09-J3000-34

Original Effective Date: 07/01/19

Reviewed: 06/11/25

Revised: 07/15/25

Subject: Cladribine (Mavenclad®) tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (CNS). It is characterized by inflammation, demyelination, and scarring of the central nervous system and manifests as pathological (immune-mediated CNS demyelination and axonal injury) and clinical (exacerbations, disability progression) dissemination in time and space. MS has been categorized into four types: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS). The most common type is RRMS, which is characterized by acute attacks followed by periods of remission. An initial attack may present as a clinically isolated syndrome (CIS); individuals presenting with this syndrome are high risk for subsequent conversion to clinically definite MS (CDMS) when coupled with MRI lesions consistent with MS.

The Food and Drug Administration (FDA) approved cladribine (Mavenclad®) in March 2019 for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. Due to the safety profile, the FDA recommends use in patient who have had an inadequate response to, or are unable to tolerate, an alternative drug indicated for the treatment of MS. It is not recommended for use in patients with clinically isolated syndrome because of its safety profile. Cladribine is a purine antimetabolite and the exact mechanism in MS is unknown but it may deplete lymphocytes through impairment in DNA synthesis. In 2018, the American Academy of Neurology published a practice guideline on the use of disease-modifying therapy for adults with multiple sclerosis which includes an assessment of the effectiveness and safety of oral cladribine in the treatment of MS. Cladribine has demonstrated a reduction as compared to placebo in measures of disease activity including clinical relapse rate, T2 lesions, and disability progression in patients with relapsing MS.

The efficacy of oral cladribine was evaluated in a double-blind, placebo-controlled study in 1326 patients with relapsing forms of MS, with at least 1 relapse in the prior 12 months. Approximately 66% of patients were treatment naïve and the median baseline neurological disability based on Kurtzke Expanded Disability Status Scale **(**EDSS) score across all treatment groups was 3.0. Patients were randomized to

receive either placebo (n = 437), or a cumulative oral dosage of cladribine 3.5 mg per kg (n = 433) over the 96-week study period in 2 treatment courses. An additional treatment arm with a cumulative oral dosage of 5.25 mg per kg body weight (n = 456) was evaluated but was associated with an increased incidence of lymphopenia without providing additional efficacy. Patients randomized to the 3.5 mg per kg cumulative dose received a first treatment course at Weeks 1 and 5 of the first year and a second treatment course at Weeks 1 and 5 of the second year. The primary outcome was annualized relapse rate (ARR) and additional outcome measures included the proportion of patients with confirmed disability progression, the time to first qualifying relapse, the mean number of T1 Gadolinium-enhancing lesions, and new or enlarging T2 hyperintense lesions. Disability progression was measured in terms of a 3-month sustained change in EDSS score. Cladribine significantly lowered the ARR (0.14 vs. 0.33, $p<0.001$) and there was a higher proportion of patient without relapse (81% vs 63%, $p<0.05$). Cladribine also had a lower proportion of patients with progression in EDSS score at 3-months (13% vs 19%) and significantly fewer brain lesions on MRI. The most common adverse events occurring at higher rate than placebo included lymphopenia, upper respiratory tract infection, and headache. In controlled and extension studies, malignancies occurred more frequently with cladribine as compared to placebo (0.27 vs 0.13 events per 100 patient years). Malignancy cases included metastatic pancreatic carcinoma, malignant melanoma, and ovarian cancer. Cladribine should not be administered after 2 treatment courses due to higher risk of malignancy.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: Avonex, Betaseron, Mavenclad, Kesimpta, Mayzent, Plegridy, Rebif, and Zeposia are the preferred brand products for treatment of relapsing forms of multiple sclerosis. The preferred generic products include dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan), and teriflunomide (generic). Dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), and teriflunomide (generic) do not require prior authorization.

Initiation of cladribine (Mavenclad®) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. The member has a diagnosis of **ONE** of the following:
    a. Relapsing-remitting MS (RRMS)
    b. Active secondary-progressive MS (SPMS)
2. Member has not previously received cladribine
3. Cladribine will not be used in combination with **ANY** of the following:
    a. Alemtuzumab (Lemtrada)
    b. Dimethyl fumarate (Tecfidera)
    c. Diroximel fumarate (Vumerity)
    d. Fingolimod (Gilenya, Tascenso ODT)
    e. Glatiramer acetate (Copaxone, Glatopa)

f. Interferon beta-1a (Avonex, Rebif)
g. Interferon beta-1b (Betaseron, Extavia)
h. Mitoxantrone (Novantrone)
i. Monomethyl fumarate (Bafiertam)
j. Natalizumab (Tysabri)
k. Ocrelizumab (Ocrevus)
l. Ofatumumab (Kesimpta)
m. Ozanimod (Zeposia)
n. Peg-interferon beta-1a (Plegridy)
o. Ponesimod (Ponvory)
p. Rituximab (Rituxan or biosimilars)
q. Siponimod (Mayzent)
r. Teriflunomide (Aubagio)
s. Ublituximab (Briumvi)

4. Member has no evidence of current malignancy
5. Member will receive varicella zoster vaccine at least 4 weeks prior to the start of cladribine if the member is antibody-negative for varicella zoster virus
6. Member has tested negative for **ALL** of the following:
    a. Hepatitis B and C
    b. Tuberculosis
    c. HIV infection
    d. Pregnancy (only for women of reproductive potential)
7. The dose does not exceed weight based dosing in Table 1 for cycle 1 and 2 of the first treatment course. The first cycle is administered as one or 2 tablets over 4 to 5 days and the second cycle is administered as one or 2 tablets over 4 to 5 days that is provided 23 to 27 days after the last dose of the first cycle.

Approval duration: 9 months (One course of two 4 to 5 day treatment cycles)

Continuation of cladribine therapy **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. The member was previously approved by Florida Blue or another healthplan OR the member previously met all indication-specific criteria for coverage
2. Member has demonstrated a beneficial response to therapy for treatment of RRMS or active SPMS
3. Cladribine will not be used in combination with **ANY** of the following:

a. Alemtuzumab (Lemtrada)
b. Dimethyl fumarate (Tecfidera)
c. Diroximel fumarate (Vumerity)
d. Fingolimod (Gilenya, Tascenso ODT)
e. Glatiramer acetate (Copaxone, Glatopa)
f. Interferon beta-1a (Avonex, Rebif)
g. Interferon beta-1b (Betaseron, Extavia)
h. Mitoxantrone (Novantrone)
i. Monomethyl fumarate (Bafiertam)
j. Natalizumab (Tysabri)
k. Ocrelizumab (Ocrevus)
l. Ofatumumab (Kesimpta)
m. Ozanimod (Zeposia)
n. Peg-interferon beta-1a (Plegridy)
o. Ponesimod (Ponvory)
p. Rituximab (Rituxan or biosimilars)
q. Siponimod (Mayzent)
r. Teriflunomide (Aubagio)
s. Ublituximab (Briumvi)

4. Member has not utilized **ANY** of the following agents since initiating treatment with cladribine:
    a. Alemtuzumab (Lemtrada)
    b. Dimethyl fumarate (Tecfidera)
    c. Diroximel fumarate (Vumerity)
    d. Fingolimod (Gilenya, Tascenso ODT)
    e. Glatiramer acetate (Copaxone, Glatopa)
    f. Interferon beta-1a (Avonex, Rebif)
    g. Interferon beta-1b (Betaseron, Extavia)
    h. Mitoxantrone (Novantrone)
    i. Monomethyl fumarate (Bafiertam)
    j. Natalizumab (Tysabri)
    k. Ocrelizumab (Ocrevus)
    l. Ofatumumab (Kesimpta)
    m. Ozanimod (Zeposia)

n. Peg-interferon beta-1a (Plegridy)
o. Ponesimod (Ponvory)
p. Rituximab (Rituxan or biosimilars)
q. Siponimod (Mayzent)
r. Teriflunomide (Aubagio)
s. Ublituximab (Briumvi)

5. Member has no evidence of current malignancy
6. Member has tested negative for **ALL** of the following:
    a. Hepatitis B and C
    b. Tuberculosis
    c. HIV infection
    d. Pregnancy (only for women of reproductive potential)
7. Member has a lymphocyte count of at least 800 cells/mL
8. Member has received less than a cumulative dose of 3.5 mg/kg of cladribine in their lifetime
9. Member completed the first course (consisting of the first course, cycle 1 and cycle 2) of cladribine at least 43 weeks prior to beginning the second treatment course (consisting of the second course, cycle 1 and cycle 2)
10. The dose does not exceed weight based dosing in Table 1 for cycle 1 and 2 of the second treatment course. The first cycle is administered over 4 to 5 days and the second cycle is provided 23 to 27 days after the last dose of the first cycle.

Approval duration: 3 months (One course of two 4 to 5 day treatment cycles)

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Cladribine is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. It is recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS due to the safety profile.
- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Assessments of the following are required prior to starting each treatment course: cancer screening, pregnancy in females of reproductive potential, complete blood count with differential including lymphocytes, HIV infection, screening for tuberculosis, hepatitis B and C, active infection, varicella zoster antibody testing, immunizations, baseline MRI due to risk of progressive multifocal leukoencephalopathy (PML), and liver enzymes.

- The cumulative dosage of 3.5 mg/kg is administered orally and divided into 2 yearly treatment courses (1.75 mg/kg per treatment course given 43 weeks apart). Each course is divided into 2 treatment cycles (separated by 23 to 27 days). Separate from other oral drugs by at least 3 hours during the treatment cycles. See prescribing information for dosing information. Following the administration of 2 treatment courses, do not administer additional treatment during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy. Treatment more than 2 years after completing 2 treatment courses has not been studied.

Dose Adjustments

- Hold treatment if the lymphocyte count is below 200 cells per microliter

Drug Availability

- 10 mg tablets

PRECAUTIONS:

Boxed Warning

- Malignancies: cladribine may increase the risk of malignancy and is contraindicated in patients with current malignancy; evaluate benefits and risks on an individual basis for patients with prior or increased risk of malignancy.
- Teratogenicity: cladribine 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

Contraindications

- Current malignancy
- Pregnant women
- Women and men of reproductive potential who do not plan to use effective contraception during treatment or for at least 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 treatment day and for 10 days after the last dose

Precautions/Warnings

- Malignancy risk is increased and benefits and risks of use in patients with prior malignancy or increased risk should be evaluated.
- Risk of teratogenicity can occur and pregnancy should be excluded prior to treatment. Effective contraception should be used during treatment and up to 6 months after the last dose in each treatment course in women and men of reproductive potential.
- Lymphopenia: Monitor lymphocyte counts before, during and after treatment.
- Infections: Serious, life-threatening infections have been reported. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients

antibody negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections.

- Progressive multifocal leukoencephalopathy (PML) has been reported in postmarketing studies of parenteral cladribine for oncology indications. A baseline MRI should be obtained before initiating the first treatment course of cladribine.
- Administer all immunizations according to guidelines prior to cladribine. Live vaccines should be administered at least 4 to 6 weeks prior to starting cladribine due to risk of active vaccine infection. Avoid live vaccines during and after cladribine while white blood cell counts are not within normal limits.
- Hematologic toxicity: Monitor complete blood count before, during and after treatment.
- Graft-versus-host-disease with blood transfusion: Irradiation of cellular blood components is recommended to decrease the risk of transfusion-associated graft-versus-host disease.
- Liver injury: Clinically significant and life-threatening liver injury has been reported. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to each treatment cycle and course. Discontinue if clinically significant injury is suspected. Use is not recommended with moderate to severe hepatic impairment.
- Hypersensitivity reactions have occurred. Do not use in patients with a history of hypersensitivity.
- Cardiac failure has occurred with both oral and parenteral cladribine.

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS

ICD-10 Diagnoses Codes That Support Medical Necessity

G35	Multiple sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

Clinically isolated syndrome (CIS): the first clinical presentation of disease that shows characteristics of inflammatory demyelination that could be MS but has yet to fulfill criteria of dissemination in time.

Primary-progressive multiple sclerosis (PPMS): Steadily progressive course from onset; occurs in 10-15% of patients with MS.

Progressive multifocal leukoencephalopathy (PML): an opportunistic viral infection of the brain that usually leads to death or severe disability.

Relapsing-remitting multiple sclerosis (RRMS): Characterized by acute attacks followed by periods of remission; primary form of MS that occurs in approximately 85% of patients.

Secondary-progressive multiple sclerosis (SPMS): An initial period of RRMS, followed by a steadily progressive course, with acute relapses (active disease) or without acute relapses (not active disease); 75-85% of patients diagnosed with RRMS will transition to SPMS.

RELATED GUIDELINES:

Alemtuzumab (Lemtrada), 09-J2000-27
Dimethyl Fumarate (Tecfidera), Diroximel fumarate (Vumerity), and Monomethyl fumarate (Bafiertam), 09-J1000-96
Fingolimod (Gilenya), 09-J1000-30
Multiple Sclerosis Self Injectable Therapy, 09-J1000-39
Natalizumab (Tysabri) IV, 09-J0000-73
Ocrelizumab (Ocrevus), 09-J2000-78
Ozanimod (Zeposia), 09-J3000-70
Siponimod (Mayzent), 09-J3000-35
Teriflunomide (Aubagio), 09-J1000-82

OTHER:

Table 1

Dose of MAVENCLAD per Cycle by Patient Weight in Each Treatment Course Weight Range [Dose in mg (Number of 10 mg Tablets) per Cycle]

Kg	First Cycle	Second Cycle
40* to less than 50	40 mg (4 tablets)	40 mg (4 tablets)
50 to less than 60	50 mg (5 tablets)	50 mg (5 tablets)
60 to less than 70	60 mg (6 tablets)	60 mg (6 tablets)
70 to less than 80	70 mg (7 tablets)	70 mg (7 tablets)
80 to less than 90	80 mg (8 tablets)	70 mg (7 tablets)
90 to less than 100	90 mg (9 tablets)	80 mg (8 tablets)
100 to less than 110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

*The use in patients weighing less than 40 kg has not been investigated.

Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days. Do not administer more than 2 tablets daily.

REFERENCES:

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11. Rae-Grant A, Day GS, Marrie RA et al. Practice guideline: Disease-modifying therapies for adults with multiple sclerosis: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. April 2018. Available at: https://www.aan.com/Guidelines/home/GuidelineDetail/898.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

07/01/19	New Medical Coverage Guideline.
10/01/19	Revision to guideline consisting of updating the position statement.
11/15/19	Revision to guideline consisting of updating the position statement, description, definitions, and references.
07/01/20	Revision to guideline consisting of updating the position statement.
10/01/20	Revision to guideline consisting of updating the position statement.
01/15/21	Revision to guideline consisting of updating the duration of approval.

04/01/21	Revision to guideline consisting of updating the position statement.
01/15/21	Revision to guideline; consisting of updating the position statement.
10/15/22	Review and revision to guideline; consisting of updating list of agents not to be used in combination.
01/01/23	Review and revision to guideline; consisting of updating the position statement to include generic fingolimod as a preferred generic and removal of Gilenya as a preferred brand.
05/15/23	Revision to guideline; consisting of updating the position statement to include generic teriflunomide as a preferred generic and removal of Aubagio as a preferred brand. Updated list of agents not to be used in combination.
11/15/23	Review and revision to guideline; consisting of updating the position statement to include Glatopa.
07/15/24	Review and revision to guideline; consisting of updating the position statement to remove step requirement.
07/15/25	Review and revision to guideline; consisting of updating the warnings and references.