Policy Number	**RX501.077**
Policy Effective Date	**09/01/2025**

Alemtuzumab

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Alemtuzumab (Lemtrada) **may be considered medically necessary** for individuals 17 years of age or older for the treatment of relapsing forms of multiple sclerosis (MS) (relapsing-remitting or active secondary progressive multiple sclerosis) when the patient meets **ALL** the following criteria:

- Inadequate response to at least two drugs indicated for the treatment of MS, and
- Human immunodeficiency virus (HIV) negative, and
- Individual does not have an active infection.

NOTE 1: The U.S. Food and Drug Administration (FDA) requires provider and patient enrollment in a Lemtrada Risk Evaluation and Mitigation Strategy (REMS) program.

Alemtuzumab (Lemtrada) **is considered experimental, investigational and/or unproven** for all other non-FDA approved indications, including but not limited to use in individuals with clinically isolated syndrome multiple sclerosis.

NOTE 2: The recommended dosage of Lemtrada is 12 mg/day administered by intravenous infusion for 2 or more treatment courses:

- First Treatment Course: 12 mg/day on 5 consecutive days (60 mg total dose).
- Second Treatment Course: 12 mg/day on 3 consecutive days (36 mg total dose) 12 months after the first treatment course.
- Following the second treatment course, subsequent treatment courses of 12 mg per day on 3 consecutive days (36 mg total dose) may be administered, as needed, at least 12 months after the last dose of any prior treatment courses.

Policy Guidelines

None.

Description

Background

Alemtuzumab (Lemtrada) is a multiple sclerosis (MS) disease-modifying agent. Lemtrada can potentially alter the course of disease by lessening the frequency of clinical exacerbations. Lemtrada is a monoclonal antibody that targets CD52, a protein abundant on T and B cells. Circulating T and B cells are thought to be responsible for the damaging inflammatory process

in MS. Lemtrada depletes circulating T and B lymphocytes after each treatment course. Lymphocyte counts then increase over time (1).

Baseline Tests (1)

Baseline laboratory tests are required prior to treatment with Lemtrada and at periodic intervals until 48 months after the last treatment course of Lemtrada to monitor for early signs of potentially serious adverse effects.

In addition, prior to starting treatment with Lemtrada:

- Complete any necessary immunizations at least 6 weeks prior to treatment.
- Determine whether the individual has a history of varicella or have been vaccinated for varicella zoster virus (VZV). If not, test the individual for antibodies to VZV and consider vaccination for those who are antibody negative. Postpone treatment with Lemtrada until 6 weeks after VZV vaccination.
- Perform tuberculosis screening according to local guidelines.
- Instruct individual to avoid potential sources of *Listeria monocytogenes*.

Recommended Premedication and Concomitant Medication (1)

Corticosteroids

- Premedicate individual with high dose corticosteroids (1,000 mg methylprednisolone or equivalent) immediately prior to Lemtrada infusion and for the first 3 days of each treatment course.

Herpes Prophylaxis

- Administer antiviral prophylaxis for herpetic viral infections starting on the first day of each treatment course and continue for a minimum of 2 months following treatment with Lemtrada or until the CD4+ lymphocyte count is at least 200 cells per microliter, whichever occurs later.

Regulatory Status

The U. S. Food and Drug Administration (FDA) approved alemtuzumab (Lemtrada) on November 14, 2014 (2). Lemtrada is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of individuals with relapsing forms of MS, including relapsing-remitting second disease and active secondary progressive disease. Because of its safety profile, the use of Lemtrada should be reserved for individuals who had an inadequate response to two or more drugs indicated for the treatment of MS. (1)

The Lemtrada label includes a boxed warning citing the risk of autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after last dose should be monitored. Lemtrada also carries boxed warnings for infusion reactions which must be administered in an appropriate setting to manage anaphylaxis or serious infusion reactions, and a boxed warning for an increased risk of

malignancy, including thyroid cancer, melanoma and lymphoproliferative disorders. Baseline and yearly skin exams should be done.

On November 29, 2018, the U.S. Food and Drug Administration (FDA) warned that rare but serious cases of stroke and tears in the lining of arteries in the head and neck have occurred in individuals with MS shortly after they received Lemtrada. These problems can lead to permanent disability and even death. As a result, a new warning has been added about these risks to the prescribing information in the drug label and to the patient Medication Guide. The risk of stroke has also been added to the existing Boxed Warning, FDA's most prominent warning. (3)

Patients or their caregivers should be educated to seek emergency treatment as soon as possible if the patient experiences signs or symptoms of a stroke or tears in the lining of the head and neck arteries, called arterial dissection, which can include (3):

- Sudden numbness or weakness in the face, arms, or legs, especially if it occurs on only one side of the body.
- Sudden confusion, trouble speaking, or difficulty understanding speech.
- Sudden trouble seeing in one or both eyes.
- Sudden trouble with walking, dizziness, or loss of balance or coordination.
- Sudden severe headache or neck pain.

Most patients taking Lemtrada who developed stroke or tears in the artery linings, developed symptoms within 1 day of receiving Lemtrada. One patient reported symptoms that occurred 3 days after treatment. (3)

Lemtrada is contraindicated in individuals with human immunodeficiency virus (HIV) infection as Lemtrada can cause prolonged reductions of CD4+ lymphocyte counts. In addition, Lemtrada is also contraindicated in individuals with an active infection and in individuals with a known hypersensitivity/anaphylactic reaction to alemtuzumab or any of the drug components. Alemtuzumab is not recommended for the treatment of clinically isolated syndrome (CIS) multiple sclerosis because of its safety profile. (1)

<u>Lemtrada REMS Program</u>

Lemtrada is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) program. The Lemtrada REMS Program, a comprehensive risk management program with frequent monitoring, is being implemented to help mitigate the serious risks associated with the medications use. (1)

Notable requirements of the LEMTRADA REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Individuals must enroll in the program and comply with ongoing monitoring requirements.
- Pharmacies must be certified with the program and must only dispense to certified healthcare facilities that are authorized to receive alemtuzumab (Lemtrada).

- Healthcare facilities must enroll in the program and verify that individuals are authorized before infusing alemtuzumab (Lemtrada).
- Healthcare facilities must have on-site access to equipment and personnel trained to manage infusion reactions. (1)

Safety and effectiveness of Lemtrada in individuals younger than 17 years of age have not been established. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for alemtuzumab (Lemtrada).

Lemtrada (1)
The efficacy of Lemtrada was demonstrated in two studies (Study 1 and 2) that evaluated Lemtrada 12 mg in patients with relapsing-remitting multiple sclerosis (RRMS). Lemtrada was administered by intravenous infusion once daily over a 5-day course, followed one year later by intravenous infusion once daily over a 3-day course. Both studies included patients who had experienced at least 2 relapses during the 2 years prior to trial entry and at least 1 relapse during the year prior to trial entry. Neurological examinations were performed every 12 weeks and at the time of suspected relapse. Magnetic resonance imaging (MRI) evaluations were performed annually.

Study 1
Study 1 was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously three times a week) controlled study in patients with RRMS. Patients entering Study 1 had Expanded Disability Status Scale (EDSS) scores of 5 or less and had to have experienced at least one relapse while on interferon beta or glatiramer acetate therapy.

Patients were randomized to receive Lemtrada (n=426) or interferon beta-1a (n=202). At baseline, the mean age was 35 years, the mean disease duration was 4.5 years, and the mean EDSS score was 2.7.

The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression. Confirmed disability progression was defined as at least a 1-point increase above baseline EDSS (1.5-point increase for patients with baseline EDSS of 0) sustained for 6 months. The MRI outcome measure was the change in T2 lesion volume.

The annualized relapse rate was significantly lower in patients treated with Lemtrada than in patients who received interferon beta-1a. Time to onset of 6-month confirmed disability progression was significantly delayed with Lemtrada treatment compared to interferon beta-

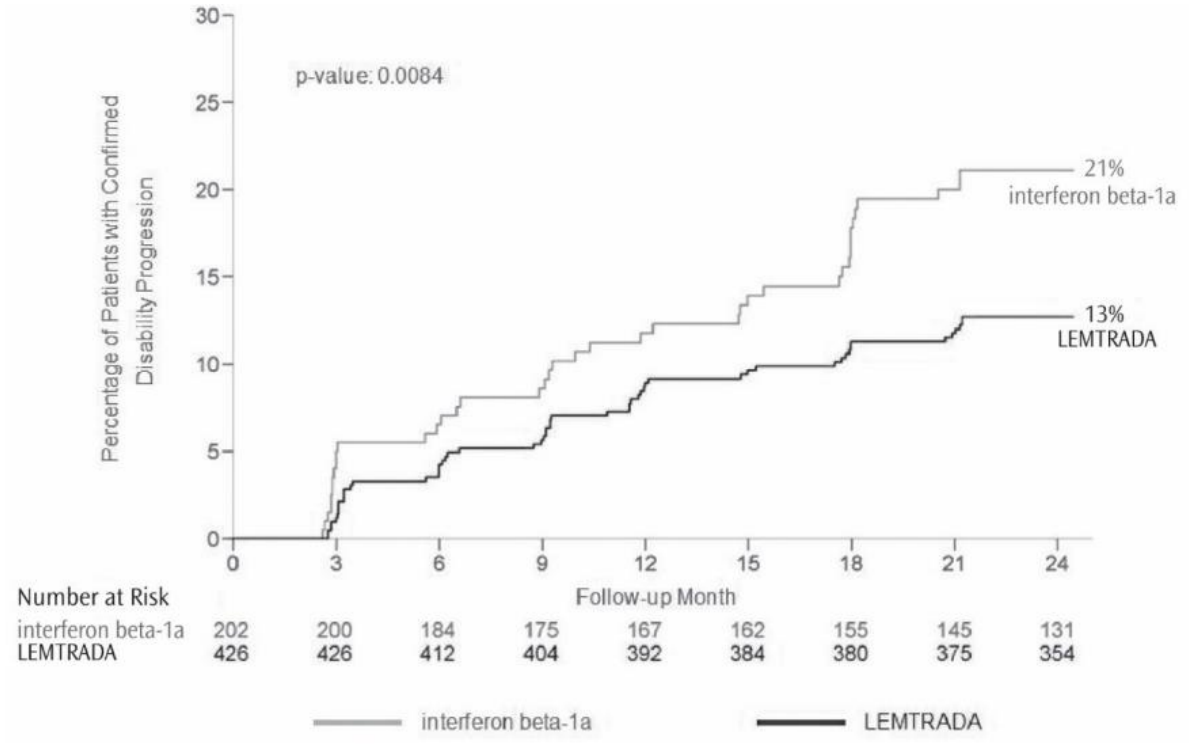
1a. There was no significant difference between the treatment groups for the change in T2 lesion volume. The results of Study 1 are shown in Table 1 and Figure 1.

Table 1: Clinical and MRI Results of Study 1

	Lemtrada (N=426)	interferon beta-1a 44 mcg (N=202)	p-value
Clinical Outcomes			
Annualized relapse rate	0.26	0.52	<0.0001
Relative reduction	49%		
Proportion of patients with disability progression at Year 2	13%	21%	0.0084
Relative risk reduction	42%		
Percent of patients remaining relapse-free at Year 2	65%	47%	<0.0001
MRI Outcomes			
Percent change in T2 lesion volume from baseline	-1.3	-1.2	0.14

MRI: Magnetic resonance imaging.

Figure 1: Time to 6-month Confirmed Disability Progression (Study 1)



Study 2

Study 2 was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously three times a week) controlled study in

patients with RRMS. Patients entering Study 2 had EDSS scores of 3 or less and no prior treatment for multiple sclerosis.

Patients were randomized to receive Lemtrada (n=376) or interferon beta-1a (n=187). At baseline, the mean age was 33 years, the mean disease duration was 2 years, and the mean EDSS score was 2.

The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression, as defined in Study 1. The MRI outcome measure was the change in T2 lesion volume.

The annualized relapse rate was significantly lower in patients treated with Lemtrada than in patients who received interferon beta-1a. There was no significant difference between the treatment groups for the time to confirmed disability progression and for the primary MRI endpoint (change in T2 lesion volume). The results for Study 2 are shown in Table 2.

Table 2: Clinical and MRI Results of Study 2

	Lemtrada (N=376)	**interferon beta-1a 44 mcg (N=187)**	**p-value**
Clinical Outcomes			
Annualized relapse rate Relative reduction	0.18 55%	0.39	<0.0001
Proportion of patients with disability progression at Year 2 Relative risk reduction	8% 30%	11%	0.22
Percent of patients remaining relapse-free at Year 2	78%	59%	<0.0001
MRI Outcomes			
Percent change in T2 lesion volume from baseline	-9.3	-6.5	0.31

MRI: Magnetic resonance imaging.

Summary of Evidence

Based on the U.S. Food and Drug Administration (FDA) label, alemtuzumab (Lemtrada) is indicated for individuals (age 17 or older) with relapsing forms of multiple sclerosis who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. To date, the safety and effectiveness of Lemtrada has not been established in individuals younger than 17 years of age. In addition, Lemtrada is also contraindicated in individuals with human immunodeficiency virus (HIV) infection or active infection. Alemtuzumab (Lemtrada**)** is considered experimental, investigational and/or unproven for all other non-FDA approved indications, including but not limited to use in individuals with clinically isolated syndrome multiple sclerosis.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0202

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. Lemtrada® Highlights of Prescribing Information. United States Food and Drug Administration. Revised 5/2024. Available at <https://www.accessdata.fda.gov> (accessed June 30, 2025).

Other:

2. Drugs.com. Lemtrada FDA Approval History. n.d. Available at <https://www.drugs.com> (accessed June 30, 2025).
3. FDA Drug Safety Communication. FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug Lemtrada (alemtuzumab). Nov 29, 2018. Available at <https://www.fda.gov> (accessed July 1, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
09/01/2025	Document updated with literature review. The following changes were made to Coverage: 1) Removed "Not used in combination with another MS disease

	modifying agent"; 2) Added "non-FDA approved" to the existing experimental, investigational and/or unproven statement. Reference 2 added; others removed/updated.
06/01/2024	Document updated with literature review. The following changes were added to the existing medically necessary statement for multiple sclerosis: 1) Added the term "active" to state "active secondary progressive multiple sclerosis"; 2) Added additional criteria "individual does not have an active infection; 3) Expanded the existing experimental, investigational and/or unproven statement to "include but not limited to use in individuals with clinically isolated syndrome multiple sclerosis." Added references 5, 7, added, others updated.
03/15/2023	Reviewed. No changes.
04/15/2022	Document updated with literature review. Coverage unchanged. References 5 and 6 added, others updated.
02/15/2021	Reviewed. No changes
04/15/2020	Document updated with literature review. The following changes were made to Coverage: 1) Moved information on Lemtrada Risk Evaluation and Mitigation Strategy (REMS) program from bulleted criteria to NOTE 1; and 2) Renumbered NOTE on dosing information to NOTE 2 and added information on subsequent dosing. References updated. Title changed from: "Alemtuzumab (Lemtrada)".
10/15/2018	Reviewed. No changes.
10/15/2017	Document updated with literature review. Coverage unchanged.
09/15/2016	Reviewed. No changes
09/01/2015	New medical document. Alemtuzumab (Lemtrada) may be considered medically necessary for patients 17 years of age or older for the treatment of relapsing forms of multiple sclerosis (MS) (relapsing-remitting or secondary progressive multiple sclerosis) when the patient meets ALL the following criteria: 1) Inadequate response to at least two drugs indicated for the treatment of MS, 2) HIV negative, 3) Not used in combination with another MS disease modifying agent, and 4) When the prescriber and patient are enrolled in the Lemtrada Risk Evaluation and Mitigation Strategy (REMS) program. In addition the following was added: Alemtuzumab (Lemtrada) is considered experimental, investigational and/or unproven for all other indications.