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Class Update with New Drug Evaluation: Disease-Modifying Drugs for Multiple Sclerosis

Date of Review: November 2017
Date of Late Review: November 2016

Literature Search: 9/1/2016 – 9/15/17

Generic Name: ocrelizumab
PDL Class: Multiple Sclerosis

Brand Name: Ocrevus™ (Genentech)
AMCP Dossier Received: Yes

Purpose for Class Update:
Evidence for the comparative effectiveness of disease modifying drugs (DMD) for multiple sclerosis (MS) was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in November 2016 as summarized in a Drug Effectiveness Review Project (DERP) report. This review examines new comparative evidence of DMDs for MS published since 2016 and summarizes the evidence for a new DMD approved to treat MS, ocrelizumab.

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

Conclusions:
- Since the last review, one systematic review and network meta-analysis was completed by the Institute for Clinical Evidence and Research (ICER) to evaluate all the DMDs used to manage MS,[1] a Cochrane systematic review compared the safety and efficacy of interferons and glatiramer in relapsing-remitting multiple sclerosis (RRMS),[2] and the National Institute for Health and Care Excellence (NICE) published guidance focused on the use of daclizumab in treating adults with RRMS.[3]
- The ICER network meta-analysis (NMA) indirectly compared daclizumab, glatiramer acetate, interferon beta-1a, peginterferon beta-1a, interferon beta-1b, dimethyl fumarate, fingolimod, teriflunomide, alemtuzumab, natalizumab, ocrelizumab and rituximab in management of RRMS. Most of the included trials were of moderate quality.[1] Alemtuzumab, natalizumab, and ocrelizumab had the greatest reduction in annualized relapse rate with about a 70% reduction compared to placebo Relative Rate (RR) of relapse: alemtuzumab: 0.28, 95% CI 0.22 to 0.35; natalizumab RR 0.31, 95% Confidence Interval (CI) 0.25 to 0.40; ocrelizumab RR 0.35, 95% CI 0.27 to 0.44).[1] Fingolimod (RR 0.46; 95% CI 0.30 to 0.5), daclizumab (RR 0.46; 95% CI, rituximab (RR 0.51; 95% CI 0.27 to 0.93), and dimethyl fumarate (RR 0.53; 95% CI 0.43 to 0.63) were also effective with 47% to 54% reduction compared to placebo.[1] The interferons, glatiramer acetate 20 mg (RR 0.67; 95% CI 0.52 to 0.86), and teriflunomide (RR 0.77; 95% CI 0.67 to 0.93) were less effective with 17% to 37% reduction versus placebo.

All DMDs were statistically significantly superior to placebo for reduction in annualized relapse rate.[1] Only 2 drugs, ocrelizumab and rituximab, were evaluated for treatment of primary progressive multiple sclerosis (PPMS) and were not included in a network meta-analysis to evaluate treatments in PPMS. Currently there is limited data from two placebo-controlled trials to evaluate the efficacy of ocrelizumab and rituximab in adults with PPMS.

- Moderate quality evidence included in a Cochrane systematic review concluded there was no difference in efficacy as measured by RRMS progression and risk of relapse between interferon and glatiramer.[2]
- NICE guidance recommends daclizumab as an option for treating RRMS in adults, only if: the person has active RRMS previously treated with DMD therapy, or rapidly evolving severe RRMS (that is, at least 2 relapses in the previous year and at least 1 gadolinium enhancing lesion at baseline MRI) and alemtuzumab is contraindicated or otherwise unsuitable.[3]
- The FDA labeling for dimethyl fumarate and fingolimod was revised to include warnings about possible progressive multifocal leukoencephalopathy (PML) infections associated with therapy.[4,5] Dimethyl fumarate labeling was revised to include risks of hepatotoxicity that could require hospitalization.[4]
- There is insufficient evidence to address the role of DMDs in managing specific subpopulations of persons with MS.
- The efficacy of ocrelizumab when compared to placebo in treatment of PPMS is based on low quality evidence from the ORATORIO trial.[6] A lower probability of short-term disease progression over 12 weeks as assessed by the Expanded Disability Score (EDSS) was demonstrated with ocrelizumab compared to placebo (32.9% vs. 39.3%, respectively; hazard ratio (HR)=0.76; 95% confidence interval (CI) 0.59 to 0.98; p = 0.03, number needed to treat (NNT) = 16).[6] The FDA advisory committee identified several aspects of the ORATORIO trial design that may have biased the researchers' conclusions.[7] Imputation of primary outcome results for patients that dropped out of the placebo arm as non-responders may have falsely increased the percentage of patients who had disability progression, which supported the researcher's hypothesis that ocrelizumab was more effective than placebo.[7] The Kaplan-Meier curve demonstrated a consistent rate of disease progression from 18 weeks through 120 weeks, suggesting the effect of ocrelizumab was limited to the first 18 weeks of treatment.[7] Finally, for 29% of patients the investigators reported the baseline EDSS after infusion of the study drug and in 67% of patients after randomization, which indicates a failure of investigators to follow protocol.[7] Despite these limitations in study design and implementation, the FDA reviewers concluded ocrelizumab should be approved to treat PPMS due an unmet treatment need in adults with PPMS.
- There is moderate quality evidence from 2 trials that compared interferon beta-1a to ocrelizumab in RRMS. In one trial, the annualized relapse rate was less with ocrelizumab at week 96 compared to interferon (0.16 vs. 0.29, respectively; HR 0.51; 95% CI 0.40-0.72; p<0.001).[8] Similar results were observed in the second trial, as patients treated with ocrelizumab had a lower annualized relapse rate at week 96 compared to interferon beta-1a (0.16 vs. 0.29, respectively; HR 0.53 (95% CI 0.40 to 0.71, p=0.001).[9]
- The most common adverse events observed with ocrelizumab treatment for patients with PPMS were infection (ocrelizumab 49% vs. placebo 43%) and infusion-related reactions (ocrelizumab 49% vs. placebo 26%).[6] In both RRMS trials, infusion reactions occurred in 34% of ocrelizumab patients compared to 10% of interferon beta-1a patients.[8] The incidence of infection was 48% with ocrelizumab compared to 38% with interferon beta-1a in these 2 RRMS trials.[8] Premedication with acetaminophen and an antihistamine may help prevent the occurrence of infusion-related reactions.[10] Ocrelizumab is contraindicated in patients with active Hepatitis B infection.[10]
- Ocrelizumab is the first drug approved by the Food and Drug Administration (FDA) to treat PPMS based on modest reductions in disease progression over 12 weeks as evaluated by EDSS. Ocrelizumab may also provide an alternative treatment option for patients with RRMS.

Recommendations:

- Apply clinical prior authorization (PA) criteria to ocrelizumab for both physician administered and point of sale pharmacy claims (see **Appendix 4**). Limit use to:
    - Funded MS conditions
    - History of inadequate response to at least 2 disease modifying agents (DMA) approved for MS; and
    - Prescribed by a neurologist.
- Create clinical PA criteria for natalizumab separate from the biologic PA criteria.
- Amend PA criteria for oral multiple sclerosis drugs to remove requirement of failure of a trial of interferon beta 1a or interferon 1b, and glatiramer.
- After evaluation of comparative costs in executive session, no changes to the PDL were recommended.
- Refer funding of ocrelizumab for PPMS to the Health Evidence Review Commission (HERC) for prioritization consideration.

Previous Conclusions:

- In the DERP network meta-analysis, ocrelizumab 600 mg infusion was considered to have the highest probability (82%) of being the best treatment to prevent relapse in relapsing-remitting multiple sclerosis (RRMS) followed by alemtuzumab 12 mg infusion (17.3%) followed by oral fingolimod 0.5mg (0.4%).
- There is moderate evidence in patients with RRMS that alemtuzumab infusion is associated with reduced relapse rates compared with interferon beta-1a 44 mcg subcutaneous (SC).
- Fingolimod is associated with lower risk of relapse compared with interferon beta-1a 30 mcg intramuscular (IM), but both agents may be also associated with increased adverse events.
- Relapse rates were increased with teriflunomide 7 mg but not 14 mg, compared to interferon beta-1a 44 mcg SC. However, treatment with teriflunomide resulted in fewer study withdrawals due to adverse events.
- Moderate quality evidence showed ocrelizumab 600 mg delayed disability progression in patients with primary progressive MS (PPMS) with no difference in serious adverse events when compared to placebo Ocrelizumab and daclizumab may be promising additions to current MS treatment, but additional comparative research is needed to draw definitive conclusions regarding benefits and harms.
- Interferon beta-1a IM (Avonex) appeared to have the lowest immunogenicity of the interferons, with rates of development of neutralizing antibodies of 0% to 14% reported, starting around 9 months of treatment. With interferon beta-1a SC (Rebif®), antibodies also appeared around 9 months, with rates of immunogenicity from 11% to 46%; with interferon beta-1b SC (Betaseron), neutralizing antibodies appeared as early as 3 months into treatment in 15% to 45% of patients.
- For patients with clinically isolated syndrome (CIS), there were no head-to-head trials of the drugs included in the DERP review. A meta-analysis of the comparative effectiveness of glatiramer, interferon, and two doses of teriflunomide found no statistically significant differences in rates of progression to MS, though the analysis estimated the highest probability (45.6%) that interferon beta-1b (Betaseron®) was the best of these drugs for CIS.
- Compared to interferon beta-1a (Avonex), withdrawals due to adverse events were more likely with teriflunomide 7 mg, glatiramer or interferon beta-1b (Betaseron), and less likely with teriflunomide 14 mg than with glatiramer. In the DERP meta-analysis, alemtuzumab 12 mg had the highest probability of being the best treatment with lower rates of study withdrawals due to adverse events (70.5%) followed by placebo (13.1%) and is consistent with Cochrane's analysis.

- There was a significant improvement in annualized relapse rates of daclizumab 150mg compared with interferon beta-1a 30 mcg IM based on age (≤ 35 years, annualized relapse rate 0.46, 95% CI 0.35 to 0.62; > 35 years, annualized relapse rate 0.74, 95% CI 0.59 to 0.92). The improvement in annualized relapse rate seen with daclizumab HYP compared with interferon beta-1a 30 mcg IM was significantly greater in those aged 35 or less.
- Fingolimod exposure in utero may be associated with increased risk of poor fetal outcomes.

Previous Recommendations:

- Revise clinical prior authorization criteria to require assessment of lymphocyte counts and confirmation of negative pregnancy test before initiating therapy with dimethyl fumarate.
- Update clinical prior authorization criteria for oral MS drugs to reflect Guideline Note 95 that restricts coverage to RRMS only.
- After evaluation of drug costs in the executive session, Glatopa was designated as nonpreferred and Copaxone was designated as a preferred agent on the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP).

Background:

MS is a chronic, inflammatory, immune-mediated disease that adversely affects the optic nerves, brain, and spinal cord. Worldwide, it is estimated that 2.3 million individuals have been diagnosed with MS.[11] In 2014, the prevalence of MS in the United States (U.S.) was estimated to be around 570,000 people.[12] Increased rates of MS have been observed in northern and southern latitudes compared with equatorial countries.[13] The age of MS onset varies between 15 and 50 years of age and occurs more frequently in women than in men.[13] The annual healthcare costs associated with MS in the U.S. are estimated to be $28 billion.[14] Epidemiologic studies assessing risks to relatives of patients with MS have identified a possible familial correlation to the disease. First-degree relatives may have a 15- to 35-times greater risk of developing MS than the general population.[15] MS may also be linked to certain environmental factors including exposure to Epstein-Barr virus, reduced sun exposure, Vitamin D deficiency, and smoking.[16]

Plaques or lesioned areas detected through magnetic resonance imaging (MRI) are a hallmark of MS. Chronic inflammation causes central nervous system (CNS) damage resulting in demyelination and axon degeneration.[17] Patients with MS encounter impaired mobility, vision, coordination, bladder function, and cognitive function. Quality of life may be adversely impacted due to chronic pain, depression and fatigue also associated with MS. The course of MS is highly unpredictable and varies from person to person. About 15% of patients have a relatively benign course, while about 60% to 70% develop secondary progression.[18] Diagnostic criteria for MS include clinical, laboratory, and radiologic assessments. Although the diagnosis can be made on clinical grounds alone, MRI can assist with lesion detection within the CNS and can further support a MS diagnosis.[19] The McDonald criterion is a tool used by clinicians to diagnosis MS based upon the number of clinical attacks and lesions.[20]

Progression of MS is assessed by the amount of disability caused by the disease. The Functional Systems Scale (FSS) and Expanded Disability Status Scale (EDSS) were developed to provide standardized measures of neurological impairment in MS. The FSS is an ordinal clinical rating scale ranging from 0 (no disability) to 6 (severe disability) which assesses eight different aspects of neurologic, bowel, bladder, sensory, and visual function in an MS patient.[21] The EDSS ranges from 0 (normal neurologic exam) to 5 (ambulatory without aid for 200 meters) to 10 (death due to MS), in increments of 0.5 with lower scores indicating more mobility and activity by the patient.[21] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[22] 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.[23] Despite these limitations, the EDSS continues to be the standard disability measure for MS clinical research. Clinical trials have defined disability progression as an increase in EDSS scale of 0.5 to 1.0 point after 3 or 6 months.[24] Some researchers have proposed that longer trials (with a

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.[25] 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. 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.[24]

The annualized relapse rate is often included as an outcome measure for MS clinical trials because it is easy to quantify. Relapses are generally defined as neurologic symptoms lasting more than 24 hours which occur at least 30 days after the onset of a preceding event.[24] 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.[24] 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.[26] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[26] 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.[24] 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.[27]

Four distinct clinical courses have been identified for MS: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS).[19] CIS 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.[28] SPMS begins as relapsing-remitting MS, but gradual worsening of symptoms is observed over time. Approximately 65% of RRMS patients will enter the secondary progressive phase.[28] PPMS 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.[13] PPMS is distributed more equally between men and women than RRMS. The majority of available direct evidence continues to reside in patients with relapsing-remitting MS rather than progressing forms of MS. To date, none of the available disease-modifying drugs (DMDs) have proven efficacious in reducing disability associated with PPMS and treatment has primarily been supportive. The Health Evidence Review Commission (HERC) has stipulated via Guideline Note 95 that once a diagnosis of primary progressive or secondary progressive multiple sclerosis is reached, immune modifying therapies are no longer covered.[29]

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. Interferons have proven efficacy in managing MS and do not require substantial clinical monitoring, so they are considered first-line agents for treating MS.[30] The development of neutralizing antibodies to interferon beta medications may lead to a decreased efficacy of these agents. However, the long term impact of neutralizing antibodies on clinical outcomes has not been fully determined. The DMDs that have been FDA approved for the treatment of MS are presented in **Table 1**. Early use of DMDs in patients with RRMS has been shown to reduce the annualized relapse rate, lessen severity of relapses, and slow progression of disability.[30] Patient preference and tolerance should be considered when comparing oral medications to injectable options. Around 25% of patients discontinue interferon therapy within 1 to 2 years due to difficulty adhering to daily or weekly injection regimens.[31]

Ocrelizumab received FDA approval for treatment of adult patients with RRMS or PPMS in March 2017. Ocrelizumab is the first 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.[9]

Table 1: Disease-Modifying Drugs used to treat MS[30]

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication	REMS Program	Major Safety Concerns	Monitoring
Oral Agents						
Fingolimod	Gilenya	0.5 mg PO once daily	RRMS	No	Viral infections, fungal infections, bradycardia with first dose, hepatic injury, and macular edema	Cardiac monitoring with the first dose. Ophthalmologic screening at baseline and 3-4 months after starting therapy. LFTs and CBC every 6 months.
Teriflunomide	Aubagio	7 mg or 14 mg PO once daily	RRMS	No	Hepatotoxicity, hypertension, teratogenicity	CBC, LFT, serum creatinine, and blood pressure every 6 months
Dimethyl Fumarate	Tecfidera	240 mg PO twice a day	RRMS	No	Lymphopenia, PML, and hepatotoxicity	CBC and LFTs every 6 months
Injectable Agents						
Mitoxantrone	Novantrone	12 mg/m^2 IV infusion every 3 months – duration of therapy limited to 2 years	RRMS SPMS		Cardiac toxicity	Cardiac function before each infusion and CBC and LFTs every 6 months
Glatiramer Acetate	Copaxone, Glatopa	20 mg SC once daily; OR 40 mg SC three times a week at least 48 hours apart	RRMS	No	Transient post injection reactions (chest pain, dyspnea, flushing, urticaria)	None
Interferons						
Interferon beta-1a	Avonex	30 mcg IM once weekly	RRMS	No	Hepatotoxicity, thrombocytopenia, and depression	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 treatment courses. Total duration of therapy: 24 months. First course: 12 mg once a day for 5 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* reserve for patients who have inadequate response to 2 MS drugs*	Yes	Serious infusion reactions, viral infections, thyroid autoimmunity, thrombocytopenia	Thyroid function every 3 months and monthly CBC/ platelet assessment.
Daclizumab HYP (High Yield Process)	Zinbryta	150 mg SC once a month	RRMS* reserve for patients who have inadequate response to 2 MS drugs*	Yes	Hepatotoxicity, serious infection	LFTs every month during treatment
Natalizumab	Tysabri	300 mg via IV infusion every 4 weeks *consider risk of PML to benefit of therapy*	RRMS	Yes	PML, hepatotoxicity	JCV antibody testing and brain MRI every 6 months. CBC and LFTs every 6 months
Ocrelizumab	Ocrevus	300 mg via IV infusion every 2 weeks for 2 doses followed by 600mg IV every 6 months	RRMS and PPMS	No	Infusion reactions, infection	Hepatitis B virus screening prior to starting therapy

Abbreviations: AML = acute myeloid leukemia; CBC = complete blood count; FDA = U.S. Food and Drug Administration; IM = Intramuscular; IV = Intravenous; JCV = John Cunningham virus; LFTs = liver function tests; 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.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

Systematic Reviews:

Cochrane Systematic Review

A 2016 Cochrane review assessed whether interferons-beta and glatiramer acetate differ in terms of safety and efficacy for treatment of people with RRMS.[2] Six trials contributed to the review and included a total of 2904 participants randomly assigned to interferons (n = 1704) and glatiramer (n = 1200). The treatment duration was 3 years for one study, 2 years for the other 4 RCTs while one study was stopped early (after 1 year).[2] The interferon products included interferon-beta 1b 250 mcg (two trials, 933 participants), interferon-beta 1a 44 mcg (three trials, 466 participants) and interferon-beta 1a 30 mcg (two trials, 305 participants).[2] All studies were at high risk for attrition bias. There was moderate quality evidence for primary clinical outcomes, but was low quality for safety and surrogate endpoints such as MRI outcomes (number of active T2 lesions).[2] Both therapies showed similar clinical efficacy at 24 months (number of participants with relapse (risk ratio (RR) 1.04, 95% confidence interval (CI) 0.87 to 1.24) or progression (RR 1.11, 95% CI 0.91 to 1.35).[2] However at 36 months, evidence from a single study suggests that relapse rates were higher in the group given interferons than in the glatiramer group (RR 1.40, 95% CI 1.13 to 1.74, p = 0.002).[2] Secondary MRI outcomes analysis showed that effects on new or enlarging T2 or new contrast-enhancing T1 lesions at 24 months were similar (mean difference (MD) -0.15, 95% CI -0.68 to 0.39, and MD -0.14, 95% CI -0.30 to 0.02, respectively).[2] The number of participants who dropped out of the study because of adverse events was similar in the two groups (RR 0.95, 95% CI 0.64 to 1.40).[2]

The effects of interferon-beta and glatiramer in the treatment of people with RRMS, including clinical (e.g. people with relapse, risk to progression) and MRI (T1 or T2 weighted lesions) measures, seem to be similar or to show only small differences.[2] When MRI lesion load accrual is considered, the effect of the two treatments differs, in that interferon-beta were found to limit the increase in lesion burden as compared with glatiramer, but the clinical significance of this observation is uncertain.[2]

Institute for Clinical and Economic Review (ICER)

ICER published a report in early 2017 that evaluated DMD therapy for RRMS and PPMS for effectiveness and value.[1] The California Technology Assessment Forum (CTAF) Panel prepared the report.[1] All panel members met conflict of interest guidelines as outlined by ICER.[1] The therapies of interest for RRMS included: daclizumab, glatiramer acetate, interferon beta-1a, peginterferon beta-1a, interferon beta-1b, dimethyl fumarate, fingolimod, teriflunomide, alemtuzumab, natalizumab, ocrelizumab and rituximab. The medications of interest for PPMS were ocrelizumab and rituximab. The literature search identified 1,834 citations. After reviewing the titles and abstracts, 113 full text articles were evaluated. There were 33 unique randomized trials with 21,768 patients for the RRMS indication and 2 randomized trials for the PPMS indication. A network meta-analysis (NMA) was performed to combine direct (head-to-head) and indirect evidence for relapse rate and sustained disability progression. NMA is a procedure that permits inferences into the comparative effectiveness of interventions that may or may not have been evaluated directly against each other.[32] Estimates of treatment effects from NMAs should be interpreted with caution as treatment rankings or probabilities can be misleading.[32] In the absence of head-to-head evidence, the strength of evidence generated from NMA is low for indirect comparisons.

The average age of the study participants was about 36 years across the RRMS trials and approximately 70% were women. The participants were predominantly white. The average duration of MS ranged from 1.1 to 10.5 years across the trials, but most averaged 5-6 years. The EDSS grade at baseline ranged from 2.0 to 3.0, indicating mild disease severity, and the average number of relapses in the prior year ranged from 1.0 to 2.2. Only 5 of the 33 studies included in the review were rated as good quality by the authors of the ICER report. The primary reasons the other trials were downgraded were lack of blinding of the study participants and staff, significant loss to follow-up, and lack of measurement of one of the key outcomes: disability progression sustained for 24 weeks.[1]

Seventeen publications were evaluated as fair quality. The remaining 11 studies included in the NMA were rated as poor quality, primarily because of greater than 20% loss to follow-up, but were included in the NMA.[1]

RRMS Efficacy

In the ICER NMA, alemtuzumab, natalizumab, and ocrelizumab had the greatest reduction in annualized relapse rate with about a 70% reduction compared to placebo (Relative rate (RR) of relapse: alemtuzumab: 0.28, 95% CI 0.22 to 0.35; natalizumab RR 0.31, 95% Confidence Interval (CI)0.25 to 0.40; ocrelizumab RR 0.35, 95% CI 0.27 to 0.44).[1] Fingolimod (RR 0.46; 95% CI 0.30 to 0.5), daclizumab (RR 0.46; 95% CI, rituximab (RR 0.51; 95% CI 0.27 to 0.93), and dimethyl fumarate (RR 0.53; 95% CI 0.43 to 0.63) were also effective with 47% to 54% reduction versus placebo.[1] The interferons, glatiramer acetate 20 mg (RR 0.67; 95% CI 0.52 to 0.86), and teriflunomide (RR 0.77; 95% CI 0.67 to 0.93) were less effective with 17% to 37% reduction, but all of the drugs were significantly better than placebo.[1] Disability progression sustained for a minimum of 24 weeks as measured by EDSS scores was evaluated in 27 trials. Most of the trials were less than 2 years in duration and enrolled few patients. In the NMA, ocrelizumab and alemtuzumab had the greatest reduction in disability progression (53% to 58% reduction compared to placebo respectively), closely followed by daclizumab (46%) and natalizumab (44%).[1] Dimethyl fumarate, peginterferon beta-1a, interferon beta-1b 250 mcg, and fingolimod were next (32% to 38%).[1] Teriflunomide, glatiramer acetate, and the remaining interferons were less effective (14% to 28%).[1] Four drugs were not significantly better than placebo (interferon beta-1a 30 mcg, interferon beta-1a 22 mcg, teriflunomide 7 mg, and glatiramer acetate 40 mg).[1]

PPMS Efficacy

At the time of the ICER publication only one published trial was available for ocrelizumab (ORATORIO)[6] and one for rituximab (OLYMPUS)[9]. For rituximab, there was no significant difference in the time to confirmed disease progression sustained for at least 12 weeks compared to placebo (HR 0.77, p=0.14).[9] For ocrelizumab, the primary endpoint of the trial was confirmed disability progression sustained for at least 12 weeks, and was significantly lower than placebo (HR 0.76, 95% CI 0.59 - 0.98, p=0.032).[6] Ocrelizumab is discussed in more depth later in this report.

Safety

Although all the DMDs have demonstrated efficacy in reducing annualized relapse rate and disability progression, their benefits should be assessed concurrent with their possible harms. A number of potentially life-threatening harms have been identified from post-marketing data leading to Black Box warnings for five of the DMDs (daclizumab, teriflunomide, natalizumab, alemtuzumab and rituximab) used to treat MS. For non-serious adverse effects, flu-like symptoms were more common in patients treated with interferons, injection site reactions were more common for all of the injectable agents, and infusion reactions were more common for the infused agents compared to other DMDs.[1]

Head to Head Trials with DMDs in MS

The DECIDE trial randomized 1841 patients to daclizumab high-yield process (HYP) 150 mg subcutaneously (SC) every 4 weeks or interferon beta-1a 30 mcg intramuscularly (IM) once weekly for up to 144 weeks.[33] Despite this trial being one of the largest and longest RCTS of the DMDs, there was considerable loss to follow-up (23%).[33]The annualized relapse rate for daclizumab was lower compared to interferon beta-1a (0.22 vs. 0.39, p<0.001, RR 0.55, 95% CI 0.47-0.64).[33] The HR for confirmed disability progression sustained for at least 12 weeks with daclizumab was 0.84 (0.66-1.07, p=0.16) and the HR for confirmed disability progression sustained for at least 24 weeks was 0.79 (0.59-1.06, p=0.012).[33] Data from the DECIDE trial found that daclizumab was significantly better than interferon beta-1a 30 mcg at reducing relapses, but not disability progression.[33] There were also more serious adverse effects with daclizumab (15%) compared to interferon beta-1a (10%).[33] Infections were more common in the daclizumab group than in the interferon beta-1a group (in 65% vs. 57%).[33] Elevations in liver

aminotransferase levels that were more than 5 times the upper limit of the normal range occurred more frequently in the daclizumab group compared to the interferon group (6% vs. 3%).[33]

The TRANSFORM trial compared oral fingolimod 0.5mg or 1.25 mg to interferon beta-1a 30 mcg IM every week over 12 months.[34] Fingolimod 0.5 mg had significantly lower annualized relapse rate compared to interferon (0.16 vs. 0.33, 95% CI 0.26 to 0.42, p<0.001), but there were no significant differences in disability progression. In the CONFIRM trial, there were no significant differences in annualized relapse rate between oral dimethyl fumarate and subcutaneous glatiramer acetate, though both were more effective than placebo.[35] In three trials of alemtuzumab versus interferon beta-1a 44 mcg, alemtuzumab was consistently better for reducing relapses and progression of disability in patients with RRMS.[36-38]

Comparative Value

ICER developed a simulation model to estimate costs of MS DMD therapy per quality-adjusted life years (QALYs). Ocrelizumab has not FDA approved when the ICER report was published, so it was not included in the QALY estimations. The estimated cost per additional QALY for glatiramer 20 mg was $1923,211.[1] When compared to generic glatiramer acetate 20 mg, almost all of the MS DMDs were more costly for cost per additional QALY including teriflunomide, interferon beta-1a, fingolimod, dimethyl fumarate, peginterferon, and natalizumab.[1] Costs per additional QALY ranged from approximately $38,277 per QALY for alemtuzumab to approximately $355,115 per QALY for interferon beta-1a 22 mcg (Rebif).[1] Most of the estimated costs associated with MS therapies per additional QALY exceed $150,000 with the exception of alemtuzumab, which is currently limited to 2 treatment courses per lifetime.

Guidelines:

National Institute for Health and Care Excellence (NICE)

NICE has published a number of guidance documents for managing MS with various treatments including alemtuzumab, interferons, glatiramer, dimethyl fumarate, natalizumab, teriflunomide and fingolimod. The NICE Pathway recommends against the use of glatiramer acetate or an interferon beta in the management of MS, except in individuals whose disease was well-managed by an agent in either class when the guidelines were released in 2002. Dimethyl fumarate and teriflunomide are recommended for individuals with RRMS, provided the patient's disease is not highly active or rapidly progressing. Alemtuzumab is recommended as an option for the treatment of RRMS. Fingolimod should be used in individuals with highly-active MS whose relapses worsened or were ineffectively controlled over the prior year despite treatment with a beta interferon. Natalizumab is recommended for use in patients with severe, rapidly-evolving RRMS, defined as at least two disabling relapses within one year, at least one gadolinium-enhancing lesion, or a significant increase in T2 lesion load in comparison with a previous MRI. Guidance for treating PPMS and RRMS with ocrelizumab are pending with a proposed July 2018 publication. The most recent published guidance was issued in April 2017 and focused on the use of daclizumab for treating RRMS.

NICE guidance recommends daclizumab as an option for treating RRMS in adults, only if:

- the person has active RRMS previously treated with DMD therapy, or rapidly evolving severe RRMS (that is, at least 2 relapses in the previous year and at least 1 gadolinium enhancing lesion at baseline MRI)[3] AND
- alemtuzumab is contraindicated or otherwise unsuitable [3]

The committee concluded that it was appropriate to consider the following subgroups and associated comparators for daclizumab:

- people with untreated active RRMS: beta interferons, glatiramer acetate, dimethyl fumarate, teriflunomide and alemtuzumab[3]
- people with previously treated active RRMS: dimethyl fumarate, teriflunomide and alemtuzumab[3]
- people with rapidly evolving severe RRMS (at least 2 relapses in the previous year at least one lesion on MRI): natalizumab and alemtuzumab[3]

- people with highly active RRMS despite previous treatment (no response after at least 1 year to treatment with DMD and at least 1 relapse or at least 1 lesion on MRI): fingolimod and alemtuzumab.[3]

A Canadian Agency for Drugs and Technologies in Health (CADTH) update on ocrelizumab is slated for publication November 2017.

New Safety Alerts:
The label for Tecfidera® (dimethyl fumarate) was revised January 2017 to include a warning of potential liver injury that could require hospitalization. The updated label clarifies that signs of liver injury resolved when those patients stopped taking the medicine. Another safety update regarding the possibility of progressive multifocal leukoencephalopathy (PML) was added to the dimethyl fumarate label as of February 2016. PML is an opportunistic viral brain infection caused by the JC virus that typically occurs in patients who are immunocompromised.[4]

The FDA issued a warning that a case of definite progressive multifocal leukoencephalopathy (PML) and a case of probable PML have been reported in patients taking Gilenya® (fingolimod) for MS. As a result, information about the risk of PML associated with fingolimod was added to the drug label under warnings and precautions section effective February 2017.[5]

New Formulations or Indications: None.

Randomized Controlled Trials:
A total of 193 citations were manually reviewed from the initial literature search. After further review, 193 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

NEW DRUG EVALUATION: Ocrelizumab (Ocrevus™)

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Ocrelizumab is a humanized monoclonal antibody that selectively depletes CD20-expressing B cells. CD20 is a cell surface antigen found on pre-B and mature B lymphocytes. B cells are involved in the activation of proinflammatory T cells, secretion of proinflammatory cytokines, and production of autoantibodies directed against myelin.[39] B cells are present in meningeal inflammation and may cause cortical demyelinating and neurodegenerative pathologic features of MS.[7] The FDA approval of ocrelizumab for the treatment of patients with MS was based on 3 randomized, double-blind multicentered clinical trials. ORATARIO was a placebo-controlled, double-blind trial conducted in PPMS patients who received at least 5 cycles of ocrelizumab. OPERA I and OPERA II were identical double-blind, double-dummy, active comparator-controlled trials in patients with RRMS. Each trial has an open-label extension phase to gather additional safety information.

ORATORIO was a phase 3, randomized, double blind, international, multi-center study that evaluated the safety and efficacy of ocrelizumab in PPMS patients. Ocrelizumab was administered as an intravenous (IV) 300 mg infusion every 2 weeks for 2 doses followed by 600 mg IV infusion every 6 months for 120 weeks (5 cycles of therapy). The drug was compared to a placebo infusion administered at the same intervals. The primary outcome was the percentage of patients with sustained disability progression over 12 weeks. Disability progression was defined as an increase in EDSS by at least 1 point from baseline for subjects with a baseline EDSS less than or equal to 5.5. Subjects with a baseline EDSS greater than 5.5 were considered responders if a 0.5 point increase from baseline EDSS was observed at 12 weeks.[6] Seven hundred thirty-two patients were randomized 2:1 to receive ocrelizumab (n=488) or placebo (n=244).[6] The mean baseline EDSS score was 4.7 in both groups, mean subject age was 44 years, and time since diagnosis of PPMS was approximately 3 years.

The percentage of patients with disability progression confirmed at 12 weeks was less with ocrelizumab compared to placebo (32.9% vs. 39.3%, respectively; HR=0.76; 95% CI 0.59 to 0.98; p = 0.03, NNT = 16).[6] A significant secondary outcome assessed disability progression at 24 weeks. The percentage of patients with disability progression confirmed at 24 weeks was 29.6% with ocrelizumab versus 35.7% with placebo (HR 0.75; 95% CI 0.58 to 0.98; p = 0.04; NNT= 17).[6] The researchers concluded there was a lower probability of short term disease progression (12 to 24 weeks) as assessed by EDSS with ocrelizumab compared to placebo. Although the impact on disability progression was shown to be statistically significant, the clinical impact appears to be modest, especially when the trial design and execution is evaluated in more depth.

The FDA advisory committee identified several aspects the ORATORIO trial design that may have biased the researchers' conclusions. The first concern noted that primary outcome events were imputed for patients that dropped out of the trial, which increased the number of chronic disability progression (CDP) events by 21 subjects or 8% of the 256 CDP events used in the pre-specified primary analysis.[7] Without imputation of results from patients that withdrew from the study, the p-value for the primary outcome changes from 0.03 to 0.14 indicating an inability to reject the null hypothesis that ocrelizumab is no different that placebo at affecting disability progression.[7] Another concern arose with the pre-specified secondary analysis, which found no treatment benefit for female patients with PPMS, as 35.5% of women in the placebo group had CDP events compared to 36.0% of the ocrelizumab group.[7] A third issue noted the Kaplan-Meier curve demonstrated a consistent rate of progression from 18 weeks through 120 weeks, suggesting the effect of ocrelizumab was limited to the first 18

weeks of treatment.[7] Finally, for 29% of patients the investigators reported the baseline EDSS after infusion of the study drug and in 67% of patients after randomization.[7] This indicates failure of investigators to follow the protocol and may indicate other breaches in protocol that are not as transparent.[7] Despite such grave concerns with the uncertainties associated with trial design and conduct, the FDA approved ocrelizumab for treatment of PPMS because there is an unmet treatment need in these patients.[7]

OPERA I and II evaluated the efficacy and safety of ocrelizumab 300 mg every 2 weeks for 2 doses followed by 600 mg every 24 weeks compared to a first-line MS treatment, interferon beta-1A 44 mcg three times a week, in patients with RRMS and SPMS over 96 weeks (4 cycles of treatment). The patients included in these trials had experienced at least 2 documented clinical attacks within the previous 2 years or 1 clinical attack within 1 year prior to screening. The primary outcome was annualized relapse rate by 96 weeks. Annualized relapse rate was defined as new or worsening neurological symptoms that persisted for more than 24 hours and were immediately preceded by stable or improved disease state for at least 30 days.[8] Eight hundred twenty-one patients were randomized 1:1 between the ocrelizumab (n= 411) and interferon (n= 410) arms in OPERA I. In OPERA II, 835 patients were randomized to ocrelizumab (n=417) and placebo (n=418). OPERA I found that ocrelizumab had a statistically significant lower annualized relapse rate at week 96 compared to interferon (ocrelizumab 0.16 vs. interferon beta-1A 0.29; HR 0.51; 95% CI 0.40-0.72; P<0.001).[8] Similar results were observed in OPERA II as ocrelizumab had a lower annualized relapse rate at week 96 compared to interferon (ocrelizumab 0.16 vs. interferon beta-1A 0.29; HR 0.53 (95% CI 0.40 to 0.71, P=0.001).[8]

Secondary efficacy endpoints included disability progression at 12 and 24 weeks, disability improvement at 12 weeks, and MSFC score change from baseline to week 96. Disability progression was defined as an increase equal to 1.0 point or greater from the baseline EDSS score that was not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score was 5.5 or less, or an increase equal to 0.5 or greater when the baseline score was above 5.5. Disability progression was confirmed when an increase in the EDSS was documented at a regularly scheduled visit at least 12 weeks or 24 weeks, after the initial documentation of neurological worsening.[8] The percentage of patients with disability progression at 12 weeks for OPERA I was less with ocrelizumab (7.6%) compared with interferon beta-1a (12.2%) [HR 0.57; 95% CI 0.37 to 0.90; p=0.01; NNT = 22].[8] The 12-week results on disability progression were similar for OPERA II: ocrelizumab 10.6% versus interferon beta-1a 15.1% (HR 0.63; 95% CI 0.42 to 0.92; p=0.02; NNT = 23).[8] There were also significant reductions in confirmed disability progression sustained for 24 weeks (HR 0.57; 95% CI 0.34-0.95 for OPERA I and HR 0.63; 95% CI 0.40-0.98 for OPERA II) through 96 weeks of follow-up.[8]

Disability improvement was analyzed only for the subgroup of patients with a baseline EDSS score equal to 2.0 or greater.[8] The same approach to data derivation was used for disability improvement as for disability progression.[8] For patients with a baseline EDSS score greater than or equal to 2 and less than or equal to 5.5, disability improvement was defined as a reduction in EDSS score as 1.0 or greater compared to baseline EDSS score. For patients with a baseline EDSS score greater than 5.5, disability improvement was defined as a reduction in EDSS score of 0.5.[8] The effect of ocrelizumab on the percent of patients with confirmed disability improvement at 12 weeks was significant in the OPERA I trial (ocrelizumab 20% vs. interferon beta-1a 12.4%, p = 0.01, no reported 95% CI, NNT = 14) but nonsignificant in the OPERA II trial (ocrelizumab 21.4% vs. interferon beta-1a 18.8%, p = 0.40).[8] The investigators prespecified the pooled analysis from OPERA I and II to show statistical significance in disability improvement at 12 weeks (ocrelizumab 20.7% vs interferon beta-1a 15.6%, p = 0.02, no reported 95% CI).[8] The difference in the adjusted mean change in the MSFC score from baseline to week 9 favored the ocrelizumab group over the interferon beta-1a group in the OPERA II trial (ocrelizumab 0.28 versus interferon beta-1a 0.17; 95% CI 0.03 to 0.18; p=0.004) but not in the OPERA I trial due to insignificant results (ocrelizumab 0.21 versus interferon beta-1a 0.17; 95% CI -0.04 to 0.12; p=0.33).[8]

In summary, for patients with RRMS, ocrelizumab was associated with lower annualized relapse rates than interferon beta-1a over 96 weeks of treatment. In addition, a lower rate of disability progression at 12 and 24 weeks was noted with ocrelizumab compared to interferon beta-1a. The pooled analysis from OPERA I and II revealed a higher rate of disability improvement with ocrelizumab compared to interferon beta-1a. The change from baseline to week 96 for MSFC score was not statistically significant in OPERA I, but it was statistically significant in OPERA II. Of note, 70% of pts had not received previous DMD therapy, which may not represent most MS patients as interferons are preferred for initial RRMS treatment. In addition, the mean EDSS score was 2.8, indicating minimal disability from MS. Finally, 25% of patients included in OPERA I and II were from the United States. Other trial sites were located in Canada, Europe, Latin America, Africa and Australia. Countries in equatorial areas may not have had as high a prevalence of MS as other countries in northern latitudes.

Clinical Safety:
The most common adverse reaction in the 120 week ORATORIO trial was infusion related reactions: 39.9% in the ocrelizumab arm and 25.5% in the placebo arm.[6] Two patients (0.4%) withdrew from ocrelizumab treatment due to infusion-related reactions.[6] Other adverse effects noted during the trial included: nasopharyngitis (22.6% ocrelizumab vs. 27.2% placebo); urinary tract infection (19.8% ocrelizumab vs. 22.6% placebo); influenza (11.5% ocrelizumab vs. 89.8% placebo) and upper respiratory tract infections (10.9% ocrelizumab vs. 5.9% placebo).[6] Serious adverse events included: serious infections (6.2% ocrelizumab vs. 5.9% placebo); breast cancer (0.8 % ocrelizumab vs. 0% placebo); basal-cell carcinoma (0.6% ocrelizumab vs. 0.4% placebo) and other carcinomas (0.8% ocrelizumab vs. 0.4 % placebo). There were more deaths (0.8% vs. 0.4%) and more neoplasms (2.3% vs. 0.8%) in the ocrelizumab group compared to placebo.

In the OPERA I and II trials conducted over 96 weeks, the most common adverse reaction was infusion site reaction with ocrelizumab compared to placebo (OPERA I 30.9% vs. 7.3% and OPERA II 37.6% vs. 12.0% respectively).[8] One patient assigned to the ocrelizumab arm withdrew from OPERA I due to bronchospasm during the first infusion.[8] Serious adverse effects were reported in 7.8% of patients in the interferon group and 6.9% of the ocrelizumab group in OPERA I and 9.6% of patients in the interferon group and 7.0% of the ocrelizumab group in OPERA II.[8] Three deaths occurred during the OPERA I and II studies (suicide and mechanical ileus in the interferon arm; suicide in the ocrelizumab group). Infections were reported in 54.3% of interferon-treated patients and 56.9% of ocrelizumab-treated patients in OPERA I and in 52.5% and 60.2%, respectively, in OPERA II.[8] Respiratory tract infections and nasopharyngitis were more common in the ocrelizumab groups, while urinary tract infections were more common in the interferon groups. Overall, serious infections were reported in 2.9% of the interferon patients and 1.3% of the ocrelizumab-treated patients.[8] No opportunistic infections were reported in the study. A total of six malignancies were reported: 2 (0.2%) in the interferon (mantle cell lymphoma [n=1] and squamous cell carcinoma [n=1]) and 4 (0.5%) in the ocrelizumab group: renal cancer [n=1], malignant melanoma [n=1], and ductal breast carcinoma [n=2]).[8]

The most common adverse events for ocrelizumab are infection and infusion-related reactions. Premedication with acetaminophen and an antihistamine may help prevent the occurrence of infusion-related reaction.[10] Ocrelizumab is contraindicated in patients with active Hepatitis B infection.[10] However, the limited numbers of patients and short follow-up contribute to the uncertainty about rare, but serious adverse events associated with ocrelizumab that may not be fully appreciated until post-marketing data are available.[40] Additional studies are needed to determine long-term efficacy and safety of ocrelizumab beyond 5 cycles of treatment.

Look-alike/Sound-alike Error Risk Potential: No agents identified.

Table 3. Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Binds to CD20-expressing B-cells to result in antibody-dependent cellular cytolysis and complement-mediated lysis
Bioavailability	100% administered via intravenous route
Distribution and Protein Binding	Volume of distribution estimated as 2.78 liters; no information is available on protein binding
Elimination	Clearance is estimated at 0.17 liters/day
Half-Life	26 days
Metabolism	Metabolism has not been studied because antibodies are cleared via catabolism.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Relapse Rate
2) Functional status (i.e., disability)
3) Quality of life
4) Early discontinuation due to adverse event
5) Serious adverse events

Primary Study Endpoints:

1) Adults with PPMS – confirmed disability progression at 12 weeks
2) Adults with RRMS and SPMS - annualized relapse rate at week 96

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1.ORATORIO[6] Phase 3, DB, PG PC, MC 182 sites in 29 countries Dates: March 2011 through July 2015 Trial duration: 4 years	1. Ocrelizumab initial loading dose of 300mg IV every 2 weeks x 2 doses followed by 600mg IV every 6 months 2. Placebo IV infusion every 2 weeks x 2 doses followed by infusion every 6 months At least 120 weeks (5 treatment cycles) or 256 CDP events	Demographics: -Adults with PPMS -Mean EDSS score = 4.7 in both arms -Approximately 50% of the patients were women -Mean subject age = 44 years -Time since PPMS diagnosis = 2.9 years in ocrelizumab group and 2.8 years in PBO group Key Inclusion Criteria: -age 18-55 years -diagnosis of PPMS -EDSS score 3.0 - 6.5 -FSS score at least 2 -duration of symptoms < 10 years Key Exclusion Criteria: -History of RRMS, SPMS, or PRMS -Previous treatment with B-cell targeted therapies or other immunosuppressants	ITT: 1. 488 2. 244 PP: 1. 387 2. 162 Attrition: 1. 21.6% 2. 33.6%	Primary Endpoint: Percent of patients with 12 week sustained increase in EDSS score 1. 32.9% 2. 39.3% HR 0.76 (95% CI, 0.59 to 0.98) p=0.03 Secondary Endpoint: 1.Percent of patients with confirmed disability progression at 24 weeks in time to event analysis 1.29.6% 2. 35.7% HR 0.75 (95% CI, 0.58 to 0.98) p=0.04	6.4%/ 16 6.1%/ 17	Any AE 1.95.1% 2.90.0% SAE 1. 20.4% 2. 22.2% D/C due to AE 1. 4.1% 2. 3.3% Infusion related reactions 1. 39.9% 2. 25.5% Nasopharyngitis 1. 22.6% 2. 27.2% Urinary tract infection 1. 19.8% 2. 22.6% Upper respiratory infection 1. 10.9% 2. 5.9% Malignancies 1. 2.3% (n=11) 2. 0.8% (n=2)	NA for all (p values not reported)	Risk of Bias (low/high/unclear): Selection Bias: LOW. Randomization performed centrally by an independent IVRS in a 2:1 sequence. Stratified by age and geographic region. Baseline characteristics balanced. Performance Bias: HIGH. Infusion related reactions may have impacted blinding as more patients in the treatment arm experienced reactions. Detection Bias: LOW. EDSS administered by an investigator blinded to therapy. MRI results analyzed at a central MRI reading center by blinded staff members. Attrition Bias: HIGH. High attrition rate: overall 25% of subjects enrolled in the study withdrew. Attrition rates different between groups. ITT analysis completed and subjects with early discontinuation considered non-responders for both arms of the trial, which may have biased conclusions regarding significance of primary outcome. Reporting Bias: HIGH. Study protocol available. Baseline EDSS for 29% of patients conducted after infusion of first dose of study drug and in 67% of patients after randomization. Study protocol not explicitly followed by researchers. Funding and data analysis supported by Hoffman La Roche. Applicability: Patient: Mean baseline EDSS = 4.7, indicating moderate disability from MS. Average age of patients was 44 years old, younger than the average age of most PPMS patients. Intervention: Dosing and premedication to alleviate infusion associated reactions were appropriate. Patients received at least 5 cycles of drug therapy.

								Comparator: Placebo comparator appropriate as no other therapies are FDA approved to treat PPMS. Outcomes: Disability evaluated by changes in EDSS, a validated measure for RRMS progression, although there is substantial interrater variability. Progression to disability over 12 weeks is a relatively short term measure for chronic disease with no cure. Not all of the subjects had baseline EDSS scores recorded. Setting: 14% of total population enrolled was from the U.S. Other countries involved in study have high prevalence of MS including Canada and Europe.
2.OPERA- I[8] Phase 3 RCT DB, DD, MC N = 821 141 sites in 32 countries Dates: August 2011 – February 2013	1. Ocrelizumab 600mg IV every 6 months 2. Interferon 8.8 mcg three times a week for weeks 1 and 2, followed by 22 mcg three times a week for weeks 3 and 4, followed by beta-1a 44 mcg SC three times a week Conducted over 96 weeks (at least 4 treatment cycles)	Demographics: Adults with RRMS and SPMS -Mean age = 37 years -66% female -6.5 years since symptom onset -4 years since MS diagnosis -Average relapses in previous year = 1.3 -70% no prior DMD therapy -Mean EDSS score = 2.8 -60% had no lesions on MRI Key Inclusion Criteria: -age 18-55 years -diagnosis of MS -EDSS score 0 to 5.5 -at least 2 documented clinical relapses within previous 2 years or 1 clinical relapse within 1 year of screening -no neurologic worsening for at least	ITT: 1. 410 2. 411 PP: 1. 366 2. 340 Attrition: 1. 11% 2. 17%	Primary Endpoint: Annualized Relapse Rate at week 96 1. 0.16 2. 0.29 RR 0.54 ; 95% CI 0.40 to 0.72 P < 0.001 Secondary Endpoints: 1.Percent of patients with disability progression confirmed at 12 weeks 1. 7.6% 2. 12.2% HR 0.57; 95% CI 0.37 to 0.90 P = 0.01 2. Percent of patients with disability improvement at 12 weeks 1. 20.0% 2. 12.4% P = 0.01 (95% CI not reported) 2.Percent of patients with disability progression confirmed at 24 weeks 1. 5.9%	NA 4.6%/22 7.6%/14 3.6%/28	Any AE 1. 80.1 % (n=327) 2. 80.9% (n=331) SAE 1. 6.9% (n=28) 2. 7.8% (n=32) D/C due to any AE 1. 3.2% (n=13) 2. 6.4% (n=26) Infusion related reaction 1. 30.9% (n=126) 2. 7.3% (n=30) Infections: 1. 56.9% (n=232) 2. 54.3% (n=222) Malignancies: 1. 0.7% (n=3) 2. 0.2% (n=1)	NA for all (p values not reported)	Risk of Bias (low/high/unclear): Selection Bias: LOW. Randomized 1:1 via a centralized independent IVRS. Stratified by region and baseline EDSS. Similar baseline characteristics. Performance Bias: HIGH. Patient in each arm received matching SC or IV placebo as appropriate, which were similar in appearance to investigational product. All subjects received methylprednisone 100mg prior to infusion. Prophylaxis with antihistamine and analgesic at the discretion of infusion center. Since infusion related reactions were more prevalent in the ocrelizumab arm this may have affected blinding. In addition, side effects with interferon are distinct from ocrelizumab and could have affected blinding. Detection Bias: LOW. Treating and examining investigators were blinded to treatment arm. MRI scans were read at a central location by independent investigators blinded to treatment arm. Laboratory results were also blinded to investigators. Attrition Bias: HIGH. ITT analysis completed on all randomized patients including premature withdrawals. Patients withdrawn from the study were considered non-responders for primary outcome. For disability progression, early withdrawals

		30 days before screening and at baseline Key Exclusion Criteria: -Diagnosis of PPMS - Previous treatment with B-cell targeted therapies or other immunosuppressants -Disease duration > 10 years -Baseline EDSS score ≤ 2		2. 9.5% HR 0.57; (95% CI 0.34 to 0.95) P = 0.03 3. Mean MSFC score at 96 weeks 1. 0.21 2. 0.17 RR 0.04 (95% CI -0.04 to 0.12) P = 0.33	NS			without subsequent EDSS data were censored. Dropout rates were not equal between groups. Reporting Bias: UNCLEAR. Detailed protocol is available. Trial designed, data analyzed and study funded by Hoffman-La Roche Applicability: Patient: 70% of pts had not had previous DMD therapy, which may not represent most MS patients as interferons are gold standard for RRMS treatment. Mean EDSS score was 2.8 indicating minimal disability from MS. Intervention: Selected dose for ocrelizumab was proven to be the lowest, maximally effective dose in Phase II trials. Comparator: Interferon, a first line drug for MS, was used as an active comparator Outcomes: Annualized relapse rate used as primary outcome, similar to other DMD trials in MS. Setting: 25% of patient population were from the U.S. Other trial sites were located in Canada, Europe, Latin America, Africa and Australia. Countries in equatorial areas may not have had as high a prevalence of MS as other countries in northern latitudes.
3.OPERA-II[8] Phase 3 RCT DB, DD, MC N = 835 166 sites in 24 countries Dates: September 2011 through March 2013	1. Ocrelizumab 300 mg IV q2weeks x 2 weeks followed by 600mg IV every 6 months 2. Interferon beta-1a 44 mcg SC three times a week	Demographics: See OPERA-1 Key Inclusion Criteria: See OPERA-1 Key Exclusion Criteria: See OPERA-1	ITT: 1. 417 2. 418 PP: 1. 360 2. 320 Attrition: 1. 14% 2. 23%	Primary Endpoint: Annualized Relapse Rate at week 96 1. 0.16 2. 0.29 HR 0.53 ; 95% CI 0.40 to 0.71 P < 0.001 Secondary Endpoints: 1.Percent of patients with disability progression at 12 weeks 1. 10.6 % 2. 15.1% HR 0.63; 95% CI 0.42 to 0.92 P = 0.02	NA 4.5%/22	Any AE 1. 86.3 % (n=360)) 2. 85.6% (n=357) SAE 1. 7.0% (n=29) 2. 9.6% (n=40) D/C due to any AE 1. 3.8% (n=16) 2. 6.0% (n=25) Infusion related reaction 1. 37.6% (n=157) 2. 12% (n=50) Infections:	NA for all p values not reported)	Risk of Bias (low/high/unclear): Selection Bias: LOW. See OPERA-1 Performance Bias: HIGH. See OPERA-1 Detection Bias: LOW. See OPERA-1 Attrition Bias: HIGH. See OPERA-1 Reporting Bias: UNCLEAR. See OPERA-1 Applicability: Patient: See OPERA-1 Intervention: See OPERA-1 Comparator: See OPERA-1 Outcomes: See OPERA-1 Setting: See OPERA-1

				2. Percent of patients with disability improvement at 12 weeks 1. 21.4% 2. 18.8% P = 0.40 (95% CI not reported) 2. Percent of patients with disability progression at 24 weeks 1. 6.9% 2. 10.5% HR 0.63; 95% CI 0.40 to 0.98 P = 0.04 3.Mean MSFC score at 96 weeks 1. 0.28 2. 0.17 RR 0.11 (0.03 to 0.18) P = 0.004	NS 3.6%/28 NA	1. 60.2% (n=251) 2. 52.0% (n=217) Malignancies: 1. 0.2% (n=1) 2. 0.2% (n=1)		

Abbreviations : AE = adverse effect; ARR = absolute risk reduction;; CDP = confirmed disability progression; CI = confidence interval; DB = double blind; DD = double dummy; DMD = disease modifying drugs; EDSS = Expanded Disability Status Scale; FSS = Functional Systems Scale; HR = hazard ratio; IFN = interferon; ITT = intention to treat; IVRS = interactive voice response system; IV = intravenous; MC = multi-center; mITT = modified intention to treat; MSFC = multiple sclerosis functional composite; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PBO = placebo; PC = placebo controlled; PP = per protocol; PG = parallel group; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SEA = serious adverse effect; SPMS = secondary progressive multiple sclerosis; U.S = United States

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Appendix 1: Current Status on Preferred Drug List

Generic	Brand	Route	PDL
GLATIRAMER ACETATE	COPAXONE	SUB-Q	Y
INTERFERON BETA-1A/ALBUMIN	AVONEX	INTRAMUSC	Y
INTERFERON BETA-1A/ALBUMIN	REBIF	SUB-Q	Y
INTERFERON BETA-1B	BETASERON	SUB-Q	Y
INTERFERON BETA-1B	EXTAVIA	SUB-Q	Y
ALEMTUZUMAB	LEMTRADA	INTRAVEN	N
DACLIZUMAB	ZINBRYTA	SUB-Q	N
DALFAMPRIDINE	AMPYRA	ORAL	N
DIMETHYL FUMARATE	TECFIDERA	ORAL	N
FINGOLIMOD HCL	GILENYA	ORAL	N
GLATIRAMER ACETATE	COPAXONE	SUB-Q	N
GLATIRAMER ACETATE	GLATOPA	SUB-Q	N
OCRELIZUMAB	OCREVUS	INTRAVEN	N
PEGINTERFERON BETA-1A	PLEGRIDY	SUB-Q	N
TERIFLUNOMIDE	AUBAGIO	ORAL	N

Appendix 2: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OCREVUS™ (ocrelizumab) injection, for intravenous use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

OCREVUS is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis (1)

DOSAGE AND ADMINISTRATION

- Hepatitis B virus screening is required before the first dose (2.1)
- Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (e.g., diphenhydramine) prior to each infusion (2.2)
- Administer OCREVUS by intravenous infusion
  - Start dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion (2.3)
  - Subsequent doses: 600 mg intravenous infusion every 6 months (2.3)
- Must be diluted prior to administration (2.3, 2.6)
- Monitor patients closely during and for at least one hour after infusion (2.3, 2.5)

DOSAGE FORMS AND STRENGTHS

- Injection: 300 mg/10 mL (30 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

- Active hepatitis B virus infection (4)
- History of life-threatening infusion reaction to OCREVUS (4)

WARNINGS AND PRECAUTIONS

- Infusion reactions: Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue OCREVUS if a life-threatening or disabling infusion reaction occurs (2.3, 5.1)
- Infections: Delay OCREVUS administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with OCREVUS and after discontinuation, until B-cell repletion (5.2)
- Malignancies: An increased risk of malignancy, including breast cancer, may exist with OCREVUS (5.3)

ADVERSE REACTIONS

The most common adverse reactions were:

- RMS (incidence ≥10% and > REBIF): upper respiratory tract infections and infusion reactions (6.1)
- PPMS (incidence ≥10% and > placebo): upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2017

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 1 2017 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 15, 2017

1 exp Multiple Sclerosis/	34523
2 exp Glatiramer Acetate/	1154
3 exp Interferon-beta/	7554
4 alemtuzumab.mp.	2491
5 daclizumab.mp.	1024
6 Dimethyl Fumarate/	383
7 exp Fingolimod Hydrochloride/	1621
8 ocrelizumab.mp.	148
9 peginterferon beta.mp.	54
10 teriflunomide.mp.	304
11 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	13653
12 1 and 11	4445
13 limit 12 to (humans and yr="2015 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	193

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:
- Fingolimod
- Teriflunomide
- Dimethyl Fumarate

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 relapsing remitting multiple sclerosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta 1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is the prescription for teriflunomide?	**Yes:** Go to #7	**No:** Go to #9
7. Is the patient of childbearing potential?	**Yes:** Go to #8	**No:** Approve for up to 6 months.
8. Is the patient currently on a documented use of reliable contraception and is there documentation of a negative pregnancy test prior to initiation of teriflunomide?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the prescription fingolimod?	**Yes:** Go to #10	**No:** Go to #13
10. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on anti-arrhythmic, beta-blockers, or calcium channel blockers?	**Yes:** Go to #12	**No:** Approve up to 6 months.
12. 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.
13. Is the prescription for dimethyl fumarate?	**Yes:** Go to # 14	**No:** Pass to RPh. Deny; medical appropriateness.
14. 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.

Fingolimod 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 with caution. A cardiology evaluation should be performed before considering treatment.
- Injectable disease modifying treatments remain first-line agents in MS therapy.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

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 ULN). 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.

Dimethyl Fumarate Clinical Notes:

- Dimethyl fumarate 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. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Dimethyl fumarate 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 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 on a quarterly basis

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

Daclizumab (Zinbryta™) and Ocrelizumab (Ocrevus™)

Goal(s):

- Restrict use of daclizumab and ocrelizumab to patients with relapsing-remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis (PPMS) who have failed multiple drugs for the treatment of PPMS or RRMS.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Zinbryta™ (daclizumab)
- Ocrevus™ (ocrelizumab)

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 AND is the requested treatment funded by the OHP for that condition? Note: Treatments referenced on an unfunded line of the prioritized list are not funded by the OHP.	**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

Approval Criteria		
5. Is the patient an adult (age ≥18 years) diagnosed with relapsing remitting multiple sclerosis (RRMS)?	**Yes:** Go to #6	**No:** Go to #10
6. 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 #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the drug daclizumab?	**Yes:** Go to # 8	**No:** Go to # 10
8. Does the patient have a higher degree of ambulatory ability (e.g., Expanded Disability Status Scale score ≤5)	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have hepatic disease or hepatic impairment, including ALT or AST ≥2-times the upper limit of normal, or have a history of auto-immune hepatitis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
10. Is the drug ocrelizumab?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the prescriber a neurologist who regularly treats RMS?	**Yes**: Approve daclizumab 150 mg once monthly for 6 months or 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		

Approval 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: *11/17 (DM); 1/17*
Implementation: *1/1/18; 4/1/17*

Peginterferon Beta-1a (Plegridy®)

Goal(s):

- Approve therapy for covered diagnosis which 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. Does the patient have a diagnosis of relapsing-remitting Multiple Sclerosis?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.
3. Will the prescriber consider a change to a Preferred MS product?	**Yes:** Inform provider of covered alternatives in the class.	**No:** Go to #4.
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny for medical appropriateness.
5. Does the patient have any of the following: • Adherence issues necessitating less frequent administration • Dexterity issues limiting ability to administer subcutaneous injections	**Yes:** Approve for up to one year.	**No:** Pass to RPH; Deny for medical appropriateness.

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

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 relapsing -remitting 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
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: *11/17 (DM); 5/16; 3/12*
Implementation: *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®)

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 Jason Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness
3. Does the patient have a diagnosis of relapsing remitting multiple sclerosis (RRMS)?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny for medical appropriateness.
6. Does the patient have Crohn's Disease?	**Yes:** Go to #7	No: Pass to RPH; Deny for medical appropriateness.
7. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #8	**No:** Pass to RPH; Deny for medical appropriateness**.**

Approval Criteria		
8. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • Has the patient tried and failed a 3 month trial of Humira?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.

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