovery, and 6 eventually returned to the level of disability they had before or during fingolimod treatment.[16] As a result, the FDA added a new warning about this risk to the prescribing information of the fingolimod drug label and patient Medication Guide as of November 2018.[16]

New Formulations or Indications:

1. Monomethyl fumarate (Bafiertam™) received tentative FDA approval in November 2018 for treatment of people with relapsing MS, including CIS, RRMS, and SPMS. Dimethyl fumarate is the prodrug of monomethyl fumarate. The FDA issued final approval of monomethyl fumarate in April 2020, as Biogen's patent for dimethyl fumarate expired in June 2020. Because of its similarity to dimethyl fumarate, the FDA based the approval of monomethyl fumarate on clinical trials that demonstrated safety and efficacy of dimethyl fumarate.

2. Fingolimod (Gilenya®) received an expanded indication as of August 2019 for use in patients aged 10 years and older. Fingolimod had previously been FDA-approved for use in adults. A phase 3 trial randomly assigned patients 10 to 17 years of age with relapsing multiple sclerosis in a 1:1 ratio to receive oral fingolimod at a dose of 0.5 mg per day (0.25 mg per day for patients with a body weight of ≤40 kg) or IM interferon beta-1a at a dose of 30 mcg per week for up to 2 years.[17] The primary end point was the ARR. The mean age of the patients was 15.3 years.[17] The adjusted ARR was 0.12 with fingolimod and 0.67 with interferon beta-1a over a 2-year period (absolute difference, 0.55 relapses; relative difference, 82%; P<0.001).[17] Adverse events, excluding relapses of multiple sclerosis, occurred in 88.8% of patients who received fingolimod and 95.3% of those who received interferon beta-1a.[17] Serious adverse events occurred in 18 patients (16.8%) in the fingolimod group and included infection (in 4 patients) and leukopenia (in 2 patients).[17] Six patients had convulsions. Serious adverse events occurred in 7 patients (6.5%) in the interferon beta-1a group and included infection (in 2 patients) and supraventricular tachycardia (in 1 patient).[17]

References:

1. Shaw B CS, Kelly R, Vintro A, Anderson R, Harrod C. Disease-modifying drugs for multiple sclerosis. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2020.
2. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014;83(3):278-286.
3. Harrison DM. In the clinic. Multiple sclerosis. *Annals of internal medicine.* 2014;160(7):ITC4-2-ITC4-18; quiz ITC14-16.
4. Inojosa H, Proschmann U, Akgün K, Ziemssen T. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *J Neurol.* 2019.
5. Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. *Handb Clin Neurol.* 2014;122:231-266.
6. Olek MJ. Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults. Gonazlez-Scarano F. ed. UpToDate. Waltham MUIhwucAJ.
7. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. *Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology.* 2018;90(17):777-788.
8. Lexicomp® Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Accessed June 19, 2020.
9. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. 2020 Available at: https://www-micromedexsolutions-com.liboff.ohsu.edu Accessed June 19, 2020.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis. *An expanded disability status scale (EDSS).* 1983;33(11):1444-1444.
11. Amato MP, Portaccio E. Clinical outcome measures in multiple sclerosis. *J Neurol Sci.* 2007;259(1-2):118-122.
12. Lavery AM, Verhey LH, Waldman AT. Outcome measures in relapsing-remitting multiple sclerosis: capturing disability and disease progression in clinical trials. *Multiple sclerosis international.* 2014;2014:262350.
13. Ebers GC, Heigenhauser L, Daumer M, Lederer C, Noseworthy JH. Disability as an outcome in MS clinical trials. *Neurology.* 2008;71(9):624-631.
14. Sormani MP, Signori A, Siri P, De Stefano N. Time to first relapse as an endpoint in multiple sclerosis clinical trials. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2013;19(4):466-474.
15. Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited. *Current opinion in neurology.* 2002;15(3):239-245.
16. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed June 23, 2020.
17. Chitnis T, Arnold DL, Banwell B, et al. Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. *N Engl J Med.* 2018;379(11):1017-1027.

Appendix 1: Current Preferred Drug List

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

Oral Multiple Sclerosis Drugs

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

Length of Authorization:
- Up to 6 months

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

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4

Approval Criteria		
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1b, glatiramer acetate, interferon beta-1a, natalizumab, or mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #7
7. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the prescription for teriflunomide?	**Yes:** Go to #9	**No:** Go to #11
9. Is the patient of childbearing potential?	**Yes:** Go to #10	**No:** Approve for up to 6 months.
10. Is there documentation that the patient is currently on a reliable form of contraception?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #12	**No:** Go to #15
12. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. 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 #14	**No:** Approve up to 6 months.
14. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
15. Is the prescription for a fumarate product?	**Yes:** Go to # 16	**No:** Go to #17

Approval Criteria		
16. 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.
17. Is the request for cladribine?	**Yes:** Go to #18	**No:** Approve for up to 6 months
18. Is the patient of reproductive potential?	**Yes:** Go to # 19	**No:** Go to # 20
19. Is there documentation that the patient (or female partner of a male patient) is on a reliable form of contraception?	**Yes:** Go to # 20	**No:** Pass to RPh. Deny; medical appropriateness
20. Has the patient had an inadequate response to or they are unable to tolerate alternative MS treatment?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

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

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

Generic Name	FDA Indication (Adults unless otherwise indicated)		
	CIS	**RRMS**	**SPMS**
Cladribine		X	X
Fingolimod	X *(≥ 10 years)*	X *(≥ 10 years)*	X *(≥ 10 years)*
Siponimod	X	X	X
Ozanimod	X	X	X
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		
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, siponimod) Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for 6 hours after initial dose in a clinically appropriate area.
- 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 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 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 women 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: *8/20 (DM); 6/20; 11/17 (DM); 11/16; 9/15; 9/13; 5/13; 3/12*
Implementation: *9/1/20; 1/1/18; 1/1/17; 1/1/14; 6/21/2012*

Ocrelizumab (Ocrevus™)

Goal(s):

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

Length of Authorization:

- 6 to 12 months

Requires PA:

- Ocrevus™ (ocrelizumab) pharmacy or physician administered claims

Covered Alternatives:

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

Approval Criteria		
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

Approval Criteria		
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: *6/20; 11/17 (DM); 1/17*
Implementation: *7/1/20; 1/1/18; 4/1/17*

Dalfampridine

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

Dalfampridine

Covered Alternatives:

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

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

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

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

Clinical Notes:

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

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

Peginterferon Beta-1a (Plegridy®)

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.
3. Will the prescriber consider a change to a Preferred MS product?	**Yes:** Inform provider of covered alternatives in the class. Additional information can be found at www.orpdl.org.	**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: *8/20 (DM); 6/20; 11/17 (DM); 9/23/14*
Implementation: *10/15*

Natalizumab (Tysabri®)

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Natalizumab (Tysabri®)

Covered Alternatives:

- 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. Has the patient been screened for Jason Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness
3. Is the request for an FDA-approved form of multiple sclerosis?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

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

P&T / DUR Action: 8/20 (DM); 11/17 (DM)
Implementation: 1/1/18