Medical Benefit Drug Policy

Multiple Sclerosis Agents (Lemtrada®, Ocrevus®, Ocrevus Zunovo™, Briumvi™)

Policy Number: MC/PC 025
Effective Date: June 1, 2025

Instructions for Use

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Related Policies

- N/A

Coverage Rationale

Relapsing Forms of Multiple Sclerosis (MS)

For initial coverage of Lemtrada (alemtuzumab) for Relapsing Forms of MS, the following will be required:

- All of the following:
  - Diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., relapsing-remitting disease, secondary progressive disease, including active disease with new brain lesions) **and**
  - Patient has not been previously treated with alemtuzumab **and**
  - Not used in combination with another disease-modifying therapy for MS **and**
  - Prescribed by or in consultation with a neurologist.

  OR
- All of the following:
  - Patient has previously received treatment with alemtuzumab **and**
  - At least 12 months have or will have elapsed since the most recent treatment course with alemtuzumab **and**
  - Not used in combination with another disease-modifying therapy for MS **and**
  - Prescribed by or in consultation with a neurologist.

For initial coverage of Briumvi (ublituximab-xiiy) for Relapsing Forms of MS, the following will be required:

- All of the following:
  - Diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., clinically isolated syndrome, relapsing-remitting disease, secondary progressive disease, including active disease with new brain lesions) **and**
  - Not used in combination with another disease-modifying therapy for MS **and**
  - Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra, Kesimpta]) **and**

- Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone) **and**
- Prescribed by or in consultation with a neurologist.

OR

- For continuation of prior therapy

For reauthorization coverage of Briumvi (ublituximab-xiiy) for Relapsing Forms of MS, the following will be required:

- Presence of positive clinical response to therapy (e.g., stability in radiologic disease activity, clinical relapses, disease progression) **and**
- Not used in combination with another disease-modifying therapy for MS **and**
- Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra, Kesimpta]) **and**
- Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone) **and**
- Prescribed by or in consultation with a neurologist.

For initial coverage of Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) for Relapsing Forms of MS, the following will be required:

- All of the following:
  - Diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., clinically isolated syndrome, relapsing-remitting disease, secondary progressive disease, including active disease with new brain lesions) **and**
  - Not used in combination with another disease-modifying therapy for MS **and**
  - Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra, Kesimpta]) **and**
  - Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone) **and**
  - Prescribed by or in consultation with a neurologist.

OR

- All of the following:
  - For continuation of prior therapy **and**
  - Not used in combination with another disease-modifying therapy for MS **and**
  - Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra, Kesimpta]) **and**
  - Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone) **and**
  - Prescribed by or in consultation with a neurologist.

For reauthorization coverage of Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq for Relapsing Forms of MS, the following will be required:

- Documentation of positive clinical response to therapy (e.g., stability in radiologic disease activity, clinical relapses, disease progression) **and**
- Not used in combination with another disease-modifying therapy for MS **and**
- Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra, Kesimpta]) **and**
- Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone) **and**
- Prescribed by or in consultation with a neurologist.

Primary Progressive Multiple Sclerosis (PPMS)

For initial coverage of Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq for Primary Progressive Multiple Sclerosis (PPMS), the following will be required:

- Diagnosis of Primary Progressive Multiple Sclerosis (PPMS) **and**
- Not used in combination with another disease-modifying therapy for MS **and**
- Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra, Kesimpta]) **and**
- Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone) **and**
- Prescribed by or in consultation with a neurologist.

For reauthorization coverage of Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq for Primary Progressive Multiple Sclerosis (PPMS), the following will be required:

- Presence of positive clinical response to therapy (e.g., stability in radiologic disease activity, clinical relapses, disease progression) **and**
- Not used in combination with another disease-modifying therapy for MS **and**
- Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra, Kesimpta]) **and**
- Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone) **and**
- Prescribed by or in consultation with a neurologist.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0202	Injection, alemtuzumab, 1 mg
J2350	Injection, ocrelizumab, 1 mg
J2329	Injection, ublituximab-xiiy, 1 mg
J2351	Injection, ocrelizumab, 1 mg and hyaluronidase-ocsq

ICD-10 Code	Description
G35	Multiple Sclerosis

Background

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination, and axonal degeneration (*Olek & Mowry 2025 [b]*). MS can lead to physical disability, cognitive impairment, and decreased quality of life (QOL) (*McGinley et al 2021*). The range of symptoms of MS includes sensory, motor, visual, and fatigue (*Giovannoni et al 2016*). The estimated prevalence of MS in the United States (U.S.) in 2017 was 362.6 per 100,000 (estimated 913,925 cases) (*Wallin et al 2019*). The worldwide prevalence of MS is more

than 2.8 million (*Walton et al 2020*). MS occurs 2 to 3 times more often in fem .8); onset typically occurs between the ages of 18 and 45 years with the highest pr up (*Wallin et al 2019*).

The treatment of MS consists of disease-modifying therapies (DMTs) which decrease neuroinflammation (*McGinley et al 2021, Rae-Grant et al 2018[a, b]*). DMTs are effective at reducing the frequency of relapses and the number of new lesions seen on MRI in patients with relapsing forms of MS; whether all or any reduce disability progression is still under investigation (*Olek & Mowry 2025[a]*). Although DMTs decrease the incidence of new relapses, they do not reverse harm caused by prior relapses, which often leave patients with residual symptoms. There are currently 21 DMTs with various mechanisms of action that have been approved by the Food and Drug Administration (FDA) for the treatment of relapsing forms of MS (*Drugs@FDA.gov 2023*).

The high efficacy DMTs include ublituximab-xiiy (Briumvi), natalizumab (Tysabri), alemtuzumab (Lemtrada), ocrelizumab (Ocrevus), and Kesimpta (ofatumumab). Lemtrada (alemtuzumab) is a monoclonal antibody that targets CD52-expressing B and T lymphocytes resulting in antibody-dependent cellular cytolysis and complement-mediated lysis. Alemtuzumab depletes circulating B and T lymphocytes after each course of treatment with a nadir at 1 month. B cell recovery occurs after approximately 6 months, and T cell counts remain below baseline 12 months after treatment. Ocrevus (ocrelizumab) is a humanized recombinant monoclonal antibody directed against CD20-expressing B cells. It is similar to Rituxan (rituximab), a chimeric murine/human monoclonal antibody, but is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile (*Sorensen et al 2016*). Ublituximab-xiiy is an anti-CD20-directed immunoglobulin G (IgG) antibody that targets a unique epitope on CD20 on B cells that is not targeted by other anti-CD20 monoclonal antibodies (*Fox et al 2021*).

Clinical Evidence

Lemtrada (alemtuzumab)
Two Cochrane reviews pooled the results of 3 randomized controlled trials (RCTs) (N = 1713) that compared alemtuzumab vs Rebif (IFN beta-1a SC) in patients with Relapse Remitting MS (RRMS) (*Riera et al 2016, Zhang et al 2017*). The trials included the pivotal active-controlled (AC) RCTs, CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012*). At 24 months, the alemtuzumab 12 mg dosing regimen was associated with a higher relapse-free survival (HR, 0.50, 95% CI, 0.41 to 0.60; 1248 patients; 2 studies; moderate quality evidence); a higher sustained disease progression-free survival (HR, 0.62, 95% CI, 0.44 to 0.87; 1191 patients; 2 studies; moderate quality evidence); and a slightly higher number of patients with at least 1 adverse event (AE) (risk ratio [RR], 1.04, 95% CI, 1.01 to 1.06; 1248 patients; 2 studies; moderate quality evidence); and a lower number of dropouts (RR, 0.31, 95% CI, 0.23 to 0.41; 1248 patients; 2 studies; I2 = 29%; low quality evidence). Long-term extension studies of CARE-MS I and II and CAMMS223 have demonstrated durable efficacy with continued low annualized relapse rate (ARR) for ≥ 8 years of follow-up (*Coles et al 2017, Havrdova et al 2017, Singer et al 2020, Steingo et al 2020, Ziemssen et al 2020*). Efficacy was maintained over 12 years in patients from the CAMMS223 study, with 73% of patients receiving no more than 3 courses. Incidences of AEs were lower than in the initial RCT; however, thyroid disorders peaked at year 3 (16.5% to 16.7%) and then declined through year 5. The safety profile at year 8 was consistent with previous years.

Briumvi (ublituximab-xiiy)
The efficacy and safety of ublituximab-xiiy were demonstrated vs teriflunomide in 2 identically designed, 96-week, Phase 3, double-blind (DB), multi-center (MC), active-controlled (AC), double-dummy (DD), randomized controlled trials (RCTs) called ULTIMATE I and II in 1094 adult patients with relapsing MS (*Steinman et al 2022*). Adults aged 18 to 55 years with relapsing MS with a baseline EDSS score 0 to 5.5 were randomized to receive either ublituximab-xiiy and oral placebo or teriflunomide and intravenous (IV) placebo. IV infusions of ublituximab-xiiy or placebo were administered with premedication of an oral antihistamine (i.e., diphenhydramine) and oral corticosteroid (i.e., dexamethasone 10 to 20 mg or equivalent) on day 1, day 15, and weeks 24, 48, and 72. The first infusion was over 4 hours, but all subsequent infusions were over 1 hour. Teriflunomide 14 mg or oral placebo were administered on day 1 through the last day of

week 95. Approximately 55% of patients (range, 50.7% [ULTIMATE II, ublituxim
ublituximab-xiiy arm) were treatment naïve to DMTs for MS. The ARR at week in
the ublituximab-xiiy groups compared with teriflunomide. In ULTIMATE I, ublituximab-xiiy vs teriflunomide, the ARR was 0.08 vs 0.19; rate ratio, 0.41; 95% confidence interval (CI), 0.27 to 0.62; p < 0.001. In ULTIMATE II, ublituximab-xiiy vs teriflunomide, the ARR was 0.09 vs 0.18; rate ratio, 0.51; 95% CI, 0.33 to 0.78; p = 0.002. On secondary endpoints, ublituximab-xiiy significantly improved MRI endpoints such as reduction in the total number of Gd-enhancing lesions on T1-weighted MRI by week 96 compared to teriflunomide (ULTIMATE 1, rate ratio, 0.03, 95% CI, 0.02 to 0.06, p < 0.001; ULTIMATE II, rate ratio, 0.04, 95% CI, 0.02 to 0.06, p < 0.001). For the total number of new or newly enlarged lesions on T2-weighted MRI by the end of the trial, ublituximab-xiiy demonstrated superiority over teriflunomide (ULTIMATE 1, rate ratio, 0.08, 95% CI, 0.06 to 0.10, p < 0.001; ULTIMATE II, rate ratio, 0.10, 95% CI, 0.07 to 0.14, p < 0.001). In the pooled data from ULTIMATE I and II, the proportions of patients with confirmed disability progression (worsening) over 12 weeks (CDP-12 weeks) were 5.2% in the ublituximab-xiiy groups and 5.9% in the teriflunomide groups (hazard ratio [HR], 0.84; 95% CI, 0.50 to 1.41; p = 0.51). In both ULTIMATE I and II studies, more patients achieved no evidence of disease activity (NEDA), defined as no confirmed relapses, no Gd-enhancing lesions and no new or enlarging T2 lesions on MRI, and no CDP-12 weeks with ublituximab-xiiy vs teriflunomide (ULTIMATE I, odds ratio [OR], 5.44, 95% CI, 3.54 to 8.38; ULTIMATE II, OR, 7.95, 95% CI, 4.92 to 12.84).

Ocrevus (ocrelizumab)

The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO (*Hauser et al 2017, Montalban et al 2017*). OPERA I and OPERA II were 2 identically designed, 96-week, Phase 3, AC, double-blind (DB), double-dummy (DD), multicenter (MC), RCTs that evaluated the efficacy and safety of ocrelizumab vs Rebif (IFN beta-1a SC) in 1656 patients with relapsing MS. The dose of ocrelizumab was 600 mg, administered as two 300 mg IV infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses, and the dose of IFN beta-1a SC was 44 mcg 3 times per week (*ClinicalTrials.gov Web site, Hauser et al 2017, Ocrevus Formulary Dossier 2018*). Ocrelizumab achieved statistically significant reductions in the ARR vs IFN beta-1a SC across both trials (primary endpoint). The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan, a secondary endpoint, were statistically significantly reduced with ocrelizumab vs IFN beta-1a SC. Treatment with ocrelizumab significantly reduced the protocol-defined annualized relapse rate at 96 weeks vs interferon beta-1a by 46% in OPERA I (p < 0.0001) and by 47% in OPERA II (p < 0.0001). In a pooled analysis of OPERA I and II, ocrelizumab treatment also significantly reduced the time to onset of both 12-week and 24-week confirmed disability progression vs interferon beta-1a by 40% for both time points (p = 0.0006 and p = 0.0025, respectively). The incidence of adverse events and serious adverse events, including serious infections, was similar between ocrelizumab and interferon beta-1a in both studies. The most common adverse events were mild-to moderate infusion-related reactions. An imbalance of malignancies was observed with ocrelizumab; across both studies through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of IFN beta-1a SC-treated patients. Among the ocrelizumab-treated patients who developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. IFN beta-1a SC-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous cell carcinoma in the chest. Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal cell skin carcinoma, and 1 case of malignant melanoma) were observed during the open-label (OL) extension (OLE) phase in which all continuing patients received ocrelizumab.

ORATORIO was an event-driven, Phase 3, DB, MC, placebo-controlled (PC), RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; administered as two 300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS (*ClinicalTrials.gov Web site, Montalban et al 2017, Ocrevus Formulary Dossier 2018*). DB treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression that was confirmed for at least 12 weeks in the trial cohort. The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions at baseline was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*Ocrevus FDA Medical and Summary Reviews 2017*). The percentages of patients with CDP-12

weeks, the primary endpoint, were 32.9% with ocrelizumab vs 39.3% with plac) = 0.03). The percentages of patients with CDP-24 weeks, a secondary endpoint, v % with placebo (HR, 0.75, 95% CI, 0.58 to 0.98; p = 0.04). From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients (p < 0.001). From Weeks 24 to 120, the annual rate of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo (p = 0.02). Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo. Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients who developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal cell carcinoma, and 1 case of each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal cell carcinoma. Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal cell skin carcinoma and 1 case of squamous cell carcinoma) were detected during the OLE phase in which all patients received ocrelizumab.

Ocrelizumab and hyaluronidase-ocsq was approved based on the data evaluating IV ocrelizumab (OPERA I, OPERAII, ORATORIO) in addition to results from the Phase 3 OCARINA II study conducted in adult patients with relapsing MS or PPMS. Studies demonstrate comparable exposure between SC ocrelizumab and hyaluronidase-ocsq and IV ocrelizumab (Ocrevus Zunovo prescribing information 2024, ClinicalTrials.gov Website).

Place in therapy

The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae-Grant et al 2018*). The main recommendations were as follows:

- Starting DMT
  - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
  - Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
  - Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT in women of childbearing potential who have MS. (Level B)
  - Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
  - Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
  - Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
  - Clinicians may initiate natalizumab treatment in people with MS with positive anti-John Cunningham virus (JCV) antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
  - Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)
- Switching DMTs
  - Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
  - Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)

- Clinicians should discuss a change to non-injectable or less frequently i) report intolerable discomfort with the injections or in those who repor s. (Level B)
- Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
- Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
- Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
- Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)
- Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
- Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
- Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)

- Stopping DMTs
  - In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
  - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or Gd-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or Gd-enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
  - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Lemtrada is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

Briumvi is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- Primary progressive MS, in adults.

Ocrevus Zunovo is a CD20-directed cytolytic antibody indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- Primary progressive MS, in adults.

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Policy History/Revision Information

Date	Summary of Changes
12/13/2023	Approved by OptumRx P&T Committee
4/17/2024	Annual Review. Updated references.
4/16/2025	Annual Review. Updated references.
5/15/2025	Added Ocrevus Zunovo to policy. Updated criteria, billing codes, background section, and references to reflect this addition.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).