Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCCNS062.1025	**MISCELLANEOUS PRODUCTS** **LEMTRADA®** (alemtuzumab for intravenous injection)
Effective Date: 1/1/2026	**Review/Revised Date**: 07/16, 09/16, 06/17, 07/18, 06/19, 02/20, 07/20, 07/21, 06/22, 08/23, 07/24, 07/25 (JEF)
Original Effective Date: 06/15	**P&T Committee Meeting Date**: 04/15, 08/16, 10/16, 08/17, 08/18, 08/19, 02/20, 08/20, 08/21, 08/22, 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:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts) for multiple sclerosis (MS), all the following criteria must be met:

1. Documentation of confirmed diagnosis of relapsing form of multiple sclerosis or active secondary progressive disease. Note: this therapy is not indicated for use in clinically isolated syndrome (CIS).
2. The patient has highly active disease defined as ONE of the following:
    a. Greater than or equal to two relapses in the previous year
    b. The patient has greater than or equal to one gadolinium enhancing lesion on MRI
    c. Presence of significant T2 lesion burden defined as ONE of the following:
        i. Greater than ten (10) T2 lesion burden as documented with MRI
        ii. Significant increase in T2 lesion load compared with a previous MRI
        iii. T2 lesion(s) located in spinal cord or brainstem
3. Inadequate response (after at least six months of continuous therapy) to ocrelizumab (Ocrevus®)
4. One of the following:

   a. 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
   b. FDA labeled contraindication to ALL the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, or generic teriflunomide
5. Dose and frequency are in accordance with FDA-approved labeling

For patients established on therapy (within the previous year), the following must be met:
1. Documentation of positive clinical response to therapy
2. Dose and frequency are in accordance with FDA-approved labeling

EXCLUSION CRITERIA:
In combination with other disease modifying therapy indicated for the treatment of multiple sclerosis

AGE RESTRICTIONS: N/A

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

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

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 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:
Alemtuzumab (Lemtrada®) is a medication given intravenously for patients with relapsing forms of multiple sclerosis (RRMS) to reduce the number of relapses. It is

a CD52-direct cytolytic monoclonal antibody that binds to and kills immune cells which attack myelin in those affected by multiple sclerosis.

Alemtuzumab (Lemtrada®) is given in two treatment courses over a two year period. The first course is 12 mg/day IV on five consecutive days, followed by 12 mg/day IV on three consecutive days, 12 months after first treatment course. Subsequent treatment courses of 12 mg daily for three days may be administered, as needed, at least 12 months after the last treatment course dose.

FDA APPROVED INDICATIONS:
Treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults.

Because of its safety profile, the use should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS

Limitations of use: Lemtrada® is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile

POSITION STATEMENT:
Alemtuzumab was initially approved in 2001 by the FDA under the trade name Campath® for first-line treatment in patients with B-cell chronic lymphocytic leukemia (B-CLL). It was also used in various types of hematological malignancies, transplant rejection, demyelinating disorders and for transplant conditioning.
Efficacy

- The FDA approval of alemtuzumab (Lemtrada®) was based on two active-controlled, randomized, rater-blinded, 2-year studies comparing alemtuzumab to high-dose interferon beta-1a (IFNB/Rebif®) efficacy in patients with RRMS.
- Both studies enrolled patients with confirmed RRMS and active disease (defined as ≥ 2 relapses in the prior two years and ≥ 1 relapse in the prior year). One study enrolled patients who were treatment naïve and the other was conducted in patients who relapsed while treated with interferon beta or glatiramer. The co-primary efficacy endpoints in both studies were relapse rate and time to 6-month sustained accumulation of disability (SAD) based on the Expanded Disability Status Scale (EDSS).

CARE-MS 1

- The study enrolled 581 patients who were treatment-naïve to DMT, EDSS score ≤ 3 and MS symptom onset within five years.
- The study reports a relapse rate of 39% in IFNB treated patients and 18% in alemtuzumab 12 mg/day treated patients by Year 2 ($p<0.0001$).

- The percentage of patients experiencing *6-months SAD* at two years was 8% of alemtuzumab-treated patients compared with 11% in the IFNB group. However, the difference did not achieve statistical significance (p=0.22).

CARE-MS 2

- The study enrolled 840 patients who had relapsed on prior non-IFNB1a DMT after receiving that therapy for ≥ 6 months, EDSS score ≤ 5 and MS symptom onset within 10 years.
- The study reports a relapse rate of 52% of IFNB treated patients and 26% of alemtuzumab 12 mg/day treated patients by year 2 (p<0.0001).
- The percentage of patients experiencing *6-months SAD* at two years was 12.7% in the alemtuzumab group compared with 21.1% in the IFNB group (p=0.0084)

While the study results appear to favor alemtuzumab (Lemtrada®) in RRMS, major limitations in the studies were identified which render the quality of evidence of uncertain validity and/or usefulness. The major limitation to the studies was the lack of user blinding of the study drugs. Although measures were taken to ensure rater-blinding, chance of bias cannot be ruled out favoring the study drug alemtuzumab. Other limitations include reporting bias (e.g., concomitant use of DMTSs was not reported in the literature), lack of intent-to-treat analysis, and protocol amendment after study had begun. Additionally, the current FDA labeling only provides dosing recommendation for the first two treatment courses. There is no recommendation for re-dosing at this time and the durability of the drug beyond two years remains to be determined.

Safety

Several Boxed Warnings in the labeling for Lemtrada®:

- Serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease
- Serious and life-threatening infusion reactions
- Serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported within three days of administration
- Increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders

The clinical safety experience with alemtuzumab (Lemtrada®) in MS included 1,486 patients and >5,400 patient-years of collective follow-up. Common adverse events reported in clinical trials include but are not limited to infusion-associated reactions, frequent infections including herpes viral infections and thyroid gland disorders.

- Patients should be monitored for complete blood count with differential, renal function, and thyroid function at baseline and at periodic intervals for 48 months following the last treatment course of alemtuzumab to detect early signs of potentially serious adverse effects.

- Due to the potential high risks associated alemtuzumab (Lemtrada®), a Risk Evaluation and Mitigation Strategy (REMS) program is in place to ensure the safe use of Lemtrada®. Key elements include certifications of prescribers, dispensing pharmacies and infusion sites; patient education and limited drug access to authorized patients; and monitoring of patients to identify autoimmune conditions and malignancies.

There are many disease-modifying therapies (DMTs) available for the treatment of MS and its subtypes. DMTs are typically used to reduce relapse rates and prevent new lesions in the CNS. The American Academy of Neurology 2018 Guidelines for the use of DMT recommend that DMT be initiated in patients "with relapsing forms of MS with recent clinical relapses or MRI activity." The guidelines do not prefer specific DMTs other than to say that "clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS." Additionally, guidelines state categorize DMT therapies for evidence for lowering relapse rate (see Table 1).

Table 1. DMT Evidence for Lowering Relapse Rate[9]

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

Table 2: Billing Guidelines and Coding Information

HCPCS code◊	Coding Description	Brand Name
J0202	Injection, alemtuzumab, 1 mg	Lemtrada
ADMINISTRATION◊		
96365	Ther/proph/diag iv inf init	
96355	Ther/proph/diag iv inf addon	
96413	Chemo iv infusion 1 hr	
96415	Chemo iv infusion addl hr	

◊ Coding/Administration Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCE/RESOURCES:

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9. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 2018;90:777–788.