Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCNS066.1025	**CENTRAL NERVOUS SYSTEM DRUGS** **MULTIPLE SCLEROSIS AGENTS** See Table 1 for Applicable Medications
Effective Date: 1/1/2026	**Review/Revised Date**: 07/24, 06/25 (JEF)
Original Effective Date: 10/23	**P&T Committee Meeting Date**: 08/23, 08/24, 10/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initiation of therapy for **multiple sclerosis (MS)**, all the following criteria (1-3) must be met:

1. Must have one of the following confirmed diagnoses:
    a. Relapsing-remitting multiple sclerosis (RRMS)
    b. Secondary progressive multiple sclerosis (SPMS)
    c. Clinically isolated syndrome (CIS). Note: Mavenclad® is not indicated for use in clinically isolated syndrome (CIS)
2. ONE of the following:
    a. The patient has highly active disease defined as ONE of the following:
        i. Greater than or equal to two relapses in the previous year
        ii. The patient has greater than or equal to one gadolinium enhancing lesion on MRI
        iii. Presence of significant T2 lesion burden defined as ONE of the following:
            1) Greater than ten (10) T2 lesion burden as documented with MRI
            2) Significant increase in T2 lesion load compared with a previous MRI
            3) T2 lesion(s) located in spinal cord or brainstem

   b. The patient has been treated with at least three multiple sclerosis agents from different drug classes
   c. Inadequate response (after at least six months of continuous therapy) or intolerance to one of the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, or generic teriflunomide
   d. FDA labeled contraindication to ALL the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, and generic teriflunomide
3. For ponesimod (Ponvory®): Trial and failure, intolerance, or contraindication to one (1) preferred brand medication or ozanimod (Zeposia®) capsule

For **patients established on therapy (**for at least three months), the following must be met:
1. Positive clinical response to therapy
2. For cladribine (Mavenclad®): Therapy has not exceeded two years in the patient's lifetime

Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy.

EXCLUSION CRITERIA:
Concurrent use with other disease modifying agents for multiple sclerosis

AGE RESTRICTIONS:
Mavenclad®: Approved for patients age 18 years of age and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a neurologist.

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary and /or benefit changes.

For Mavenclad®: May be approved for up to two years, ensuring the cumulative duration of therapy does not exceed two years in a lifetime. Treatment beyond two years will not be authorized.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case

INTRODUCTION:

Multiple Sclerosis is a disease that affects nearly 1 million people in the United States. It is a central nervous system disorder characterized by inflammation, demyelination, and axonal degeneration that can present as a variety of symptoms including fatigue/weakness, dizziness/vertigo, gait difficulties, numbness/tingling, spasticity, vision disturbances, cognitive changes, and bladder/bowel problems.

Disease modifying therapy (DMT) for multiple sclerosis should be initiated as early as possible. The choice of initial DMT should be individualized to consider of safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability.

FDA APPROVED INDICATIONS:

Table 1. Self-administered multiple sclerosis medications

Drug	Class	RRMS	SPMS	CIS
Cladribine (Mavenclad®)	Pure antimetabolite	X	X	
Interferon-beta 1a (Avonex®, Rebif®, Plegridy®)	Interferon	X	X	X
Interferon-beta 1b (Betaseron®)	Interferon	X	X	X
Ponesimod (Ponvory®)	Sphingosine 1-phosphate (S1P) receptor 1 modulator	X	X	X
Siponimod fumaric acid (Mayzent®)	S1P receptor 1 modulator	X	X	X
Ofatumumab (Kesimpta®)	Anti-CD20 monoclonal antibody	X	X	X

MOA = mechanism of action, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis, CIS = clinically isolated syndrome

Table 2. Preferred and Non-preferred self-administered medications (pharmacy benefit)

Preferred Brand Medications	Non-preferred Brand Medications
• Ozanimod hydrochloride (Zeposia®) • Siponimod fumaric acid (Mayzent®) • Ofatumumab (Kesimpta®) • Cladribine (Mavenclad®) • Interferon-beta 1a (Avonex®, Rebif®, Plegridy®) • Interferon-beta 1b (Betaseron®)	• Ponesimod (Ponvory®)

POSITION STATEMENT:

Preferred multiple sclerosis medications

Guidelines for Multiple Sclerosis include the American Academy of Neurology Publication "Comprehensive Systematic Review Summary: Disease-Modifying Therapies for Adults with Multiple Sclerosis" published in 2018 and a consensus paper by the Multiple Sclerosis Coalition titled "The Use of Disease-Modifying Therapies in Multiple Sclerosis" published in 2019. Guidelines state that initiating a disease modifying therapy (DMT) should be offered to patients as early as possible. The choice of initial DMT should be individualized to consider safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability. When switching therapies after failure of an agent, disease activity, adherence, AE profiles, and mechanisms of action should be considered when selecting a new agent to start. For advanced, aggressive, or highly active disease guidelines recommend fingolimod (Gilenya®), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), or alemtuzumab (Lemtrada®). Additionally, guidelines state categorize DMT therapies for evidence for lowering relapse rate (see Table 3).[18]

The Companies have chosen to favor the use of generic DMT therapy for patients who do not have highly active disease or have tried multiple different classes of multiple sclerosis agents.

Table 3. DMT Evidence for Lowering Relapse Rate[18]

Very Low	Low	Moderate	Strong
Immunoglobulins	Cyclophosphamide	Azathioprine	Alemtuzumab
Methotrexate	Mycophenolate Mofetil	Interferon beta-1b	Cladribine
Rituximab			Dimethyl Fumarate†
Corticosteroids			Fingolimod†

			Glatiramer Acetate†
			Interferon beta-1a
			Mitoxantrone
			Natalizumab
			Ocrelizumab
			Pegylated Interferon
			Teriflunomide†

† Generic Available

Cladribine (Mavenclad®)

Cladribine tablet is the first short-course oral therapy for the treatment of adults with relapsing forms of multiple sclerosis. It has a unique dosing regimen of two treatment courses for 4-5 days for year one and again for year two (See below for dosing recommendation). No drug is given in years three or four, although the drug remains active during this time.

The FDA approval of cladribine tablet was based on a 96-week double-blind trial in 1,326 patients with relapsing- remitting MS. Patients received either placebo or cumulative oral dosage of cladribine 3.5 mg/kg or cladribine 5.25 mg/kg over two years. The annualized relapse rate for patients on placebo was 0.33, 0.14 for cladribine 3.5 mg/kg 0.14 and 0.15 for cladribine 5.25 mg/kg. The cladribine 5.25 mg/kg cumulative dose did not add any clinically meaningful benefit compared to the 3.5 mg.kg dose but was associated with a higher incidence in grade 3 lymphopenia or higher. The 3.5 mg/kg group had a 47% reduction in the risk of six-month confirmed EDSS progression by 47% compared with placebo. A post-hoc analysis of this study has found that patients with highly active disease had an 82% reduction in the six-month confirmed EDSS progression, compared with placebo. Based on this data cladribine tablet may reduce relapses and slow the progression of disability compared with placebo for people with relapsing–remitting multiple sclerosis. However, there are no large randomized clinical trials comparing cladribine tablet to other disease modifying therapy. Further studies are also needed to understand the use of cladribine in patients with highly active disease based on the post-hoc analysis results and future studies are in progress. Additionally, the FDA granted cladribine tablet a broad labeling for relapsing form of MS including active secondary progressive disease, although the clinical trial only included patients with relapsing remitting disease.

MS treatment guidelines have not been updated since the approval of cladribine tablet.

Cladribine tablet is contraindicated in: patients with current malignancy, pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during cladribine dosing and for six months after the last dose in each treatment course as cladribine may cause fetal harm, patients infected with the human immunodeficiency virus, patients with active chronic infections (e.g., hepatitis or tuberculosis), patients with a history of hypersensitivity to cladribine, and women intending to breastfeed on a cladribine treatment day and for 10 days after the last dose. Cladribine has the following warnings and precautions: malignancies, risk of teratogenicity, lymphopenia, infections, hematological toxicity, risk of graft-versus-host disease with blood transfusions, liver injury, hypersensitivity, and cardiac failure. Due to potential safety concerns with this therapy the FDA notes that "use of cladribine tablet is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS." Therefore, it is appropriate to require failure of other MS therapies prior to the approval of this therapy.

Dosage & Administration Considerations:

- The recommended cumulative dosage of cladribine tablet is 3.5 mg/kg body weight administered orally and divided into two yearly treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into two treatment cycles:
    - Administration of first treatment course:
        - First course/first cycle: start any time
        - First course/second cycle: administer 23 to 27 days after the last dose of first course/first cycle
    - Administration of second treatment course
        - Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle
        - Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle
    - The cycle dosage should be administered as one or two tablets once daily over four or five consecutive days. More than two tablets daily should not be administered.
    - Following the administration of two treatment courses, additional cladribine tablet treatment should not be administered during the next two years. Treatment during these two years may further increase the risk of malignancy. The safety and efficacy of reinitiating cladribine tablet more than two years after completing two treatment courses has not been

studied. Although no additional drug is given, the drug remains active during this time.

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 of MAVENCLAD in patients weighing less than 40 kg has not been investigated.

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