Multiple Sclerosis Agents
Prior Authorization (through preferred) with Quantity Limit Program Summary

Your health benefit plan may not cover certain prescription drug products or drug categories included in this document. Please consult your benefit plan materials for details about your particular benefit.

This document may include drugs that are not included on your plan's formulary. For drug coverage status, please consult your plan's formulary.

FDA APPROVED INDICATIONS AND DOSAGE[1-15,28]

Agent(s)	Indication(s)	Dosage
Aubagio® (teriflunomide) Tablet	Treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	7 mg or 14 mg orally once daily, with or without food
Avonex® (interferon β-1a) Injection for intramuscular use	Treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	May be titrated: starting with 7.5 mcg for first week, to reduce flu-like symptoms. Increase dose by 7.5 mcg each week for next 3 weeks until recommended dose of 30 mcg once weekly Maintenance dose: 30 mcg once a week
Bafiertam™ (monomethyl fumarate) Delayed-release capsule	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	The starting dose is 95 mg twice daily orally for 7 days. After 7 days, the dosage should be increased to the maintenance dose of 190 mg (administered as two 95 mg capsules) twice a day orally
Betaseron® (interferon β-1b) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	Initial titration: 0.0625 mg (0.25 mL) every other day, and increase over a six-week period to 0.25 mg (1 mL) every other day Maintenance dose: 0.25 mg every other day
Copaxone® (glatiramer acetate)[a] Injection for subcutaneous use	Treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	20 mg administered once per day or 40 mg administered three times per week at least 48 hours apart (Copaxone 20 mg per mL and Copaxone 40 mg per mL are not interchangeable)
Extavia® (interferon β-1b)	Treatment of relapsing forms of Multiple Sclerosis, to include clinically isolated syndrome,	Initial titration: 0.0625 mg (0.25 mL) every other day, and increase

Agent(s)	Indication(s)	Dosage
Injection for subcutaneous use	relapsing-remitting disease, and active secondary progressive disease, in adults	over a six-week period to 0.25 mg (1 mL) every other day Maintenance dose: 0.25 mg every other day
Gilenya® (fingolimod) Capsule	Treatment of relapsing forms of Multiple Sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older	10 years of age and above, weighing less than or equal to 40 kg: 0.25 mg orally once daily with or without food Adults and pediatric patients 10 years of age and older and weighing more than 40 kg: 0.5 mg orally once daily with or without food
Glatopa® (glatiramer acetate) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	20 mg administered once daily or 40 mg administered three times per week and at least 48 hours apart (Glatopa 20mg/mL and Glatopa 40/mL are not interchangeable)
Kesimpta® (ofatumumab) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	**Initial dosing:** 20 mg by subcutaneous injection at Weeks, 0, 1, and 2 **Subsequent dosing:** 20 mg by subcutaneous injection once monthly starting at week 4
Mavenclad® (cladribine) Tablet	• Treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease in adults Limitation of use: Mavenclad is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile	Cumulative dosage of 3.5 mg/kg orally and divided into 2 treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles Administration of cycles: First course/first cycle: start anytime First course/second cycle: start 23-27 days after last dose of first course/first cycle Second course/first cycle: start at least 43 weeks after the last dose of first course/second cycle Second course/second cycle: start 23-27 days after last dose of second course/first cycle If a dose is missed do not double doses, extend cycle by 1 day. If 2 doses are missed, extend cycle by 2 days.

Agent(s)	Indication(s)	Dosage
		If lymphocyte count is less than 800 cells/µL delay second course for up to 6 months. If recovery takes longer than 6 months the patient should not receive further treatment with Mavenclad
Mayzent® (siponimod) Tablet	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	**Patients with CYP2C9 genotypes *1/*1, *1/*2, or *2/*2:** 0.25 mg orally daily for 2 days, then 0.5 mg orally daily for 1 day, then 0.75 mg orally daily for 1 day, then 1.25 mg orally daily for 1 day. After treatment titration, the recommended maintenance dose is 2 mg orally once daily **Patients with CYP2C9 genotypes *1/*3 or *2/*3:** 0.25 mg orally daily for 2 days, then 0.5 mg orally daily for 1 day, then 0.75 mg orally daily for 1 day. After treatment titration, the recommended maintenance dosage is 1 mg orally once daily If a titration dose is missed or if 4 or more consecutive daily doses are missed during maintenance treatment, reinstate Day 1 of the dose titration
Plegridy® (peginterferon β-1a) Injection for subcutaneous use Injection for intramuscular use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	Dose titration: 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29 Maintenance dose:125 mcg subcutaneously every 14 days
Ponvory™ (Ponesomid) Tablet	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	Dose titration: Days 1 and 2: 2 mg Days 3 and 4: 3 mg Days 5 and 6: 4 mg Day 7: 5 mg Day 8: 6 mg Day 9: 7 mg Day 10: 8 mg Day 11: 9 mg Days 12, 13, and 14: 10 mg Maintenance dose: 20 mg once daily starting on day 15

Agent(s)	Indication(s)	Dosage
Rebif® (interferon β-1a) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	Titration: Generally, the starting dose should be 20% of the prescribed dose three times per week, and increased over a 4 week period to the targeted recommended dose of either 22 mcg or 44 mcg injected subcutaneously three times per week Maintenance dose: 22 mcg or 44 mcg injected subcutaneously three times per week
Tecfidera® (dimethyl fumarate)[a] Capsule	Treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	Starting dose: 120 mg orally twice daily for 7 days Maintenance dose: 240 mg twice daily
Vumerity® (diroximel fumarate) Delayed-release capsule	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	Starting dose: 231 mg twice daily for 7 days Maintenance dose: 462 mg twice daily

a- Generic available

CLINICAL RATIONALE

Multiple sclerosis

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.[16]

Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances, and elimination dysfunction), resulting in a significant impact on quality of life for patients and their families. Diagnosis of MS is primarily based on clinical presentation. The core requirement for the diagnosis is demonstration of CNS lesion dissemination and presence of symptoms such as visual loss, motor function loss, difficulty with balancing, and vertigo. There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).[23]

Clinically isolated syndrome

CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system. The episode, which by definition must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a diagnosis of MS because people who experience a CIS may or may not go on to develop MS. When CIS is accompanied by lesions on a brain MRI that are similar to those seen in MS, the person has a high likelihood of a

second episode of neurologic symptoms and diagnosis of relapsing-remitting MS. When CIS is not accompanied by MS-like lesions on brain MRI, the person has a much lower likelihood of developing MS.[23] When caused by an acute inflammatory demyelinating event, approximately 85% of all patients subsequently develop MS. The relationship between conventional brain MRI features and the short-term risk of CIS patients developing definite MS has been assessed by several studies and allows for the diagnosis of MS based on the 2017 McDonald criteria. However, in CIS patients with initial multifocal clinical symptom presentation the abnormal MRI did not stratify the risk for clinically definite disease conversion.[28]

CIS cohort studies spanning 7 through 20 years of follow-up investigated the long-term risk of MS development and found conversions rates of 65-80% for patients with an abnormal conventional MRI and 8-20% for those with an inconspicuous baseline MRI.[28]

Relapsing remitting multiple sclerosis (RRMS)
RRMS is characterized by clearly defined attacks (relapses) of new or increasing neurologic symptoms. These relapses are followed by periods of partial or complete recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability. The course of MS varies, however, about 85-90% of individuals with MS demonstrate a relapsing pattern at onset, which transitions over time in the majority of untreated patients to a pattern of progressive worsening with few or no relapses or MRI activity (SPMS).[23]

Secondary progressive multiple sclerosis (SPMS)
SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Typically, when SPMS stage is reached, the relapse rate is also reduced. Prior to the era of disease-modifying agents (DMAs), approximately half of patients diagnosed with relapsing MS would progress to SPMS by 10 years, and 80-90% would do so by 25 years.[23]

2017 McDonald Criteria for the diagnosis of Multiple Sclerosis:
Diagnostic criteria for multiple sclerosis combining clinical, imaging, and laboratory evidence have evolved over time. The increasing incorporation of paraclinical assessments, especially imaging, to supplement clinical findings has allowed earlier, more sensitive, and more specific diagnosis.[21-22]

The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time.[21]

Misdiagnosis of multiple sclerosis remains an issue in clinical practice, and several factors that potentially increase this risk have been identified. Multiple sclerosis has heterogeneous clinical and imaging manifestations, which differ between patients over time. There is no single pathognomonic clinical feature or diagnostic test; diagnosis of multiple sclerosis relies on the integration of clinical, imaging, and laboratory findings. MRI abnormalities associated with other diseases and non-specific MRI findings, which are common in the general population, can be mistaken for multiple sclerosis. The increasingly strong focus on timely diagnosis to alleviate uncertainty for patients and allow initiation of disease-modifying therapies might also increase the risk of misdiagnosis.[21]

With increasing availability and use of MRI, incidental T2 hyperintensities on brain imaging are common, the subset of individuals with MRI findings that are strongly suggestive of multiple sclerosis lesions but with no neurological manifestations or other clear-cut explanation are said to have radiologically isolated syndrome. There is no consensus on whether patients with radiologically isolated syndrome will develop MS. Some practitioners argue that these patients have a high likelihood of developing MS while others argue that up to two-thirds of these patients will not receive a diagnosis of MS in 5 years. A consensus panel decided to require clinical

manifestations to make the diagnosis of MS (2017 McDonald Criteria for the diagnosis of Multiple Sclerosis).[21]

The 2017 McDonald criteria to diagnose MS is shown in the chart below.[21-22]

Clinical Presentation	Additional Data needed to make MS diagnosis
In a person with a typical attack/CIS at onset	
greater than or equal to 2 attacks and objective clinical evidence of greater than or equal to 2 lesions OR greater than or equal to 2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space[a] and dissemination in time[b] have been met
greater than or equal to 2 attacks and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional clinical attack implicating different CNS site OR greater than or equal to 1 symptomatic or asymptomatic MS-typical T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord
1 attack and objective clinical evidence of greater than or equal to 2 lesions	**ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF specific (i.e., not in serum) oligoclonal bands
1 attack and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional attack implicating different CNS site OR greater than or equal to 1 MS-Typical symptomatic or asymptomatic T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord **AND** **ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan)

	OR CSF-specific (i.e., not in serum) oligoclonal bands

a - Dissemination in space is defined as one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in 2 or more of four areas of the CNS (periventricular, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord) demonstrated by an additional clinical attack implicating a different CNS site or by MRI.[21]
b - Dissemination in time is defined as simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI. The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.[21]

Treatment of MS

Both the Multiple Sclerosis Coalition and the American Academy of Neurology recommend initiating treatment with a DMA FDA approved for the patient's phenotype as soon as possible following the diagnosis of multiple sclerosis. There are several DMAs with at least 10 mechanisms of action available to people with MS. The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and the treating clinician.[16,19]

There is a subgroup of RRMS patients who have a more aggressive disease course marked by a rapid accumulation of physical and cognitive deficit, despite treatment with 1 or more DMTs. In the past, this disease phenotype was called aggressive MS; it is now called highly active MS. It is generally agreed that the severe nature of this phenotype requires different treatment decisions. There is no consensus on the definition of highly active MS or the treatment algorithm.[26] The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.[20]

The Multiple Sclerosis Coalition recommends that clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, natalizumab or ocrelizumab for newly diagnosed individuals with highly active MS. Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another DMA regardless of the number of previously used agents.[16] The American Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS.[19]

Lack of response to DMAs is hard to define, as most patients with MS are not free of all disease activity. Relapses or new MRI detected lesions may develop after initiation of a DMA and before the treatment becomes effective for patients. When determining efficacy, sufficient time for the DMA therapy to take full effect and patient adherence are important considerations. Evidence of one or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination while being treated with a DMA for a 1 year period suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.[18] A National MS Society consensus statement recommends changing from one disease modifying therapy to another only for medically appropriate reasons (e.g. lack of efficacy, adverse effects, or if better treatments options become available).[16]

Existing MS therapies are partly effective in halting ongoing inflammatory tissue damage and clinical progression. MS pathogenesis is complex and probably heterogeneous among patient, suggesting that combination therapy strategies that target a range of disease mechanisms might be more effective than medications used as monotherapy. Although preliminary studies have provided favorable results, however, several subsequent large, randomized, controlled trials have had negative of conflicting results. There also may be more adverse reactions associated with combination therapies due to the additive effect.[24]

In 2020 a Canadian MS working group published recommendations on optimal therapy in relapsing forms of MS. This group notes that there are few studies that have directly compared injectable and oral DMTs. A recent network meta-analysis suggested that pegylated interferon-β-1a and dimethyl fumarate have superior efficacy to other base therapies, there are insufficient data to demonstrate that one base injectable or oral DMT is superior to another. As a result, the choice of initial treatment will need to be individualized according to disease activity, severity, and comorbidities.[25]

In addition to base therapies, the working group considers 5 DMTs to be of higher efficacy which although can be used as initial therapy, they are generally reserved for patients with a poor response or tolerability with a base therapy. Patients presenting with high disease activity or aggressive/rapidly evolving MS at onset could be considered to initiate therapy with one of these more effective therapies, but the most common treatment initiation is to start on a base therapy with the view of switching within 6 -12 months. The 5 agents considered to be of higher efficacy are:[25]

- Oral agents
    - Fingolimod
    - Cladribine
- Monoclonal antibodies
    - Natalizumab
    - Ocrelizumab
    - Alemtuzumab

The MS working group discussed the criteria for switching therapies in RRMS and recommends a change in DMT is indicated for patients who meet any of the Major criteria below:[25]

	Minor	**Major**
Relapse rate	• One relapse in first 2 years of treatment	• greater than or equal to 2 relapses in first year of treatment
Severity	• Mild • No functional impairment (school, work, daily activities, etc.) • No motor/cerebellar/brain stem /sphincter involvement	• Moderate to severe • Functional impairment • Motor/cerebellar/brain stem/sphincter involvement
Recovery	• Full recovery at 6 months • No functional impairment • EDSS change from baseline less than or equal to1 point at 6 months unless baseline EDSS greater than 5.5	• Incomplete recovery • Functional impairment • If EDSS at baseline was 0 then greater than a1.5 point change from baseline • If EDSS greater than 0 but less than 5.5 at baseline then greater than 1 point change at 6 months • If EDSS greater than 5.5 any change would be a major concern
MRI	• One new lesion	• greater than or equal to 3 new lesions during treatment excluding spinal cord lesions

		• greater than 1 spinal cord lesion

The workgroup does note that on-treatment relapses should only be performed once the drug has achieved a full clinical effect (typically 2-6 months after drug initiation). Relapses that occur before the maximal efficacy of the drug has been reached should be given less weight, but major criteria should take precedence regardless of timing.[25]

For patients with SPMS the workgroup states that is generally advised to continue with the current DMT after onset of SPMS since many patients will have ongoing inflammatory disease and subclinical disease activity may worsen if treatment is withdrawn. A change in treatment may be warranted in patients with active SPMS who continue to have relapses or new MRI lesions, with the caveat that there is insufficient evidence to identify criteria for a suboptimal response in patients with SPMS.[25]

For patients with primary progressive MS clinicians should offer ocrelizumab to patients with active disease provided the benefits outweigh the risks. Caution is recommended when considering treatment for PPMS subgroups that are less likely to benefit from treatment, such as older patients, those with long-standing stable disease, and/or significant neurological deficits, since the limited benefits may not justify the risk associated with treatment. Rituximab may be considered as an alternative therapy for PPMS in regions that permit off-label use in MS due to cost or other considerations.[25]

Safety[1-15]

- **Aubagio** (teriflunomide) has a black box warning with the following:
  - Hepatotoxicity: clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with Aubagio in the post marketing setting. Concomitant use of Aubagio with other hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of Aubagio and monitor ALT levels at least monthly for six months. If drug induced liver injury is suspected, discontinue Aubagio and start accelerated elimination procedure
  - Embryofetal toxicity: teratogenicity and embryolethality occurred in animals administered teriflunomide. Exclude pregnancy prior to initiating Aubagio therapy. Advise use of effective contraception in females of reproductive potential during treatment and during an accelerated drug elimination procedure. Stop Aubagio and use an accelerated drug elimination procedure if the patient becomes pregnant
- **Aubagio** (teriflunomide) is contraindicated in:
  - Severe hepatic impairment
  - Pregnancy
  - Hypersensitivity reaction to teriflunomide, leflunomide, or any of the inactive ingredients in Aubagio
  - Current leflunomide treatment
- **Avonex** (interferon β-1a) is contraindicated in:
  - History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation
- **Bafiertam** (monomethyl fumarate) is contraindicated in:
  - Known hypersensitivity to monomethyl fumarate, dimethyl fumarate, diroximel fumarate, or any of the excipients of Bafiertam
  - Co-administration with dimethyl fumarate or diroximel fumarate
- **Betaseron** (interferon β-1b) is contraindicated in:
  - History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol

- **Copaxone** (glatiramer) is contraindicated in:
  - Known hypersensitivity to glatiramer acetate or mannitol
- **Extavia** (interferon β-1b) is contraindicated in:
  - History of hypersensitivity to natural or recombinant interferon beta, Albumin (Human), USP, or any other component of the formulation
- **Gilenya** (fingolimod) is contraindicated in:
  - Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure
  - History of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker
  - Baseline QTc interval greater than or equal to 500 msec
  - Treatment with Class Ia or Class III anti-arrhythmic drugs
  - Hypersensitivity to fingolimod or its excipients
- **Glatopa** (glatiramer) is contraindicated in:
  - Known hypersensitivity to glatiramer acetate or mannitol
- **Kesimpta** (ofatumumab) is contraindicated in:
  - Active HBV infection
- **Mavenclad** (cladribine) contains a black box warning with the following:
  - Malignancies: Mavenclad may increase the risk of malignancy. Mavenclad is contraindicated in patients with current malignancy; evaluate the benefits and risks on an individual basis for patients with prior or increased risk of malignancy
  - Risk of teratogenicity: Mavenclad is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the risk of fetal harm
- **Mavenclad** (cladribine) is contraindicated in:
  - Patients with current malignancy
  - Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during Mavenclad dosing and for 6 months after the last dose in each treatment course
  - HIV infection
  - Active chronic infections (e.g., hepatitis or tuberculosis)
  - History of hypersensitivity to cladribine
  - Women intending to breastfeed on a Mavenclad treatment day and for 10 days after the last dose
- **Mayzent** (siponimod) is contraindicated in:
  - Patients with a CYP2C9 *3/*3 genotype
  - Patients who in the last 6 months have experienced: myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
  - Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker
- **Plegridy** (peginterferon β-1a) is contraindicated in:
  - History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation
- **Ponvory** (ponesimod) is contraindicated in:
  - Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure
  - Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker
- **Rebif** (interferon β-1a) is contraindicated in:
  - History of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation

- **Tecfidera** (dimethyl fumarate) is contraindicated in:
  - Known hypersensitivity to dimethyl fumarate or any of the excipients of Tecfidera
- **Vumerity** (diroximel fumarate) is contraindicated in:
  - Known hypersensitivity to diroximel fumarate, dimethyl fumarate, or to any of the excipients of Vumerity
  - Co-administration with dimethyl fumarate

For additional clinical information see Prime Therapeutics Formulary Chapter 9.6C Multiple Sclerosis Agents.

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Multiple Sclerosis Agents Prior Authorization with Quantity Limit – Through Preferred

See Intravenous (IV) Multiple Sclerosis (MS) Agents Prior Authorization criteria for intravenously administered agents (e.g. Tysabri, Lemtrada, Ocrevus).

TARGET AGENT(S)
Preferred generic agent(s)
Dimethyl fumarate
Glatiramer

Preferred brand agent(s)
Aubagio® (teriflunomide)
Avonex® (interferon β-1a)
Betaseron® (interferon β-1b)
Gilenya® (fingolimod)
Kesimpta® (ofatumumab)
Mavenclad® (cladribine)
Mayzent® (siponimod)
Plegridy® (peginterferon β-1a)
Rebif® (interferon β-1a)

Non-Preferred agent(s)
Bafiertam™ (monomethyl fumarate)
Copaxone® (glatiramer)[a]
Extavia® (interferon β-1b)
Glatopa® (glatiramer)[a]
Ponvory™ (ponesimod)
Tecfidera® (dimethyl fumarate)[a]
Vumerity® (diroximel fumarate)
a -generic available

FDA Approved Indication	FDA Approved Agent(s)
Clinically Isolated Syndrome (CIS)	Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mayzent, Plegridy, Ponvory, Rebif, Tecfidera, Vumerity
Relapsing Remitting Multiple Sclerosis (RRMS)	Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mavenclad, Mayzent, Plegridy, Ponvory, Rebif, Tecfidera, Vumerity
Active Secondary Progressive Multiple Sclerosis	Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mavenclad, Mayzent, Plegridy, Ponvory, Rebif, Tecfidera, Vumerity

Brand (generic)	GPI (NDC)	Multisource Code	Quantity Limit (per day or as listed)
Aubagio (teriflunomide)			
7 mg tablet	62404070000320	M, N, O, or Y	1 tablet
14 mg tablet	62404070000330	M, N, O, or Y	1 tablet
Avonex (interferon β-1a)			
30 mcg/0.5 mL Autoinjector pen	6240306045F530	M, N, O, or Y	1 kit (4 pens)/28 days

Brand (generic)	GPI (NDC)	Multisource Code	Quantity Limit (per day or as listed)
30 mcg/0.5 mL prefilled syringe	6240306045F830	M, N, O, or Y	1 kit (4 syringes)/28 days
Bafiertam (monomethyl fumarate)			
95 mg delayed release capsule	62405550006520	M, N, O, or Y	4 capsules
Betaseron (interferon β-1b)			
0.3 mg vial	62403060506420 (50419-0524-01, 50419-0524-35)	M, N, O, or Y	14 vials/28 days
Copaxone (glatiramer)[a]			
20 mg/mL syringe	6240003010E520 (68546-0317-30)	M, N, O, or Y	1 syringe
40 mg/mL syringe	6240003010E540 (68546-0325-06, 68546-0325-12)	M, N, O, or Y	12 syringes/28 days
Extavia (interferon β-1b)			
0.3 mg vial	62403060506420 (00078-0569-12, 00078-0569-61, 00078-0569-99)	M, N, O, or Y	15 vials/30 days
Gilenya (fingolimod)			
0.25 mg capsule	62407025100110	M, N, O, or Y	1 tablet
0.5 mg capsule	62407025100120	M, N, O, or Y	1 tablet
Glatiramer			
20 mg/mL prefilled syringe	6240003010E520 (00378-6960-32 00378-6960-93)	M, N, O, or Y	1 syringe
40 mg/mL prefilled syringe	6240003010E540 (00378-6961-12 00378-6961-32)	M, N, O, or Y	12 syringes/28 days
Glatopa (glatiramer)			
20 mg/mL prefilled syringe	6240003010E520 (00781-3234-34 00781-3234-71)	M, N, O, or Y	1 syringe
40 mg/mL prefilled syringe	6240003010E540 (00781-3250-71, 00781-3250-89)	M, N, O, or Y	12 syringes/28 days
Kesimpta (ofatumumab)			
20 mg/0.4 mL auto-injector	6240506500D520	M, N, O, or Y	0.4 mL (1 pen)/28 days
Mavenclad (cladribine)			
10 mg (4 tablet pack)	6240101500B718	M, N, O, or Y	8 tablets/301 days
10 mg (5 tablet pack)	6240101500B722	M, N, O, or Y	10 tablets/301days
10 mg (6 tablet pack)	6240101500B726	M, N, O, or Y	12 tablets/301 days

Brand (generic)	GPI (NDC)	Multisource Code	Quantity Limit (per day or as listed)
10 mg (7 tablet pack)	6240101500B732	M, N, O, or Y	14 tablets/301 days
10 mg (8 tablet pack)	6240101500B736	M, N, O, or Y	8 tablets/301 days
10 mg (9 tablet pack)	6240101500B740	M, N, O, or Y	9 tablets/301 days
10 mg (10 tablet pack)	6240101500B744	M, N, O, or Y	20 tablets/301 days
Mayzent (siponimod)			
Starter Pack – 0.25 mg tablet	6240707020B710	M, N, O, or Y	1 pack (7 tablets)/180 days
Starter Pack – 0.25 mg tablet	6240707020B720	M, N, O, or Y	1 pack (12 tablets)/180 days
0.25 mg tablet	62407070200320	M, N, O, or Y	4 tablets
1 mg tablet	62407070200330	M, N, O, or Y	1 tablet
2 mg tablet	62407070200340	M, N, O, or Y	1 tablet
Plegridy (peginterferon β-1a)			
125 mcg/0.5mL pen-injector for subcutaneous (SQ) injection	6240307530D220	M, N, O, or Y	2 pens (1 mL)/28 days)
Starter kit- pen-injector for subcutaneous (SQ) injection	6240307530D250	M, N, O, or Y	1 kit/180 days
125 mcg/0.5 mL syringe for subcutaneous (SQ) injection	6240307530E520	M, N, O, or Y	2 syringes (1 mL)/28 days)
Starter kit- syringe for subcutaneous (SQ) injection	6240307530E550	M, N, O, or Y	1 kit/180 days
125 mcg/0.5 mL prefilled syringe for intramuscular (IM) injection	6240307530E521	M, N, O, or Y	2 syringes (1 mL)/28 days
Ponvory (ponesimod)			
Starter pack	6240706000B720	M, N, O, or Y	14 tablets/180 days
20 mg tablet	62407060000320	M, N, O, or Y	1 tablet
Rebif (interferon β-1a)			
22 mcg/0.5 mL prefilled syringe	6240306045E520	M, N, O, or Y	12 syringes (6 mL)/28 days
44 mcg/0.5 mL prefilled syringe	6240306045E540	M, N, O, or Y	12 syringes (6 mL)/28 days
Titration pack: (6 x 8.8 mcg/0.2 mL + 6 x 22 mcg/0.5 mL) prefilled syringes	6240306045E560	M, N, O, or Y	1 kit (4.2 mL)/180 days
Rebif Rebidose 22 mcg/0.5 mL autoinjector	6240306045D520	M, N, O, or Y	12 syringes (6 mL)/28 days
Rebif Rebidose 44 mcg/0.5 mL autoinjector	6240306045D540	M, N, O, or Y	12 syringes (6 mL)/28 days

Brand (generic)	GPI (NDC)	Multisource Code	Quantity Limit (per day or as listed)
Rebif Rebidose Titration Pack autoinjectors	6240306045D560	M, N, O, or Y	1 kit (4.2 mL)/180 days
Tecfidera (dimethyl fumarate)[a]			
Starter kit (14 x 120 mg capsules + 46 x 240 mgcapsules)	62405525006320	M, N, O, or Y	60 capsules/180 days
120 mg capsule	62405525006520	M, N, O, or Y	56 capsules/180 days
240 mg capsule	62405525006540	M, N, O, or Y	2 capsules
Vumerity (diroximel fumarate)			
Starter bottle 231 mg delayed release capsule	62405530006520	M, N, O, or Y	106 capsules/180 days
231 mg delayed release capsule	62405530006540	M, N, O, or Y	4 capsules

a -generic available

PRIOR AUTHORIZATION WITH QUANTITY LIMIT CRITERIA FOR APPROVAL THROUGH PREFERRED AGENT(S)

Mavenclad (cladribine) Initial Evaluation

Mavenclad (cladribine) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:
      i. Information has been provided that the patient has been treated with the requested agent within the past 90 days
      OR
      ii. The prescriber states the patient has been treated with the requested agent within the past 90 days AND the patient is at risk if therapy is changed

Agents Eligible for Continuation of Therapy
Mavenclad (cladribine)

   OR
   B. The patient has an FDA approved diagnosis for the requested agent

   AND
2. ONE of the following:
   A. The patient has highly active MS disease activity AND BOTH of the following:
      i. The patient has greater than or equal to 2 relapses in the previous year
      AND
      ii. ONE of the following:
         1. The patient has greater than or equal to 1 gadolinium enhancing lesion on MRI
         OR
         2. The patient has significant increase in T2 lesion load compared with a previous MRI

   OR
   B. The patient has NOT been previously treated with the requested agent AND ONE of the following:
      i. The patient has been treated with at least 3 MS agents from different drug classes
      OR
      ii. The patient has tried and had had an inadequate response to ONE preferred generic agent FDA approved for the treatment of the requested indication
      OR

iii. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE preferred generic agent FDA approved for the treatment of the requested indication
OR
iv. The patient has FDA labeled contraindication to ALL preferred generic agents FDA approved for the treatment of the requested indication
OR
v. The prescriber has provided information in support of using the requested agent over ALL preferred generic agents FDA approved for the treatment of the requested indication

OR

C. The patient has been previously treated with the requested agent AND BOTH of the following:
i. The prescriber has provided the number of courses the patient has completed (one course consists of 2 cycles of 4-5 days each)
AND
ii. The patient has NOT completed 2 courses of the requested agent (one course consists of 2 cycles of 4-5 days each)

AND

3. A complete CBC with differential including lymphocyte count has been performed
AND
4. The lymphocyte count is within normal limits
AND
5. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
AND
6. ONE of the following:
A. The patient will NOT be using the requested agent with an additional disease modifying agent (DMA) for the requested indication
OR
B. BOTH of the following:
i. The patient is currently using the requested agent
AND
ii. Information has been provided supporting the use of the additional DMA (e.g., relapse between cycles)

AND

7. ONE of the following:
A. The patient's age is within FDA labeling for the requested indication for the requested agent
OR
B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication

AND

8. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
9. The requested quantity (dose) does not exceed the FDA labeled maximum dose based on the patient's weight
AND
10. ONE of the following:
A. The requested quantity (dose) does not exceed the program quantity limit
OR
B. BOTH of the following
i. The requested quantity (dose) is greater than the program quantity limit
AND

ii. The requested quantity (dose) cannot be achieved with a lower quantity of packs and a higher pack size (e.g., two 10 tablet packs instead of four 5 tablet packs) that does not exceed the program quantity limit

Length of Approval: 36 weeks for new starts OR if patient is currently taking the requested agent, approve for remainder of the annual course (1 course consists of 2 cycles of 4-5 days)

Mavenclad (cladribine) Renewal Evaluation

Mavenclad (cladribine) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process
   AND
2. The patient has had clinical benefit with the requested agent
   AND
3. A complete CBC with differential including lymphocyte count has been performed
   AND
4. The patient has a lymphocyte count of at least 800 cells/µL
   AND
5. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
6. ONE of the following:
   A. The patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication
      OR
   B. Information has been provided supporting the use of the additional DMA (e.g., relapse between cycles)

   AND
7. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
8. It has been at least 35 weeks but not more than 67 weeks since the last dose of the requested agent
   AND
9. BOTH of the following:
   A. The prescriber has provided the number of courses the patient has completed (one course consists of 2 cycles of 4-5 days each)
      AND
   B. The patient has NOT completed 2 courses with the requested agent (one course consists of 2 cycles of 4-5 days)

   AND
10. The requested dose does not exceed the maximum FDA labeled dose for the patient's weight
    AND
11. ONE of the following:
    A. The requested quantity (dose) does not exceed the program quantity limit
       OR
    B. ALL of the following
       i. The requested quantity (dose) is greater than the program quantity limit
          AND
       ii. The requested quantity (dose) cannot be achieved with a lower quantity of packs and a higher pack size (e.g., two 10 tablet packs instead of four 5 tablet packs) that does not exceed the program quantity limit

Length of Approval: 3 months

Initial Evaluation
Target Agent(s) (excluding Mavenclad [cladribine]) will be approved when ALL of the following are met:

1. ONE of the following:
    A. The requested agent is eligible for continuation of therapy AND ONE of the following:
        i. Information has been provided that the patient has been treated with the requested agent within the past 90 days
        OR
        ii. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed

Agents Eligible for Continuation of Therapy
All target agents except the following are eligible for continuation of therapy: Brand Copaxone Glatopa Brand Tecfidera

    OR
    B. The patient has a diagnosis of a relapsing form of MS AND ALL of the following:
        i. The patient has an FDA labeled indication for the requested agent
        AND
        ii. ONE of the following:
            1. The patient has a diagnosis of clinically isolated syndrome (CIS) AND ALL of the following:
                a. The patient had a single event that lasted at least 24 hours
                AND
                b. The event was not due to fever or infection
                AND
                c. The patient has MS-like brain lesion(s) confirmed by magnetic resonance imaging (MRI)
            OR
            2. The patient has a diagnosis of relapsing remitting multiple sclerosis (RRMS) or secondary progressive multiple sclerosis (SPMS)
        AND
        iii. ONE of the following:
            1. The requested agent is a preferred generic agent
            OR
            2. The requested agent is a preferred brand agent AND ONE of the following:
                a. The patient has highly active MS disease activity AND BOTH of the following:
                    i. The patient has greater than or equal to 2 relapses in the previous year
                    AND
                    ii. ONE of the following:
                        1. The patient has greater than or equal to 1 gadolinium enhancing lesion of MRI
                        OR
                        2. The patient has significant increase in T2 lesion load compared with a previous MRI
                OR
                b. The patient has been treated with at least 3 MS agents from different drug classes

OR

c. The patient has tried and had an inadequate response to ONE preferred generic agent FDA approved for the treatment of the requested indication

OR

d. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE preferred generic agent FDA approved for the treatment of the requested indication

OR

e. The patient has an FDA labeled contraindication to ALL preferred generic agents FDA approved for the treatment of the requested indication

OR

f. The prescriber has provided information in support of using the requested agent over ALL preferred generic agents FDA approved for the treatment of the requested indication

OR

3. The requested agent is a non-preferred agent AND BOTH of the following:
    a. ONE of the following:
        i. The patient has tried and had an inadequate response to ONE preferred generic agent FDA approved for the treatment of the requested indication (medical records required)

        OR

        ii. The patient has an intolerance (defined as an intolerance to drug or its excipients, not to the route of administration) or hypersensitivity to ONE preferred generic agent FDA approved for the requested indication

        OR

        iii. The patient has an FDA labeled contraindication to ALL preferred generic agents FDA approved for the requested indication

    AND

    b. ONE of the following:
        i. The patient has tried and had an inadequate response to ONE preferred brand agent or Zeposia (ozanimod) that is FDA approved for the treatment of the requested indication (medical records required)

        OR

        ii. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE preferred brand agent or Zeposia (ozanimod) FDA approved for the treatment of the requested indication

        OR

        iii. The patient has an FDA labeled contraindication to ALL preferred brand agents AND Zeposia (ozanimod) FDA approved for the treatment of the requested indication

OR

4. The patient has highly active MS disease activity AND BOTH of the following: (medical records including chart notes required)
    a. The patient has greater than or equal to 2 relapses in the previous year

AND

b. ONE of the following:
   i. The patient has greater than or equal to 1 gadolinium enhancing lesion of MRI
   OR
   ii. The patient has significant increase in T2 lesion load compared with a previous MRI

OR

5. The patient has been treated with at least 3 MS agents from different drug classes (medical records including chart notes required)

AND

iv. If the requested agent is Aubagio, the prescriber has obtained transaminase and bilirubin levels within 6 months prior to initiating treatment
AND
v. If the requested agent is Gilenya the prescriber has performed an electrocardiogram within 6 months prior to initiating treatment

AND

2. ONE of the following:
   A. The requested agent is Glatopa or a brand product with a corresponding generic equivalent (listed below) AND ONE of the following:
      i. The patient has an intolerance or hypersensitivity to the corresponding generic equivalent that is not expected to occur with the requested agent
      OR
      ii. The patient has an FDA labeled contraindication to the corresponding generic equivalent that is not expected to occur with the requested agent
      OR
      iii. The prescriber has provided information to support the use of the requested agent over the corresponding generic equivalent

Non-Preferred products	Corresponding generic equivalent
Copaxone, Glatopa	Glatiramer
Tecfidera	Dimethyl fumarate

   OR
   B. The requested agent is another targeted agent

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. ONE of the following:
   A. The patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication
   OR
   B. ALL of the following:
      i. The patient will be using the requested agent in combination with another DMA used for the treatment of MS
      AND
      ii. The requested agent will be used in combination with Mavenclad (cladribine)
      AND
      iii. Information has been provided supporting the use of the requested agent in combination with Mavenclad (e.g., relapse between cycles of Mavenclad)

AND

5. ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent
   OR

B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication

AND

6. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
7. ONE of the following:
   A. The requested quantity (dose) is does not exceed the program quantity limit
   OR
   B. ALL of the following
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
      ii. The requested quantity (dose) is does not exceed the maximum FDA labeled dose for the requested indication
      AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
   OR
   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
      AND
      iii. Information has been provided in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months. **NOTE**: For agents requiring a starter dose for initial use, the starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months.

Renewal Evaluation
Target Agent(s) (excluding Mavenclad [cladribine]) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process AND ONE of the following:
   A. The requested agent is Glatopa or a brand product with a generic equivalent AND ONE of the following: (listed below)
      i. The patient has an intolerance to hypersensitivity to the corresponding generic equivalent that is not expected to occur with the requested agent
      OR
      ii. The patient has an FDA labeled contraindication to the corresponding generic equivalent that is not expected to occur with the requested agent
      OR
      iii. The prescriber has provided information to support the use of the requested agent over the corresponding generic equivalent

Non-Preferred products	Corresponding generic equivalent
Copaxone, Glatopa	Glatiramer
Tecfidera	Dimethyl fumarate

   OR
   B. The requested agent is any other targeted agent

AND

2. The patient has had clinical benefit with the requested agent
AND

3. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
4. ONE of the following:
   A. The patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication
      OR
   B. BOTH of the following:
      i. The requested agent will be used in combination with Mavenclad
         AND
      ii. Information has been provided supporting the use of the requested agent in combination with Mavenclad (e.g., relapse between cycles of Mavenclad)

   AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
6. ONE of the following:
   A. The requested quantity (dose) does not exceed the program quantity limit
      OR
   B. ALL of the following
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

      OR
   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
         AND
      iii. Information has been provided in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months

