

**POLICY:** Multiple Sclerosis – Lemtrada® (alemtuzumab injection for intravenous use)

**DATE REVIEWED:** 11/13/2019

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## OVERVIEW

Lemtrada, a CD52-directed cytolytic monoclonal antibody, is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to include relapsing remitting disease and active secondary progressive MS in adults.<sup>1</sup> Due to its safety profile, use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS. **Limitations of Use.** Lemtrada is not recommended for use in patients with clinically isolated syndrome because of its safety profile. The recommended dose of Lemtrada is 12 mg/day given by intravenous (IV) infusion for two treatment courses. The first treatment course is 12 mg/day IV on 5 consecutive days (60 mg total dose) and the second treatment course is 12 mg/day IV on 3 consecutive days (36 mg total dose) given 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 given, as needed, at least 12 months after the last dose of any prior treatment course. Infuse Lemtrada over 4 hours and administer the agent in a setting that has equipment and personnel to appropriately manage anaphylaxis or serious infusion reactions.<sup>1</sup> Lemtrada contains the same active ingredient found in Campath® (alemtuzumab injection for IV use), which is FDA-approved for the treatment of B-cell chronic lymphocytic leukemia.<sup>6</sup>

## 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.<sup>2</sup> 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. Advances in the understanding of the MS disease process, as well as in MRI technology, spurred updated disease course descriptions in 2013,<sup>3</sup> as well as in 2017.<sup>4</sup> The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.<sup>2-4</sup> 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 disease (or not active), 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.

Many disease-modifying MS agents are FDA-approved for use in patients with relapsing forms of MS.<sup>2</sup> Options include self-administered injectable agents (e.g., glatiramer acetate products, and interferon beta agents), oral agents (i.e., Tecfidera® [dimethyl fumarate delayed-release capsules], Gilenya® [fingolimod capsules], Mayzent® [siponimod tablets]), Aubagio® [teriflunomide tablets], Mavenclad® [cladribine

tablets], Vumerity™ [diroximel fumarate delayed-release capsules]), and intravenously infused agents (i.e., Tysabri® [natalizumab injection for intravenous use], Ocrevus® [ocrelizumab injection for intravenous use], and mitoxantrone injection for intravenous use). Ocrevus is the only agent FDA-approved for primary progressive MS.

### Guidelines

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Lemtrada for patients with MS who have highly active disease.<sup>5</sup>

### Safety

Lemtrada is available only through a restricted Risk Evaluation Mitigation Strategy (REMS) program called the LEMTRADA REMS Program due to the risks of autoimmunity, infusion reactions, stroke, and malignancies.<sup>1</sup> Some program requirements include that prescribers must be certified with the program by enrolling and completing training. Also, patients must enroll in the program and comply with ongoing monitoring requirements. Pharmacies are required to be certified with the program and must only dispense Lemtrada to certified healthcare facilities that are authorized to receive Lemtrada. It is required that healthcare facilities enroll in the program and verify that patients are authorized before infusing Lemtrada. Healthcare facilities must have on-site access to equipment and personnel trained to manage infusion reactions.

### POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Lemtrada. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lemtrada, as well as the monitoring required for adverse events and long-term efficacy, approval requires Lemtrada to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Documentation:** In the *Multiple Sclerosis – Lemtrada Care Continuum Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and magnetic resonance imaging (MRI) reports.

### RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lemtrada is recommended in those who meet one of the following criteria:

#### FDA-Approved Indications

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**1. Multiple Sclerosis (MS).** Approve for the duration of therapy noted if the patient meets one of the following criteria (A or B):

**A) Initial Therapy** (this includes patients who have started but not completed the first course of Lemtrada Therapy). Approve for 5 days in patients who meet all of the following criteria (i, ii, iii, and iv):

**i.** The patient is  $\geq 17$  years of age; AND

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- ii. The patient has a relapsing form of MS; AND
  - iii. Lemtrada is prescribing by or in consultation with a neurologist or a physician that specializes in the treatment of multiple sclerosis; AND
  - iv. The patient meets one of the following (a or b):
    - a) According to the prescriber the patient has had an inadequate response or is unable to tolerate two disease-modifying agents used for MS (e.g., Avonex, Rebif, Betaseron, Extavia, Copaxone, Plegridy, Gilenya, Glatopa, glatiramer acetate injection, Aubagio, Tecfidera, Mavenclad, Mayzent, Vumerity, Tysabri, or Ocrevus); OR
    - b) 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. The patient has demonstrated rapidly-advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation, severe changes in strength or coordination) **[documentation required]**; OR
      - 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 (e.g., new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions) **[documentation required]**; OR
      - 4. Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; OR
- B) Patient Who Has Completed a Previous Course of Lemtrada Therapy.** Approve for 3 days in patients who meet all of the following criteria (i, ii, iii, and iv):
- i. The patient is  $\geq 17$  years of age; AND
  - ii. The patient has a relapsing form of MS; AND
  - iii. Lemtrada is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of MS; AND
  - iv. At least 12 months has elapsed from the last dose of any prior Lemtrada treatment course.

**Dosing.** Approve the following dosing regimens (A or B).

- A) First treatment course of 12 mg/day by intravenous infusion on 5 consecutive days (60 mg total dose); OR
- B) For additional treatment courses the dose is 12 mg/day by intravenous infusion on 3 consecutive days (36 mg total dose) administered 12 months after the last Lemtrada treatment course.

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#### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lemtrada has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Note: Examples of disease-modifying agents used for MS include Betaseron<sup>®</sup>/Extavia<sup>®</sup> (interferon beta-1b injection), Rebif<sup>®</sup> (interferon beta-1a injection [subcutaneous]), Copaxone<sup>®</sup>/Glatopa<sup>®</sup> (glatiramer acetate injection), glatiramer acetate injection, Avonex<sup>®</sup> (interferon beta-1a injection [intramuscular]), Plegridy<sup>®</sup> (peginterferon beta-1a injection), Gilenya<sup>®</sup> (fingolimod tablets), Aubagio<sup>®</sup> (teriflunomide tablets), Mavenclad<sup>®</sup> (cladribine tablets), Mayzent<sup>®</sup> (siponimod tablets), Tecfidera<sup>®</sup> (dimethyl fumarate delayed-release capsules), Vumerity<sup>™</sup> (diroximel fumarate delayed-release capsules),

Tysabri® (natalizumab injection for intravenous use), and Ocrevus® (ocrelizumab injection for intravenous use). Lemtrada should not be given in combination with other disease-modifying agents used for MS. Concomitant use of Lemtrada with immunosuppressive therapies could increase the risk of immunosuppression.<sup>1</sup>

2. **Human Immunodeficiency Virus (HIV) Infection (Patients With).** Use of Lemtrada is contraindicated in patients who are infected with HIV because Lemtrada causes prolonged reductions of CD4+ lymphocyte counts.<sup>1</sup>
3. **Non-Relapsing Forms of Multiple Sclerosis.** Note: An example of a non-relapsing form of MS is primary progressive MS. The efficacy of Lemtrada has not been established in patients with MS with non-relapsing forms of the disease.<sup>1</sup>
4. **Clinically Isolated Syndrome.** Lemtrada is not recommended for use in patients with clinically isolated syndrome due to its safety profile.<sup>1</sup>
5. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Lemtrada® injection for intravenous use [prescribing information]. Cambridge, MA: Genzyme Corporation; October 2019.
2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: [https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT\\_Consensus\\_MS\\_Coalition.pdf](https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf). Accessed on November 7, 2019.
3. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
4. 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.
5. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-788.
6. Campath® injection for intravenous use [prescribing information]. Cambridge, MA: Genzyme; November 2018.

**HISTORY**

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Removed Zinbrya from the list of medications in which Lemtrada should not be used with concomitantly since the agent was removed from the market. Also, the option of Zinbrya was deleted from the listing of MS disease modifying agents which count as a trial. Added “relapsing forms of” to the diagnosis of MS. Approvals for patients who have highly-active or aggressive MS according to the prescribing physician can receive approvals if the patient meets one of the following, with documentation required: the patient has demonstrated rapidly-advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation, severe changes in strength or coordination); OR the patient has disabling relapse(s) with suboptimal response to systemic corticosteroids [documentation required]; OR magnetic resonance imaging [MRI] findings suggest highly-active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions); OR the patient has manifestations of multiple sclerosis-related cognitive impairment.	10/31/2018
Selected revision	<p><b>1. Multiple Sclerosis, Relapsing Forms:</b> For initial therapy, Mavenclad and Mayzent were added among the list of disease-modifying multiple sclerosis agents that count as a trial towards the requirement that patients must have tried two agents and had an inadequate response or are unable to tolerate. The criteria were revised to reflect the recent change to the prescribing information that more than two Lemtrada treatment courses can be given. The wording which described directives following completion of “one prior course of Lemtrada” was changed to state that the patient “has completed a previous course” with the requirement added that at least 12 months has elapsed from the last dose of any prior Lemtrada treatment course. The wording regarding the dosing was modified to reflect that more than two Lemtrada treatment courses can be administered.</p> <p><b>2. Conditions Not Recommended for Approval:</b> The condition of Patient with Relapsing Forms of Multiple Sclerosis who is Requesting a Third (or more) Course of Lemtrada Therapy was removed. For clarity, Mavenclad and Mayzent were added to the list of disease-modifying multiple sclerosis therapies in which Lemtrada should not be used with concomitantly.</p>	5/29/2019
Annual revision	<p>The following criteria changes were made:</p> <p><b>1. Multiple Sclerosis:</b> The phrase “Relapsing forms” was removed from the stated indication. Criteria were revised such that the examples of relapsing forms of multiple sclerosis were removed. The word “prescriber” replaced in phrase of “prescribing physician” in applicable criteria. Vumerity and glatiramer acetate injection were added as medications trials that count toward the requirement of a trial of two disease-modifying agents used for multiple sclerosis.</p> <p><b>2. Conditions Not Recommended for Approval:</b> “Children with Multiple Sclerosis Who Are &lt; 17 Years of Age” was removed as this is duplicative to the requirement in the approval criteria. The Regarding “Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis”, the examples of glatiramer acetate injection, Vumerity, Mavenclad and Mayzent were added. The criteria that stated “Primary Progressive (Chronic Progressive) Multiple Sclerosis” was changed to state “Non-Relapsing Forms of Multiple Sclerosis” with a note that an example is Primary Progressive Multiple Sclerosis. Clinically Isolated Syndrome was added as a Condition Not Recommended for Approval as now recommended in the Lemtrada prescribing information.</p>	11/13/2019