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Drug Class Literature Scan: Multiple Sclerosis

Date of Review: October 2025

Date of Last Review: October 2024
Literature Search: 7/31/2023–8/1/2025

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

Plain Language Summary:

- Multiple sclerosis (MS) is a condition where the body's immune system mistakenly attacks nerves in the spinal cord which affects communication between the brain and the rest of the body. This damage causes symptoms including feeling tired, arm and leg numbness, pain, blurred vision, muscle weakness, memory problems, and trouble with balance and walking. These symptoms can cause serious disability in people with MS.
- There are 2 main types of MS. Most people have "attacks" when new symptoms develop or existing symptoms worsen (called a relapse), followed by periods with no changes to their symptoms (called remittance). This type of MS is called relapsing-remitting MS and is the most common form of MS. In primary progressive MS, people's symptoms gradually worsen over time, without periods of improvement.
- There is no cure for MS. There are about 20 medicines approved by the Food and Drug Administration to reduce the number of relapses and slow the progression of MS. Some medicines can be taken by mouth, and other medicines are injected under the skin or given as an intravenous infusion.
- Recently published guidelines are in line with current Oregon Health Plan (OHP) policies.
- The OHP fee-for-service (FFS) Preferred Drug List (PDL) pays for many medications for MS. The nonpreferred medicines will require providers to submit documentation explaining why a person needs treatment with one of these medicines. This process is called prior authorization.

Conclusions:

- Since the last P & T Committee review, 4 high quality systematic reviews and 5 high quality clinical guidelines have been updated or recently published.
- A March 2025 Cochrane systematic review assessed the safety and efficacy of rituximab in adults with any form of MS.[1] Compared with dimethyl fumarate, rituximab may reduce the recurrence of relapse in people with relapsing-remitting MS (RRMS) over 24 months (odds ratio [OR] 0.16, 95% confidence interval (CI) 0.04 to 0.57; n=195; low-certainty evidence).[1] In a placebo-controlled randomized controlled trial (RCT) conducted in adults with primary progressive MS (PPMS), rituximab likely resulted in little to no difference in the number of participants who had disability worsening compared with placebo (OR 0.71, 95% CI 0.45 to 1.11; 1 study, n=439; moderate-certainty evidence).[1] There is limited evidence for long-term adverse events of rituximab in people with MS.[1] Evidence for serious adverse events (SAEs), cancer, and mortality was of very low certainty due to few events reported in the literature.[1]
- A September 2024 Cochrane network meta-analysis (NMA) assessed the safety and efficacy of disease-modifying therapies (DMTs) used to treat adults with PPMS.[2] Moderate-certainty evidence shows the number of people with relapses due to PPMS is reduced with rituximab at 2 years, and interferon beta-1b at 3 years, compared to placebo.[2] Low or very low certainty evidence was found relating to disability progression for the included DMTs compared to placebo, largely due to imprecision.[2]

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- A January 2024 Cochrane NMA evaluated the efficacy and safety of DMTs in adults with RRMS.[3] High-certainty evidence shows that compared to placebo, 2-year treatment with natalizumab, cladribine, or alemtuzumab decreases relapses more than with other DMTs.[3] Moderate-certainty evidence shows that 2-year treatment with natalizumab may slow disability progression.[3] Compared to those on placebo, people with RRMS showed a higher frequency of treatment discontinuation due to adverse events (moderate-certainty evidence) with fingolimod, teriflunomide, interferon beta-1a, laquinimod, natalizumab and daclizumab, while certainty with other DMTs is lower.[3] Moderate certainty evidence shows that treatment with alemtuzumab is associated with fewer discontinuations due to adverse events than placebo, and moderate-certainty evidence shows that interferon beta-1b results in a slight reduction in SAEs, but certainty with regard to other DMTs is lower.[3]
- In June 2023, a Cochrane review concluded that compared with interferon beta-1a, alemtuzumab may improve relapse-free survival and sustained disease progression-free survival, and makes little to no difference on the proportion of participants with at least one adverse event for people with RRMS at 36 months.[4] The certainty of the evidence for these results was very low to low.[4]
- Canada's Drug Agency (CDA) recently published one updated reimbursement review for cladribine and natalizumab in adults with RRMS. Previous CDA 2018 guidance recommended initiation of cladribine in patients who have had at least one relapse in the previous 12 months and after inadequate response to one DMT therapy for RRMS.[7] Guidance from 2009 for natalizumab recommended initiation of natalizumab after failure to respond to full and adequate courses of treatment with at least 2 DMTs.[7]
  - Cladribine and natalizumab are recommended as first-line agents in treatment of patients diagnosed with RRMS according to current clinical criteria including the magnetic resonance imaging (MRI) evidence.[7]
- National Institute for Health and Care Excellence (NICE) recently published 4 documents to guide the use of DMTs in RRMS.
  - NICE recommends ublituximab as an option for treating RRMS in adults.[28]
  - NICE recommends cladribine as an option for treating active RRMS in adults when high-efficacy DMTs (i.e., cladribine, alemtuzumab, ocrelizumab, ofatumumab) would be offered.[29]
  - NICE recommends alemtuzumab for treating RRMS in adults with highly active disease despite a full and adequate course of treatment with at least one DMT or rapidly evolving RRMS defined by 2 or more relapses in the previous year, and baseline MRI evidence of disease activity.[30]
  - NICE recommends natalizumab for the treatment only of rapidly evolving severe RRMS in adults, defined by 2 or more relapses in the previous year, and baseline MRI evidence of disease activity.[31]
- A new subcutaneous formulation, OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) received FDA approval as in September 2024.[34] This product is indicated for treatment of adults with relapsing forms of MS including RRMS, clinically isolated syndrome (CIS), and active secondary progressive MS (SPMS), and adults with PPMS.[34]
- In August 2023, FDA approved a biosimilar product for natalizumab, TYRUKO (natalizumab-sztn).[35] TYRUKO is approved for treatment of relapsing forms of MS including RRMS, CIS, and SPMS in adults.[35] It is also approved for inducing and maintaining clinical response and remission in adults with moderately to severely active Crohn's disease (CD) who have had an inadequate response to, or unable to tolerate conventional CD therapies and inhibitors of tumor necrosis factor (TNF).[35]
- Recent FDA safety alerts are presented in **Table 1.** A black boxed warning was added to glatiramer prescribing information because cases of life-threatening and fatal anaphylaxis have been reported with this medication. All the sphingosine-1-phosphate (S1P) receptor modulators (fingolimod, ozanimod, ponesimod, siponimod) received updated information to the prescribing information for the risk of progressive multifocal leukoencephalopathy (PML) and macular edema. A new warning about the risk of cutaneous malignancies, which was identified in post-marketing surveillance, was added to the prescribing information for all S1P receptor modulators.

Recommendations:

- Maintain OCREVUS ZUNOVO and TYRUKO as non-preferred on the Preferred Drug List (PDL) and add this product the prior authorization (PA) criteria for injectable MS drugs. Based on review of current evidence, no other PDL changes are recommended.
- Revise PA criteria for the oral MS drugs to include a skin exam prior to initiation of S1P receptor modulators, based upon FDA safety alerts of the risk of cutaneous malignancies associated with administration of these medications.
- After review of costs in executive session, no changes were made to the PDL.

Summary of Prior Reviews and Current Policy

- Evidence for the comparative effectiveness of DMTs for MS was last reviewed by the Oregon Pharmacy & Therapeutic (P&T) Committee in October 2024. The March 2024 drug class report on DMTs for MS by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. After review of the materials, the P&T Committee recommended adding ublituximab to the PA criteria for injectable MS medications and to maintain ublituximab as non-preferred on the FFS PDL.
- The PDL status of MS drugs is presented in **Appendix 1**. Interferons, peginterferon, and glatiramer are preferred on the PDL and do not require PA. All oral MS medications are non-preferred and require PA to ensure they are being used safely. Injectable medications including natalizumab, ocrelizumab, and ofatumumab are also non-preferred with specific PA criteria, which are presented in **Appendix 6**. A summary of DMTs used to manage MS is presented in **Appendix 2**.
- During the second quarter of 2025 (April 1 through June 30), a total of 3 pharmacy claims were processed for diroximel fumarate and teriflunomide. In the first quarter of 2025 (January 1 through March 30), there was 1 claim for the physician-administered ocrelizumab infusion.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

Cochrane Review: Rituximab for Adults with Multiple Sclerosis

A March 2025 Cochrane systematic review updated a previous review that assessed the safety and efficacy of rituximab in adults with any form of MS.[1] Rituximab is not FDA-approved for management of MS, but there is compendial support for its off-label use in RRMS.[8] Literature was searched through December 21, 2023.[1] In the 2025 update, the number of study participants increased from 16,429 (15 studies) to 37,443 (28 studies; 13 new studies: 1 RCT and 12 non-randomized studies).[1] The largest study involved 8600 participants and the smallest, 27 participants.[1] Most studies investigated the effects of rituximab on people with RRMS (19 studies; 27,500 (73%) participants).[1]

One RCT compared rituximab to dimethyl fumarate, with 24 months of follow-up in adults with active RRMS.[1] The data showed rituximab may reduce the recurrence of relapse (odds ratio (OR) 0.16, 95% confidence interval (CI) 0.04 to 0.57; n=195; low-certainty evidence). The evidence is very uncertain on disability worsening and serious adverse events.[1] Rituximab may result in little to no difference in upper respiratory tract infections (rate ratio (RR) 1.03, 95% CI 0.79 to 1.34; low-certainty evidence).[1] The evidence is very uncertain for urinary tract, skin, and viral infections.[1] Quality of life, cancer, and mortality were not reported.[1]

In a placebo-controlled RCT conducted in adults with PPMS, rituximab likely resulted in little to no difference in the number of participants who had disability worsening compared with placebo (OR 0.71, 95% CI 0.45 to 1.11; 1 study, n=439; moderate-certainty evidence).[1] The evidence was very uncertain about the effect of rituximab on relapse and serious adverse events (SAEs) over 24 months of follow-up compared with placebo (relapse: OR 0.60, 95% CI 0.18 to 1.99; SAEs: OR 1.25, 95% CI 0.71 to 2.20; very low-certainty evidence for both outcomes).[1] The evidence was very uncertain about the effect of rituximab on common infections compared with placebo (OR 1.14, 95% CI 0.75 to 1.73; very low-certainty evidence).[1] Infections reported in more than 10% of either group included upper respiratory infections, urinary tract infections, and nasopharyngitis.[1]

One retrospective, register-based cohort study compared rituximab to other MS DMTs with 24 months follow-up in adults with active RRMS.[1] Disability worsening was not reported.[1] Compared with interferon beta or glatiramer acetate, rituximab likely delays relapse (hazard ratio (HR) 0.14, 95% CI 0.05 to 0.39; 1 study, n=335; moderate-certainty evidence).[1] Compared with dimethyl fumarate and natalizumab, rituximab may delay relapse (dimethyl fumarate: HR 0.29, 95% CI 0.08 to 1.00; 1 study, n=206; low-certainty evidence; natalizumab: HR 0.24, 95% CI 0.06 to 1.00; 1 study, n=170; low-certainty evidence).[1] The evidence for relapse is very uncertain when rituximab was compared to fingolimod.[1] The effect on serious adverse events is uncertain due to very few events in all the comparison groups.[1] No deaths were reported.[1] Quality of life, common infections, and cancer were not reported.[1]

In summary, the protective effect of rituximab against disability worsening in adults with RRMS is uncertain.[1] There is limited information to determine the effect of rituximab in adults with PPMS.[1] There is limited evidence for long-term adverse events of rituximab in people with MS.[1] Evidence for serious adverse events, cancer, and mortality was of very low certainty due to few events.[1]

Cochrane Review: Immunomodulators for Progressive Multiple Sclerosis

A September 2024 Cochrane NMA assessed the safety and efficacy of DMTs used to treat PPMS.[2] Literature was searched through August 2022 for comparative head-to-head RCTs, or RCTs that compared DMTs to placebo.[2] Twenty studies compared DMTs to placebo, and 3 studies compared different DMTs to each other.[2] Twenty-three RCTs (n=10,167) met inclusion critiera.[2] In these trials, the efficacy and safety of alemtuzumab, cladribine, cyclophosphamide, dimethyl fumarate, diroximel fumarate, fingolimod, fludarabine, glatiramer acetate, immunoglobulins, interferon beta-1b, interferon beta-1a, leflunomide, methotrexate, mitoxantrone, mycophenolate mofetil, natalizumab, ocrelizumab, ofatumumab, ozanimod, pegylated interferon beta-1a, ponesimod, rituximab, siponimod, corticosteroids, and teriflunomide for PPMS were assessed.[2]

Results:

- Relapses over 24 months were assessed in 6 studies (n=1622).[2] The number of people with clinical relapses is reduced with rituximab compared to placebo (risk ratio (RR) 0.60, 95% CI 0.19 to 1.95; 1 RCT; n=439; moderate-certainty evidence).[2] None of the remaining treatments (methotrexate, immunoglobulins, and interferons) showed moderate- or high-certainty evidence in reducing relapses at 24 months compared to placebo.[2]
- Relapses over 36 months were assessed in 4 studies (n=2095).[2] The number of people with clinical relapses is reduced with interferon beta-1b (RR 0.82, 95% CI 0.73 to 0.93; 2 RCT; n=1,657; moderate-certainty evidence).[2] None of the remaining treatments (azathioprine and interferon beta-1a) showed moderate- or high-certainty evidence in reducing relapses at 36 months compared to placebo.[2]

- Disability worsening over 24 months was assessed in 11 studies (n=5284).[2] None of the treatments (glatiramer, immunoglobulins, interferons, methotrexate, natalizumab, siponimod, and rituximab) showed moderate- or high-certainty evidence in preventing disability worsening at 24 months compared to placebo.[2]
- Disability worsening over 36 months was assessed in 5 studies (n=2827 participants).[2] None of the treatments (interferon beta-1a, interferon beta-1b, azathioprine, and ocrelizumab) showed moderate- or high-certainty evidence in preventing disability worsening at 36 months compared to placebo.[2]
- Serious adverse events were assessed in 15 studies (n=8019).[2] None of the treatments (rituximab, interferon beta-1a, interferon beta-1b, methotrexate, immunoglobulins, glatiramer, natalizumab, siponimod, fingolimod, and ocrelizumab) have moderate- or high-certainty evidence compared to placebo.[2]
- Discontinuation due to adverse events was assessed in 21 studies (n=9981).[2] The number of people who discontinued treatment due to adverse events is increased with interferon beta-1a (OR 2.93, 95% CI 1.64 to 5.26; 4 RCTs; n=1,455; high-certainty evidence), interferon beta-1b (OR 2.98, 95% CI 1.92 to 4.61; 2 RCTs; n=1,657; moderate-certainty evidence), glatiramer acetate (OR 3.98, 95% CI 1.48 to 10.72; 1 RCT; n=943; moderate-certainty evidence), and fingolimod (OR 2.29, 95% CI 1.46 to 3.60; 1 RCT; n=823; moderate-certainty evidence).[2]

Cochrane Review: Immunomodulators for Relapsing-Remitting Multiple Sclerosis

A January 2024 Cochrane NMA updated a previous Cochrane review that evaluated the efficacy and safety of DMTs in RRMS.[3] Literature was searched through August 8, 2022.[3] Fifty studies (n=36,541; 68.6% female and 31.4% male) met inclusion criteria.[3] Median treatment duration was 24 months, and 25 (50%) studies were placebo-controlled. Considering the risk of bias, the most frequent concern was related to the role of the sponsor in the authorship of the study report or in data management and analysis, for which 68% of the studies were at high risk of other bias. The other frequent concerns were performance bias (34% judged as having high risk) and attrition bias (32% judged as having high risk).[3]

Results:

- For relapses over 12 months, data were provided in 18 studies (n=9,310).[3] Compared to placebo, natalizumab reduces relapses at 12 months (RR 0.52, 95% CI 0.43 to 0.63; 1 RCT; n=942; high-certainty evidence).[3] Fingolimod (RR 0.48, 95% CI 0.39 to 0.57; indirect evidence; moderate-certainty evidence) and immunoglobulins (RR 0.60, 95% CI 0.47 to 0.79; 2 RCTs; n=91; moderate-certainty evidence) probably reduce relapses at 12 months compared with placebo.[3] Compared with placebo, mitoxantrone (RR 0.40, 95% CI 0.21 to 0.74; 1 RCT; n=51; low-certainty evidence), teriflunomide (RR 0.66, 95% CI 0.55 to 0.78; 1 RCT; n=1,169; low-certainty evidence), pegylated interferon beta-1a (RR 0.68, 95% CI 0.56 to 0.82; 1 RCT; n=1,512; low-certainty evidence) or glatiramer acetate (RR 0.64, 95% CI 0.55 to 0.75; 2 RCTs; n=1,454; low-certainty evidence) may reduce relapses at 12 months.[3] Treatment with interferon beta-1a (RR 0.76, 95% CI 0.68 to 0.85; 1 RCT; n=560; low-certainty evidence) may reduce relapses at 12 months compared to placebo.[3]
- For relapses over 24 months, data were reported in 28 studies (n=19,869).[3] Compared with placebo, cladribine (RR 0.53, 95% CI 0.44 to 0.64; 1 RCT, n=1,326; high-certainty evidence), alemtuzumab (RR 0.57, 95% CI 0.47 to 0.68; indirect evidence; high-certainty evidence) and natalizumab (RR 0.56, 95% CI 0.48 to 0.65; 1 RCT; n=942; high-certainty evidence) reduced relapses at 24 months.[3] Fingolimod (RR 0.54, 95% CI 0.48 to 0.60; 2 RCTs; n=2,355; moderate-certainty evidence), dimethyl fumarate (RR 0.62, 95% CI 0.55 to 0.70; 2 RCTs; n=2,307; moderate-certainty evidence), and ponesimod (RR 0.58, 95% CI 0.48 to 0.70; indirect evidence; moderate-certainty evidence) probably reduce relapses at 24 months compared with placebo.[3] Compared to placebo, glatiramer acetate (RR 0.84, 95%, CI 0.76 to 0.93; 3 RCTs; n=1,014; moderate-certainty evidence) and interferon beta-1a (RR 0.84, 95% CI 0.78 to 0.91; 3 RCTs; n=1,629; moderate-certainty evidence) also reduce relapses at 24 months.[3]
- Disability worsening over 24 months was assessed in 31 studies (n=24,303).[3] Compared to placebo, natalizumab probably results in a reduction of disability worsening (RR 0.59, 95% CI 0.46 to 0.75; 1 RCT; n=942; moderate-certainty evidence) at 24 months.[3] Dimethyl fumarate (RR 0.65, 95% CI 0.55 to 0.77; 2 RCTs; n=2,307; low-certainty evidence), alemtuzumab (RR 0.67, 95% CI 0.46 to 0.99; indirect evidence; low-certainty evidence), and fingolimod (RR 0.68, 95% CI 0.56 to 0.83; 2 RCTs; n=2,355; low-certainty evidence) may reduce disability worsening.[3] Cladribine (RR 0.72, 95% CI 0.56 to 0.91; 1 RCT; n=1,326; low-

certainty evidence) and interferon beta-1b (RR 0.77 95% CI 0.62 to 0.94; 1 RCT; n=372; low-certainty evidence) may result in a reduction of disability worsening.[3] Mitoxantrone (RR 0.20, 95% CI 0.05 to 0.83; 1 RCT; n=51; very low-certainty evidence) may reduce disability worsening compared to placebo.[3]

- Treatment discontinuation due to adverse events data were available from 43 studies (n=35,410).[3] Alemtuzumab is associated with reduced treatment discontinuation due to adverse events (OR 0.39, 95% CI 0.19 to 0.79; indirect evidence; moderate-certainty evidence).[3] Fingolimod (OR 1.84, 95% CI 1.31 to 2.57; 2 RCTs; n=2,355; moderate-certainty evidence), teriflunomide (OR 1.82, 95% CI 1.19 to 2.79; 2 RCTs; n=2,253; moderate-certainty evidence), interferon beta-1a (OR 1.48, 95% CI 0.99 to 2.20; 2 RCTs; n=1,457; moderate-certainty evidence), natalizumab (OR 1.57, 95% CI 0.81 to 3.05; 1 RCT; n=939; moderate-certainty evidence), and glatiramer acetate (OR 1.48, 95% CI 1.01 to 2.14; 4 RCTs; n=2,419; moderate-certainty evidence) are associated with higher treatment discontinuation due to adverse events.[3]

In summary, natalizumab, cladribine, and alemtuzumab decrease relapses over 2 years (high-certainty evidence), compared to placebo.[3] Natalizumab may slow disability progression over 2 years (moderate-certainty evidence).[3] People with RRMS treated with most of the DMTs assessed result in higher rates of treatment discontinuation due to adverse events (moderate-certainty evidence).[3] Alemtuzumab is associated with fewer discontinuations due to adverse events (moderate-certainty evidence), and interferon beta-1b may slightly reduce serious adverse events, but certainty with regard to other DMTs is lower.[3] Insufficient evidence is available to evaluate the efficacy and safety of DMTs for longer than 2 years, which is a relevant issue for a chronic condition like MS that develops over decades.[3]

Cochrane Review: Alemtuzumab for Multiple Sclerosis

In June 2023, a Cochrane review evaluated the safety and efficacy of alemtuzumab in people with any form of MS.[4] Literature was searched through June 21, 2022 for comparative head-to-head or placebo-controlled trials with alemtuzumab.[4] Three RCTs (n=1,713) were identified that compared intravenous (IV) alemtuzumab with subcutaneous (SC) interferon beta-1a in patients with RRMS.[4] Participants were treatment-naive (2 RCTs) or had experienced at least one relapse after interferon or glatiramer (one RCT).[4] Alemtuzumab was given at doses of 12 mg per day or 24 mg per day for five days at months 0 and 12, or 24 mg per day for three days at months 12 and 24. Participants in the interferon beta-1a group received 44 mcg three times weekly.[4]

Results:

- Alemtuzumab 12 mg and 24 mg may improve relapse-free survival at 36 months (12 mg: HR 0.31, 95% CI 0.18 to 0.53; and 24 mg: HR 0.21, 95% CI 0.11 to 0.40; 1 RCT, n=221; low-certainty evidence for both doses) versus interferon beta-1a.[4]
- Alemtuzumab 12 mg and 24 mg may improve sustained disease progression-free survival at 36 months (12 mg: HR 0.25, 95% CI 0.11 to 0.56; 1 RCT; n=221; and 24 mg: HR 0.33, 95% CI 0.16 to 0.69; 1 RCT, n=223; low-certainty evidence for both doses) versus interferon beta-1a.[4]
- No difference in the proportion of participants who experience at least one adverse event at 36 months was found between interferon beta-1a and alemtuzumab 12 mg (RR 1.00, 95% CI 0.98 to 1.02; 1 RCT, n=224; low-certainty evidence) or alemtuzumab 24 mg (RR 0.99, 95% CI 0.97 to 1.02; 1 RCT, n=215; low-certainty evidence).[4] The proportion of participants with at least one adverse event was high with both alemtuzumab and interferon.[4]
- Alemtuzumab 12 mg and 24 mg may slightly reduce disability at 36 months (12 mg: mean difference [MD] −0.70, 95% CI −1.04 to −0.36; 1 RCT, n=223; low-certainty evidence and 24 mg: MD −0.83, 95% CI −1.16 to −0.50; 1 RCT, n=221; low-certainty evidence).[4]

For quality of life, fatigue, and participants free of clinical disease activity, the studies either did not consider these outcomes or they used different measuring tools to those planned in this review.[4] Compared with interferon beta-1a, alemtuzumab may improve relapse-free survival and sustained disease progression-free survival, and make little to no difference on the proportion of participants with at least one adverse event for people with relapsing–remitting MS at 36 months.[4] The certainty of the evidence for these results was very low to low.[4]

After review, 18 systematic reviews were excluded due to poor quality(e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria),[9-12] wrong study design of included trials (e.g., observational),[13-19] comparator (e.g., no control or placebo-controlled),[20-23] or outcome studied (e.g., non-clinical).[24-27]

New Guidelines:

Canada's Drug Agency: Cladribine and Natalizumab for Relapsing-Remitting Multiple Sclerosis

In March 2025, Canada's Drug Agency (CDA) issued a reimbursement recommendation for the use of cladribine monotherapy or natalizumab monotherapy as first-line treatment for patients with RRMS.[7] Currently, there are 2 approaches to MS treatment. The traditional escalation approach involves initiating treatment with DMTs with relatively favorable safety profiles but with only low to moderate efficacy and then escalating to more effective DMTs based on continued disease activity and inadequate symptom control.[7] An alternative approach is early intensive or high-efficacy treatment, which involves starting treatment with a higher efficacy DMT that may have less favorable safety profiles.[7] Historically, the escalation approach has been used with high-efficacy DMTs reserved for patients with poor response to a traditional first-line (lower efficacy) drug.[7] There has been a recent paradigm shift in the treatment for RRMS, where early intensive or high-efficacy treatment is preferred, with the goal to achieve disease control rapidly to minimize neurological damage and risk of disability worsening.[7] There are 2 high-efficacy DMTs currently recommended as first-line treatment of RRMS, ocrelizumab and ofatumumab, which share similar mechanisms of action.[7] Clinicians who treat MS have expressed a need for more treatment options for the first-line treatment of RRMS that have different mechanisms of action and modes of administration for patients with different treatment needs.[7]

The CDA's Formulary Management Expert Committee (FMEC) concluded that cladribine and natalizumab are more effective than most lower efficacy DMTs in reducing the frequency of relapses over 2 years of treatment.[7] Although there is some uncertainty in the clinical value of the efficacy and safety, FMEC concluded that both cladribine and natalizumab address important unmet clinical needs that are not met by treatment options currently recommended in the first-line setting of RRMS (i.e., B-cell therapies).[7] The FMEC noted from discussion with guest specialists that B-cell therapies may not be suitable for patients with conditions such as inflammatory bowel disease or with severe immunodeficiency.[7] There are currently no published clinical trials directly comparing natalizumab or cladribine with other high-efficacy DMTs for RRMS.[7] Findings from a Cochrane NMA[3] predict natalizumab and cladribine are more effective than all but one of the lower efficacy DMTs of interest (dimethyl fumarate) in reducing the frequency of relapses over 2 years of treatment.[7] Using placebo as a common comparator, treatment with cladribine (RR = 0.53; 95% CI, 0.44 to 0.64; high-certainty evidence) and natalizumab (RR = 0.56; 95%; 0.48 to 0.65; high-certainty evidence) resulted in a large decrease in the number of people who experienced MS relapses.[7] Treatment with natalizumab or cladribine resulted in a larger decrease in the number of people who had MS relapses over 24 months compared with glatiramer acetate, interferon beta 1a, interferon beta 1b, and teriflunomide.[7] However, there were no data available for comparison with ocrelizumab and ofatumumab for this outcome.[7] The lack of such data adds to the uncertainty in the clinical value of natalizumab and cladribine.[7]

The Cochrane NMA showed no difference between treatment with natalizumab and with cladribine and other treatment comparators with respect to the number of people who experienced SAEs.[7] However, there is concern for PML with the use of natalizumab as well as mitigation strategies in place to minimize the risk of PML, such as monitoring the John Cunningham virus (JCV) titer .[7]

Previous CDA 2018 guidance recommended initiation of cladribine in patients who have had at least one relapse in the previous 12 months and after inadequate response to one therapy for RRMS.[7] Guidance from 2009 for natalizumab recommended initiation of natalizumab after failure to respond to full and adequate courses of treatment with at least 2 DMTs or have contraindications to, or be intolerant of, these therapies. In addition, the patient should have a significant increase in T2 lesion load compared to a previous MRI or least 1 gadolinium-enhancing lesion and experience 2 or more disabling relapses in the previous years.[7] Revised 2025 guidance recommends both agents as first-line treatments for RRMS as outlined below.

CDA Updated 2025 Recommendations for the use Cladribine and Natalizumab as First-Line Agent in RRMS:

- Patients must have a diagnosis of RRMS established according to current clinical criteria including the MRI evidence.[7]
- Patients must be under the care of a specialist with experience in the diagnosis and management of MS.[7]
- Tolerability issues with a moderate-efficacy disease-modifying therapy could entail a switch to a high efficacy DMT in some cases (e.g., comorbidities, pharmacological interactions, and so forth).[7]

National Institute for Health and Care Excellence: Ublituximab for Treating Relapsing Multiple Sclerosis

A December 2024 NICE publication provides recommendations for the use of ublituximab in managing RRMS.[28] Treatment options for active RRMS include immunomodulatory treatments such as teriflunomide and anti-CD20 monoclonal antibodies such as ocrelizumab and ofatumumab.[28] Ublituximab is another treatment option that works in a similar way to ocrelizumab and ofatumumab and would be offered to the same population.[28] Clinical trial evidence shows that ublituximab is more effective at reducing the number of relapses than teriflunomide.[28] Ublituximab has not been directly compared in a clinical trial with ocrelizumab and ofatumumab.[28]

- NICE recommends ublituximab as an option for treating RRMS in adults.[28]

National Institute for Health and Care Excellence: Cladribine for Treating Active Relapsing Forms of Multiple Sclerosis

In April 2025, NICE updated guidance for the use of cladribine in patients with active RRMS.[29] High-efficacy DMTs for active RRMS include ocrelizumab and ofatumumab.[29] Ponesimod, dimethyl fumarate and diroximel fumarate may be used because they are taken orally in patients with active RRMS.[29] Clinical trial evidence shows that cladribine reduces relapses and increases the time until disability progresses compared with placebo.[29] Indirect comparisons suggest that the relapse rate with cladribine is similar to that of ocrelizumab and ofatumumab.[29] The committee discussed that cladribine oral treatment taken in 2 short courses over 2 years would be less disruptive than some MS available treatments. Clinical experts highlighted the long-acting effect of cladribine, which can delay relapses and the need for subsequent DMTs. The committee concluded that cladribine's dosing schedule has benefits compared with existing treatment options. They considered these benefits, especially for people who would find it hard to travel for treatment, in their decision making.[29]

- NICE recommends cladribine as an option for treating active RRMS in adults when high-efficacy DMTS would be offered.[29]

National Institute for Health and Care Excellence: Alemtuzumab for Treating Highly Active Relapsing-Remitting Multiple Sclerosis

NICE updated guidance for the use of alemtuzumab in highly active RRMS in May 2024.[30] The recommended dosage of alemtuzumab is 12 mg per day administered by IV infusion for 2 treatment courses.[30] The initial treatment course lasts 5 consecutive days, followed 12 months later by the second treatment course of 3 consecutive days.[30] The appraisal committee heard from clinical specialists that the currently available first-line treatments (i.e., beta interferons) for active RRMS need to be injected weekly or several times per week and can be associated with unpleasant side effects (such as injection-site reactions, flu-like symptoms, fatigue and depression) and can significantly affect emotional wellbeing.[30] Clinical specialists reported that alemtuzumab would be considered as a first-line treatment option, alongside beta interferons or glatiramer acetate, for people with active RRMS eligible for treatment under the Association for British Neurologists' guidelines.[30] While effective therapies should ideally be offered early in disease, offering effective treatments later in disease is even more important because these patients have a higher risk for more severe complications.[30] While alemtuzumab's marketing authorization permits its use as a first-line treatment, it is more likely to be offered to people for whom other DMTs have not been effective.[30] Advantages to alemtuzumab treatment are that it is highly effective, does not cause the flu-like symptoms associated with beta interferons, and does not need to be discontinued by patients planning a pregnancy, although effective contraceptive measures should be taken when receiving alemtuzumab and for 4 months following a course of treatment according to the summary of product characteristics.[30] The main disadvantages of alemtuzumab treatment are the possible SAEs observed during the trials, including idiopathic

thrombocytopenic purpura, kidney disease or failure, thyroid disease and death.[30] Patients require monthly platelet and white cell counts and quarterly assessment of thyroid and renal function for 4 years after the last alemtuzumab treatment.[30] The Committee concluded that alemtuzumab is associated with significant benefits, but also significant harms, and that adhering to the recommended monitoring schedule is important.[30]

- NICE recommends alemtuzumab for treating highly active RRMS in adults with highly active disease despite a full and adequate course of treatment with at least one DMT or rapidly evolving RRMS defined by 2 or more relapses in the previous year, and baseline MRI evidence of disease activity.[30]

National Institute for Health and Care Excellence: Natalizumab for the Treatment of Adults with Highly Active Relapsing-Remitting Multiple Sclerosis

NICE update guidance for the use of natalizumab in adults with highly active RRMS in May 2024.[31] The wording in 2014 recommendations was updated to address concerns raised by the clinical community that the previously used definition of rapidly evolving severe MS was overly restrictive, as the requirement for 2 MRI scans placed significant burden on a limited diagnostic and monitoring resources.[31] The wording has now been changed to better reflect current clinical practice.[31]

- NICE recommends natalizumab for the treatment only of rapidly evolving severe RRMS in adults, defined by 2 or more relapses in the previous year, and baseline MRI evidence of disease activity.[31]

After further review, 2 guidelines were excluded due to poor quality.[32,33]

New Formulations:

- A new SC formulation, OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) received FDA approval September 2024.[34] This product is indicated for treatment of adults with relapsing forms of MS including RRMS, CIS, and SPMS, and adults with PPMS.[34] This product must be administered by a health care professional. Patients should be pre-medicated with an oral corticosteroid and antihistamine at least 30 minutes prior to each injection. The dosing is 23 mL of OCREVUS ZUNOVO (920 mg ocrelizumab and 23,000 units hyaluronidase) SC in the abdomen over approximately 10 minutes every 6 months.[34] The safety and efficacy of ocrelizumab in managing relapsing forms of MS and PPMS was demonstrated in trials conducted with IV-administered ocrelizumab.[34] A multicenter, open-label RCT (n=236) demonstrated the comparable bioavailability, pharmacokinetics, pharmacodynamics, safety, and immunogenicity of OCREVUS ZUNOVO relative to IV ocrelizumab in adults with either RMS (n=213) or PPMS (N=23).[34]

- In August 2023, FDA approved a biosimilar product for natalizumab, TYRUKO (natalizumab-sztn).[35] TYRUKO is FDA-approved for treatment of relapsing forms of MS, including RRMS, CIS, and SPMS in adults.[35] It is also approved for inducing and maintaining clinical response and remission in adults with moderately to severely active CD who have had an inadequate response to, or unable to tolerate conventional CD therapies and inhibitors of TNF.[35] The safety, efficacy, and immunogenicity of the biosimilar product was compared with the reference product in a phase 3 RCT (n=264) with adults with RRMS.[36] At week 24, the mean difference in the cumulative number of new active lesions was similar between treatment groups.[36] No significant differences between treatment groups were observed across secondary efficacy end points, safety, tolerability, or immunogenicity assessments.[36]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[37]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)

Glatiramer Acetate	COPAXONE, GLATOPA	1/2025	Boxed Warning	**WARNING: ANAPHYLACTIC REACTIONS** Cases of life-threatening and fatal anaphylaxis have been reported with glatiramer acetate. Anaphylaxis can occur at any time following initiation of therapy, from as early as after the first dose, up to years following initiation of therapy. • Make patients aware of the symptoms of anaphylaxis, which may overlap with those of an immediate post-injection reaction; instruct them to seek immediate medical care should these symptoms occur. Prompt identification of anaphylaxis is important to avoid a delay in treatment, • Glatiramer is contraindicated in patients with a history of hypersensitivity reactions to glatiramer, including anaphylaxis. If an anaphylactic reaction occurs, treatment with glatiramer must be immediately discontinued. Unless a clear alternative etiology is identified, glatiramer must be permanently discontinued.
Fingolimod Ozanimod Ponesimod Siponimod	GILENYA ZEPOSIA PONVORY MAYZENT	June 2024	Warnings and Precautions	**Progressive Multifocal Leukoencephalopathy (PML)** Longer treatment duration increases the risk of PML in patients treated with sphingosine-1 phosphate (S1P) receptor modulators; most cases of PML associated with S1P receptor modulators have occurred in patients treated for at least 18 months. **Macular Edema** S1P receptor modulators have been associated with an increased risk of macular edema. Obtain a baseline evaluation of the fundus, including the macula, near the start of treatment with S1P receptor modulators. Perform an examination of the fundus, including the macula, periodically while on therapy, and any time there is a change in vision. **Cutaneous Malignancies** Cases of other cutaneous malignancies, including melanoma, have also been reported in patients treated with other S1P receptor modulators. Kaposi's sarcoma and Merkel cell

				carcinoma have also been reported in patients treated with S1P receptor modulators in the post-marketing setting. Skin examinations are recommended prior to or shortly after the start of treatment and periodically thereafter for all patients, particularly those with risk factors for skin cancer.

References:

1. Filippini G, Kruja J, Del Giovane C. Rituximab for people with multiple sclerosis. *Cochrane Database of Systematic Reviews*. 3:CD013874. doi:https://dx.doi.org/10.1002/14651858.CD013874.pub3
2. Ridley B, Minozzi S, Gonzalez-Lorenzo M, et al. Immunomodulators and immunosuppressants for progressive multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews*. 9:CD015443. doi:https://dx.doi.org/10.1002/14651858.CD015443.pub2
3. Gonzalez-Lorenzo M, Ridley B, Minozzi S, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews*. 1:CD011381. doi:https://dx.doi.org/10.1002/14651858.CD011381.pub3
4. Riera R, Torloni MR, Martimbianco ALC, Pacheco RL. Alemtuzumab for multiple sclerosis. *Cochrane Database of Systematic Reviews*. 2023;(6)doi:10.1002/14651858.CD011203.pub3
5. Canada's Drug Agency. Teriflunomide Reimbursement Review. January 2025. https://www.cda-amc.ca/sites/default/files/DRR/2025/SX0752_Teriflunomide_FMEC_Recommendation.pdf Accessed 8/11/2025.
6. Canada's Drug Agency. Dimethyl Fumarate Reimbursement Recommendation. January 2025. https://www.cda-amc.ca/sites/default/files/DRR/2025/SX0751_Dimethyl_FMEC_Recommendation.pdf Accessed 8/11/2025.
7. Canada's Drug Agency. Cladribine and Natalizumab for Relapsing-Remitting Multiple Sclerosis. March 2025. https://www.cda-amc.ca/sites/default/files/DRR/2025/TS0004_cladribine_natalizumab_Final%20Rec.pdf Accessed 8/8/2025.
8. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed August, 4, 2025.
9. Etemadifar M, Nouri H, Sedaghat N, et al. Anti-CD20 therapies for pediatric-onset multiple sclerosis: A systematic review. *Multiple Sclerosis and Related Disorders*. 91:105849. doi:https://dx.doi.org/10.1016/j.msard.2024.105849
10. Etemadifar M, Kaveyee H, Ebne-Ali-Heydari Y, et al. Dimethyl Fumarate for Pediatric-Onset Multiple Sclerosis: A Systematic Review. *Pediatric Neurology*. 167:52-59. doi:https://dx.doi.org/10.1016/j.pediatrneurol.2025.03.008
11. Dang YL, Yong VT, Sharmin S, Perucca P, Kalincik T. Seizure risk in multiple sclerosis patients treated with disease-modifying therapy: A systematic review and network meta-analysis. *Multiple Sclerosis*. 29(6):657-667. doi:https://dx.doi.org/10.1177/13524585231151400
12. Montalban X, Matthews PM, Simpson A, et al. Real-world evaluation of ocrelizumab in multiple sclerosis: A systematic review. *Ann*. 10(3):302-311. doi:https://dx.doi.org/10.1002/acn3.51732
13. Chen C, Zhang E, Zhu C, et al. Comparative efficacy and safety of disease-modifying therapies in patients with relapsing multiple sclerosis: A systematic review and network meta-analysis. *J Am Pharm Assoc (2003)*. 63(1):8-22.e23. doi:https://dx.doi.org/10.1016/j.japh.2022.07.009
14. Samjoo IA, Drudge C, Walsh S, et al. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. *Journal of Comparative Effectiveness Research*. 12(7):e230016. doi:https://dx.doi.org/10.57264/cer-2023-0016

15. Sabet H, Zanaty MA, Arafa A, et al. Safety and effectiveness of diroximel fumarate in relapsing forms of multiple sclerosis: a systematic review and meta-analysis. *Neurol Sci*. 46(8):3477-3490. doi:https://dx.doi.org/10.1007/s10072-025-08140-8
16. Brown JD, Muston BT, Massey J. Switching from natalizumab to an anti-CD20 monoclonal antibody in relapsing remitting multiple sclerosis: A systematic review. *Multiple Sclerosis and Related Disorders*. 86:105605. doi:https://dx.doi.org/10.1016/j.msard.2024.105605
17. Pipek LZ, Mahler JV, Nascimento RFV, Apostolos-Pereira SL, Silva GD, Callegaro D. Cost, efficacy, and safety comparison between early intensive and escalating strategies for multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders*. 71:104581. doi:https://dx.doi.org/10.1016/j.msard.2023.104581
18. de Souza Wagner PH, de Paiva FA, Mello JS, et al. Clinical outcomes after switching from fingolimod to B-cell-depleting therapies in multiple sclerosis: systematic review and meta-analysis. *J Neurol*. 272(8):546. doi:https://dx.doi.org/10.1007/s00415-025-13283-x
19. Jimenez-Sanchez S, Maksoud R, Eaton-Fitch N, Marshall-Gradisnik S, Broadley SA. The role of alemtuzumab in the development of secondary autoimmunity in multiple Sclerosis: a systematic review. *Journal of Neuroinflammation*. 21(1):281. doi:https://dx.doi.org/10.1186/s12974-024-03263-9
20. Sui Z, Zhu H, Luo J, Yu J, Li L, Zheng Q. Quantitative comparison of the efficacy of clinical drug treatments for primary progressive multiple sclerosis. *Journal of Clinical Neuroscience*. 113:45-53. doi:https://dx.doi.org/10.1016/j.jocn.2023.04.003
21. Sabahi Z, Daei Sorkhabi A, Sarkesh A, Naseri A, Asghar-Rezaei N, Talebi M. A systematic review of the safety and efficacy of monoclonal antibodies for progressive multiple sclerosis. *Int Immunopharmacol*. 120:110266. doi:https://dx.doi.org/10.1016/j.intimp.2023.110266
22. Sladowska K, Mocko P, Brzostek T, Kawalec P. Efficacy and safety of disease-modifying therapies in pediatric-onset multiple sclerosis: A systematic review of clinical trials and observational studies. *Multiple Sclerosis and Related Disorders*. 94:106263. doi:https://dx.doi.org/10.1016/j.msard.2025.106263
23. Nabizadeh F, Mohamadi M, Rahmani S, et al. Safety and efficacy of cladribine in multiple sclerosis: a systematic review and meta-analysis. *Neurol Sci*. 44(9):3045-3057. doi:https://dx.doi.org/10.1007/s10072-023-06794-w
24. Ashkar A, Baig MMA, Arif A, Ali MM, Yousuf F, Ashkar R. Prognostic significance of neurofilament light in Fingolimod therapy for Multiple Sclerosis: A systemic review and meta-analysis based on randomized control trials. *Multiple Sclerosis and Related Disorders*. 69:104416. doi:https://dx.doi.org/10.1016/j.msard.2022.104416
25. Alonso-Moreno M, Ladron-Guevara M, Ciudad-Gutierrez P. Systematic review of gender bias in clinical trials of monoclonal antibodies for the treatment of multiple sclerosis. *Neurologia*. 38(9):695-706. doi:https://dx.doi.org/10.1016/j.nrleng.2021.01.008
26. Vitturi BK, Rahmani A, Montecucco A, Dini G, Durando P. Occupational outcomes of people with multiple sclerosis during the COVID-19 pandemic: a systematic review with meta-analysis. *Frontiers in Public Health*. 11:1217843. doi:https://dx.doi.org/10.3389/fpubh.2023.1217843
27. Petrou DP. Untackling the economics of multiple sclerosis: A systematic review of economic evaluations of disease-modifying therapies indicated for multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 92:106161. doi:https://dx.doi.org/10.1016/j.msard.2024.106161
28. National Institute for Health and Care Excellence (NICE). Ublituximab for Treating Relapsing Multiple Sclerosis. December 2024. https://www.nice.org.uk/guidance/ta1025 Accessed 8/12/2025.
29. National Institute for Health and Care Excellence (NICE). Cladribine for Treating Active Relapsing Forms of Multiple Sclerosis. April 2025. https://www.nice.org.uk/guidance/ta1053 Accessed 8/8/2025.
30. National Institute for Health and Care Excellence (NICE). Alemtuzumab for Treating Highly Active Relapsing-Remitting Multiple Sclerosis. May 2024. https://www.nice.org.uk/guidance/ta312 Accesseed 8/12/2025.
31. National Institute for Health and Care Excellence (NICE). Natalizumab for the Treatment of Adults with Highly Active Relapsing-Remitting Multiple Sclerosis. May 2024. https://www.nice.org.uk/guidance/ta127 Accessed 8/12/2025.
32. Canada's Drug Agency. Review of Guidelines on Second-Line Therapy for Patients with Relpasing-Remitting Multiple-Sclerosis: A 2024 Update. July 2024. https://www.cda-amc.ca/sites/default/files/pdf/htis/2024/RC1541-2nd-Line-Therapy-RRMS.pdf Accessed 8/11/2025.

33. Capela C, Santos E, Palavra F, et al. Multiple Sclerosis Disease-Modifying Treatment Algorithms: 2025 Positioning of the Portuguese Multiple Sclerosis Study Group. *Acta Medica Portuguesa*. 38(6-7):414-426. doi:https://dx.doi.org/10.20344/amp.22380
34. OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) subcutaneous injection. Prescribing Information. South San Francisco, CA; Genentech, Inc. September 2024.
35. TYRUKO (natalizumab-sztn) intravenous injection. Prescribing Information. Princeton, NJ; Sandoz, Inc. August 2023.
36. Hemmer B, Wiendl H, Roth K, et al. Efficacy and Safety of Proposed Biosimilar Natalizumab (PB006) in Patients With Relapsing-Remitting Multiple Sclerosis: The Antelope Phase 3 Randomized Clinical Trial. *JAMA Neurology*. 80(3):298-307. doi:https://dx.doi.org/10.1001/jamaneurol.2022.5007
37. Food and Drug Administration (FDA) Drug Safety Labeling Changes. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm Accessed July 16, 2025.
38. Lexicomp® Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Accessed March 8, 2021.
39. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. 2020 Available at: https://www-micromedexsolutions-com.liboff.ohsu.edu Accessed March 8, 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
interferon beta-1a	AVONEX PEN (4 PACK)	INTRAMUSC	PEN IJ KIT	Y
interferon beta-1a	AVONEX	INTRAMUSC	SYRINGE	Y
peginterferon beta-1a	PLEGRIDY	INTRAMUSC	SYRINGE	Y
interferon beta-1a	AVONEX (4 PACK)	INTRAMUSC	SYRINGEKIT	Y
interferon beta-1b	BETASERON	SUBCUT	KIT	Y
peginterferon beta-1a	PLEGRIDY PEN	SUBCUT	PEN INJCTR	Y
interferon beta-1a/albumin	REBIF REBIDOSE	SUBCUT	PEN INJCTR	Y
glatiramer acetate	COPAXONE	SUBCUT	SYRINGE	Y
peginterferon beta-1a	PLEGRIDY	SUBCUT	SYRINGE	Y
interferon beta-1a/albumin	REBIF	SUBCUT	SYRINGE	Y
ublituximab-xiiy	BRIUMVI	INTRAVEN	VIAL	N
alemtuzumab	LEMTRADA	INTRAVEN	VIAL	N
ocrelizumab	OCREVUS	INTRAVEN	VIAL	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAP DS PK	N
fingolimod HCl	FINGOLIMOD	ORAL	CAPSULE	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAPSULE	N
monomethyl fumarate	BAFIERTAM	ORAL	CAPSULE DR	N
dimethyl fumarate	DIMETHYL FUMARATE	ORAL	CAPSULE DR	N
dimethyl fumarate	TECFIDERA	ORAL	CAPSULE DR	N
diroximel fumarate	VUMERITY	ORAL	CAPSULE DR	N
siponimod	MAYZENT	ORAL	TAB DS PK	N
ponesimod	PONVORY	ORAL	TAB DS PK	N
dalfampridine	AMPYRA	ORAL	TAB ER 12H	N
dalfampridine	DALFAMPRIDINE ER	ORAL	TAB ER 12H	N
fingolimod lauryl sulfate	TASCENSO ODT	ORAL	TAB RAPDIS	N
teriflunomide	AUBAGIO	ORAL	TABLET	N
cladribine	MAVENCLAD	ORAL	TABLET	N
siponimod	MAYZENT	ORAL	TABLET	N
ponesimod	PONVORY	ORAL	TABLET	N
teriflunomide	TERIFLUNOMIDE	ORAL	TABLET	N
ofatumumab	KESIMPTA PEN	SUBCUT	PEN INJCTR	N
glatiramer acetate	COPAXONE	SUBCUT	SYRINGE	N
glatiramer acetate	GLATIRAMER ACETATE	SUBCUT	SYRINGE	N
glatiramer acetate	GLATOPA	SUBCUT	SYRINGE	N
interferon beta-1b	BETASERON	SUBCUT	VIAL	N
ocrelizumab-hyaluronidase-ocsq	OCREVUS ZUNOVO	SUBCUT	VIAL	N
natalizumab*	TYSABRI	INTRAVEN	VIAL	N

* Located in Targeted Immune Modulators class on Preferred Drug list

Appendix 2: Therapies for Management of Multiple Sclerosis

Table 1. FDA-Approved Disease-Modifying Therapies for Multiple Sclerosis.[38,39]

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

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

Natalizumab and biosimilars	TYSABRI, TYRUKO	300 mg via IV infusion every 4 weeks	CIS RRMS SPMS	Yes	Black Box Warnings: PML Other Warnings: infections, hypersensitivity, teratogenicity, thrombocytopenia, hepatotoxicity **Consider risk of PML vs. benefit of therapy**	JCV antibody testing and brain MRI every 6 months. CBC and LFTs every 6 months.
Ocrelizumab Ocrelizumab hyaluronidase-ocsq	OCREVUS OCREVUS ZUNOVO	600 mg IV every 6 months (maintenance) 920 mg SC every 6 months	CIS RRMS SPMS PPMS	No	Infusion reactions, infections and PML	Hepatitis B virus screening prior to starting therapy.
Ofatumumab	KESIMPTA	20 mg SC every 4 weeks	CIS RRMS SPMS	No	Infusion reactions and infections, PML	Hepatitis B virus screening prior to starting therapy.
Ublituximab	BRIUMVI	450 mg via IV infusion every 6 months	CIS RRMS SPMS	No	Infusion reactions and infections, PML	Hepatitis B virus screening prior to starting therapy.
Others						
Mitoxantrone	NOVANTRONE	12 mg/m^2 IV infusion every 3 months – duration of therapy limited to 2 years and cumulative dose of 140 mg/m^2	RRMS SPMS	No	Black Box Warning: Dose-related Cardiotoxicity **Considered as last resort treatment for patients that have failed other therapies**	ECG and LVEF before each infusion. CBC and LFTs every 6 months.
Glatiramer Acetate	COPAXONE, GLATOPA	20 mg SC once daily; OR 40 mg SC three times a week	CIS RRMS SPMS	No	Transient post injection reactions (chest pain, dyspnea, tachycardia, anxiety, palpitations, flushing, urticaria) and hepatoxicity	None required

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

Appendix 3: New Comparative Clinical Trials

A total of 122 citations were manually reviewed from the initial literature search. After further review, 122 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to August 01, 2025>

1	exp Multiple Sclerosis/	75750
2	exp Glatiramer Acetate/	1561
3	exp Interferons/	149624
4	exp Alemtuzumab/	2410
5	exp Cladribine/	1859
6	exp Dimethyl Fumarate/	1201
7	ozanimod.mp. or exp Sphingosine-1-Phosphate Receptors/	1522
8	peginterferon.mp.	6893
9	teriflunomide.mp.	1178
10	ublituximab.mp.	95
11	Dimethyl Fumarate/	1201
12	diroximel fumarate.mp. or Fumarates/	4914
13	siponimod.mp. or Sphingosine 1 Phosphate Receptor Modulators/	494
14	Sphingosine-1-Phosphate Receptors/ or ponesimod.mp.	1334
15	dalfampridine.mp. or 4-Aminopyridine/	4233
16	Fingolimod Hydrochloride/	2996
17	ofatumumab.mp.	939
18	ocrelizumab.mp.	1267
19	peginterferon.mp.	6893
20	monomethyl fumarate.mp.	156
21	Natalizumab/	2097
22	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	173301
23	1 and 22	10185
24	limit 23 to (english language and humans and yr="2023 -Current")	957
25	limit 24 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review")	122

Appendix 5: Key Inclusion Criteria

Population	People with multiple sclerosis , all ages
Intervention	Disease modifying therapies for management of multiple sclerosis
Comparator	Other disease modifying therapies for management of multiple sclerosis or placebo
Outcomes	Changes in annualized multiple sclerosis relapse rates, disability rates and frequency of adverse events
Timing	12-36 months
Setting	Outpatient

Multiple Sclerosis, Injectable Drugs

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

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred injectable or infused multiple sclerosis drugs (both pharmacy or provider administered claims).
- Note: Natalizumab should be reviewed under separate Natalizumab PA criteria.
- Note: Requests for Arzerra™ (ofatumumab) should be reviewed under the Oncology PA.

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis (see Table 1)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the drug prescribed by or in consultation with a neurologist?	**Yes**: Go to # 5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the patient on concurrent treatment with a disease modifying drug (i.e., glatiramer, interferon, mitoxantrone, natalizumab, ofatumumab, ocrelizumab, or peginterferon) to treat MS?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the request for a drug with potential risks during pregnancy (e.g., ofatumumab, mitoxantrone, or ublituximab)?	**Yes**: Go to #8	**No**: Approve for up to 1 year
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to 1 year
9. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10
10. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for up to 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's condition stabilized (i.e., reduced activity seen on magnetic resonance imaging (MRI), fewer relapses, and/or minimal or no disease progression) as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1. FDA-Approved Indications for Injectable MS Drugs

Generic Name	Brand Name	FDA Indication			
		CIS	RRMS	SPMS	PPMS
Alemtuzumab	LEMTRADA		X	X	

Glatiramer acetate	GLATOPA, COPAXONE	X	X	X	
Interferon beta-1a	AVONEX, REBIF	X	X	X	
Interferon beta-1b	BETASERON, EXTAVIA	X	X	X	
Mitoxantrone	NOVANTRONE		X	X	
Ocrelizumab	OCREVUS	X	X	X	X
Ocrelizumab and hyaluronidase-ocsq	OCREVUS ZUNOVO	X	X	X	X
Ofatumumab	KESIMPTA	X	X	X	
Ublituximab	BRIUMVI	X	X	X	
Abbreviations: CIS = clinically isolated syndrome; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis					

Table 2. FDA-Recommended Baseline Safety Assessments

	LFTs	CBC	Thyroid Function Tests	Hepatitis B Virus Screening	Other Screening
Alemtuzumab	X	X	X		VZV and TB Screening, SCr, UA, up to date with all vaccinations, completed screening for John Cunningham (JC) virus
Glatiramer acetate					
Interferon beta-1a	X	X	X		
Interferon beta-1b	X	X	X		
Mitoxantrone	X	X			ECG and LVEF, negative pregnancy test
Ocrelizumab				X	Serum immunoglobulins, up to date with all vaccinations, completed screening for John Cunningham (JC) virus
Ocrelizumab hyaluronidase-ocsq				X	Serum immunoglobulins, up to date with all vaccinations, completed screening for John Cunningham (JC) virus

Ofatumumab				X	Serum immunoglobulins, up to date with all vaccinations, negative pregnancy test, completed screening for John Cunningham (JC) virus
Ublituximab				X	Serum immunoglobulins, up to date with all vaccinations, negative pregnancy test prior to each infusion, completed screening for John Cunningham (JC) virus
Abbreviations: CBC = complete blood count; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; JCV = John Cunningham Virus; LFTs = liver function tests; LVEF= left ventricular ejection fraction; PML = progressive multifocal leukoencephalopathy; SCr = serum creatinine; TB = tuberculosis; UA = urinalysis; VZV = varicella zoster virus					

P&T / DUR Action: *10/25 (DM); 10/24 (DM); 10/22 (DM)*
Implementation: *1/1/26; 12/1/2024; 1/1/23*

Multiple Sclerosis, Oral Drugs

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

Length of Authorization:
- Up to 12 months

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

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for ozanimod to treat moderate-to-severe ulcerative colitis?	**Yes:** Go to #3	**No:** Go to #4
3. Has the patient failed to respond or had an inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication these conventional therapies? AND • Has the patient tried and failed a 3-month trial of a Humira® product?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Is the medication being prescribed by or in consultation with a neurologist or gastroenterologist (if the diagnosis is ulcerative colitis)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1b, glatiramer acetate, interferon beta-1a, natalizumab, ofatumumab, ocrelizumab, or mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8

Approval Criteria		
8. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #9
9. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the prescription for teriflunomide?	**Yes:** Go to #15	**No:** Go to #11
11. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #12	**No:** Go to #14
12. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #13	**No:** Go to #15
13. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for cladribine?	**Yes:** Go to # 15	**No:** Go to #17
15. Is the patient of childbearing potential?	**Yes:** Go to #16	**No:** Approve for up to 12 months
16. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #17
17. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months	**No: Pass** to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's condition stabilized (i.e. reduced activity seen on magnetic resonance imaging (MRI), fewer relapses, and/or minimal or no disease progression) as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

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

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

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

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Varicella Zoster Antibodies	CYP2C9 genotype	Other Screening
Fumarate salts		X	X (>500)				
Fingolimod*	X	X	X	X	X		JCV, skin examination
Ozanimod*	X	X	X	X	X		JCV, skin examination
Ponesimod*	X	X	X	X	X		JCV, skin examination
Siponimod*	X	X	X	X	X	X	JCV, skin examination
Teriflunomide	X (box warning)	X (box warning)	X				

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

* Sphingosine 1-phosphate receptor modulators

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

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

Teriflunomide Clinical Notes:

Before starting teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in individuals of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.

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

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

- Fumarate salts may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 $x10^3$ cells/mm^3 (equivalent to <0.8 cells/µL). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

- Fumarate salts should be held if the WBC falls below 2 x10^3 cells/mm^3 or the lymphocyte count is below 0.5 x10^3 cells/mm^3 (cells/µL) and permanently discontinued if the WBC did not increase to over 2 x10^3 cells/mm^3 or lymphocyte count increased to over 0.5 x10^3 cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored every 6 to 12 months.

Cladribine Clinical Notes:

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

P&T/DUR Review: 10/25 (DM);10/24 (DM); 10/22; 10/21; 8/21; 6/20; 6/20; 11/17; 11/16; 9/15; 9/13; 5/13; 3/12
Implementation: 1/1/26; 12/1/2024; 1/1/2023, 1/1/2022, 9/1/20; 1/1/18; 1/1/17; 1/1/14

Natalizumab

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Natalizumab (Tysabri®) and biosimilars (pharmacy or provider administered claims)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Has the patient been screened for John Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPh; Deny; medical appropriateness
3. Does the patient have a diagnosis of relapsing multiple sclerosis (CIS, RRMS, or SPMS)?	**Yes:** Go to #4	**No:** Go to #5
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh; Deny; medical appropriateness.
5. Does the patient have Crohn's Disease?	**Yes:** Go to #6	No: Pass to RPh; Deny; medical appropriateness.
6. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny; medical appropriateness**.**
7. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have 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 Review: *10/25 (DM); 10/24 (DM); 10/22; 6/2; 10/20; 11/17*
Implementation: *12/1/24; 1/1/18*