PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis (Oral – Other) – Cladribine Prior Authorization Policy
- Mavenclad® (cladribine tablets – EMD Serono, generic)

REVIEW DATE: 07/23/2025; selected revision 12/17/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Cladribine, a purine antimetabolite, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS), including relapsing remitting disease and active secondary progressive disease, in adults.[1] Due to its safety profile, use of cladribine is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternative drug for the treatment of MS.[1] A Limitation of Use is that cladribine is not recommended for use in patients with clinically isolated syndrome because of its safety profile.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is

heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active (or not active) disease, as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS), an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

Cladribine has a Boxed Warning regarding malignancies and the risk of teratogenicity.[1] Cladribine may increase the risk of malignancy. Also, cladribine is a cytotoxic drug. Special handling instructions and disposal procedures should be followed. There are several contraindications associated with the use of cladribine, including: patients with current malignancy; pregnant women, women and men of reproductive potential who do not plan to use effective contraception during cladribine dosing and for 6 months after the last dose in each treatment course; human immunodeficiency virus (HIV); active chronic infection (e.g., hepatitis or tuberculosis); history of hypersensitivity to cladribine; and women intending to breastfeed on a treatment day in which cladribine is administered and for 10 days after the last dose. Warnings and Precautions for cladribine include lymphopenia, infections, hematologic toxicity, graft-versus-host disease with blood transfusion, and liver injury.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of cladribine. All approvals are provided for the duration cited below. Because of the specialized skills required for evaluation and diagnosis of patients treated with cladribine as well as the monitoring required for adverse events and long-term efficacy, approval requires cladribine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of cladribine at initiation for MS as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, magnetic resonance imaging (MRI) reports, and/or other information. All documentation must include patient-specific identifying information.

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is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.
     - **ii.** Patient meets ONE of the following (a, b, c, or d):
       - **a)** According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to two disease-modifying agents used for multiple sclerosis; OR
         Note: See Appendix for examples.
       - **b)** According to the prescriber, patient has experienced inadequate efficacy or significant intolerance to one of Kesimpta (ofatumumab subcutaneous injection), a natalizumab intravenous product (Tysabri, biosimilar), Briumvi (ublituximab-xiiy intravenous infusion), Lemtrada (alemtuzumab intravenous infusion), Ocrevus (ocrelizumab intravenous infusion) or Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq subcutaneous injection); OR
       - **c)** Patient has received cladribine in the past; OR
       - **d)** According to the prescriber, the patient has highly active or aggressive multiple sclerosis by meeting ONE of the following [(1), (2), (3), or (4)]:
         - **(1)** Patient has demonstrated rapidly advancing deterioration(s) in physical functioning **[documentation required]**; OR
           Note: Examples include loss of mobility or lower levels of ambulation and severe changes in strength or coordination.
         - **(2)** Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR
         - **(3)** Magnetic resonance imaging (MRI) findings suggest highly active or aggressive multiple sclerosis **[documentation required]**; OR
           Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions.
         - **(4)** Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND
     - **iii.** The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Cladribine for ≥ 1 Year. Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2

lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

b) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iii. The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Clinically Isolated Syndrome.** Cladribine is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[1]

2. **Current Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

3. **Non-Relapsing Forms of Multiple Sclerosis.** The efficacy of cladribine has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1] Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

REFERENCES

1. Mavenclad® tablets [prescribing information]. Rockland, MA: EMD Serono; May 2024.
2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019.
3. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
4. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
5. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/08/2023

Selected Revision	**Multiple Sclerosis:** For Initial Therapy, a requirement was added that the patient meet one of the following: 1) according to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to two disease-modifying agents used for multiple sclerosis; or 2) according to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to one of Kesimpta (ofatumumab subcutaneous injection), a natalizumab intravenous product (Tysabri, biosimilar), Briumvi (ublituximab-xiiy intravenous infusion), Lemtrada (alemtuzumab intravenous infusion), or Ocrevus (ocrelizumab intravenous infusion), or 3) patient has received Mavenclad in the past.	05/29/2024 (effective 07/01/2024)
Annual Revision	Ocrevus Zunovo was added to the Appendix.	10/09/2024
Selected Revision	**Multiple Sclerosis:** For initial therapy, for the criteria that requires the patient to try one alternative (and has experienced inadequate efficacy or significant intolerance [according to the prescriber]), Ocrevus Zunovo was added to the list of disease-modifying multiple sclerosis drugs that count toward meeting this requirement.	10/16/2024
Early Annual Revision	The name of the policy was changed to add "Oral – Other." Also, Extavia was removed from the Appendix. In addition, for Multiple Sclerosis, Initial Therapy, an exception was added if the patient has highly active or aggressive multiple sclerosis by meeting ONE of the following [(1), (2), (3), or (4)]: **(1)** Patient has demonstrated rapidly advancing deterioration(s) in physical functioning [documentation required]; OR Note: Examples include loss of mobility or lower levels of ambulation and severe changes in strength or coordination. **(2)** Disabling relapse(s) with suboptimal response to systemic corticosteroids [documentation required]; OR **(3)** Magnetic resonance imaging (MRI) findings suggest highly active or aggressive multiple sclerosis [documentation required]; OR Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions. **(4)** Manifestations of multiple sclerosis-related cognitive impairment [documentation required].	07/23/2025
Selected Revision	The name of the policy was changed from Multiple Sclerosis (Oral – Other) – Mavenclad to Multiple Sclerosis (Oral – Other) – Cladribine. The generic to Mavenclad was added to the policy with related changes made in criteria. In the Appendix, it was noted that Mavenclad is available as a generic. Also, Tysabri and Tyruko are now cited in the Appendix as follows: Natalizumab Intravenous Products (Tysabri, biosimilar).	12/17/2025

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets, generic)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi® (ublituximab-xiiy intravenous infusion)	Intravenous infusion
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets, generic)	Oral
Mayzent® (siponimod tablets)	Oral
Natalizumab Intravenous Products (Tysabri, biosimilar)	Intravenous infusion
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Ocrevus Zunovo™ (ocrelizumab and hyaluronidase-ocsq subcutaneous injection)	Subcutaneous injection (not self-administered)
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT® (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral