Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM118	**Last Approval:**	06/14/2018
Title:	Alemtuzumab (Lemtrada®)		
Approved By:	Medical Management Leadership Team		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Lemtrada (Alemtuzumab): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Age -Diagnosis - Medication list (current and past) to include start and end dates of previous trials of disease-modifying agents used for MS -Prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of MS -Dosing -Initial/Extended Approval -Duration of therapy.

BACKGROUND

Lemtrada, a CD52-directed cytolytic monoclonal antibody, is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS).[1] 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. 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. 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. Observe patients for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Patients should complete any needed immunizations at least 6 weeks prior to Lemtrada therapy initiation. Before Lemtrada treatment, determine whether patients have a history of varicella or have been vaccinated for varicella zoster virus (VZV). If not, test the patient for antibodies to VZV and consider vaccination for patients who are antibody-negative. It is recommended to premedicate patients with high dose corticosteroids (1,000 mg methylprednisolone or equivalent) immediately prior to the first Lemtrada infusion and for the first 3 days of each treatment course. Administer antiviral prophylaxis for herpetic viral infections commencing on the first day of each treatment course and continue for a minimum of 2 months after Lemtrada therapy or until the CD4+ lymphocyte count is ≥ 200 cells per microliter. Perform tuberculosis screening according to local guidelines. Instruct patients to avoid potential sources of *Listeria monocytogenes*. Two pivotal trials assessed the efficacy of Lemtrada in patients with relapsing-remitting MS (RRMS). One study involved patients who had at least one relapse while receiving interferon beta or glatiramer acetate therapy and the other study involved patients who were treatment naïve.[1-3] Lemtrada contains the same active ingredient found in Campath® (alemtuzumab injection for IV use), which is approved by the Food and Drug Administration (FDA) for the treatment of B-cell chronic lymphocytic leukemia.[4]

Risk Evaluation and Mitigation Strategy (REMS)

Lemtrada is available only through a restricted REMS program called the LEMTRADA REMS Program due to the risks of autoimmunity, infusion reactions, and malignancies.[1] 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.

Multiple Sclerosis (MS)

MS is a chronic disabling disease of the central nervous system (CNS) characterized by inflammation, demyelination, and degenerative changes.[5-6] Patients experience relapses followed by remission of neurological symptoms. MS lesions occur in many different parts of the CNS and the symptoms and clinical course of the disease are highly variable. Some common signs and symptoms of the disease include vision problems (e.g., nystagmus), ambulation problems, pain, fatigue, spasticity, cognitive dysfunction, depression, ataxia, sensory loss, bladder disturbances, bowel dysfunction, dizziness, and vertigo.[5] In general, patients with MS may have diminished ratings on vitality and physical functions.[6]

Most people with MS are diagnosed between the ages of 20 and 50 years, but MS can manifest in young children and older adults.[5] Approximately 450,000 people are living with MS in the US.[6] Women are impacted 2 to 3 times more commonly than men, and MS is more predominant in Caucasians compared with other racial groups.

Four different clinical courses of MS have been delineated.[5] A relapse is defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least one month. RRMS is characterized by acute attacks usually followed by almost complete recovery with limited progression. Disease progression is minimal between attacks. Approximately 85% of people are initially diagnosed with RRMS. Secondary progressive MS (SPMS) begins as relapsing-remitting course but the disease transitions in many patients to a steadily progressive form with increased loss of function. Of the 85% of patients who initially have RRMS, more than 50% of patients will develop to SPMS within 10 years and 90% of patients within 25 years. Primary-progressive MS (PPMS) is noted by a steady decline in function from the onset without noted relapses. Around 10% of patients are diagnosed with primary-progressive. Progressive-relapsing MS (PRMS) starts with disease progression at onset with occasional acute relapses and continued disease progression. Only a small minority of patients (< 5%) have PRMS. About 10% of the MS population has a benign disease course, which is generally determined retrospectively. Among those with relapsing forms of MS, the severity, duration, and frequency of relapses vary widely among patients. The Expanded Disability Scale Score (EDSS) is the scale most often used to assess neurologic disability and evaluates cerebellar, pyramidal, brainstem, sensory, bowel, bladder, visual, and mental functional systems on a scale that ranges from 0 (normal neurologic examination) to 10 (death due to MS). Magnetic resonance imaging (MRI) evaluations are used to assess current MS disease activity, as well as to monitor for permanent neurologic damage.

Other Disease-Modifying Drug Therapies for Multiple Sclerosis

Interferon beta therapies indicated for use in relapsing forms of MS include Avonex® (interferon beta-1a for intramuscular [IM] injection),[7] Rebif® (interferon beta1-a for subcutaneous [SC] injection),[8] and Betaseron®/Extavia® (interferon beta-1b for SC injection).[9-10] Dosing of these products is intramuscularly (IM) once weekly (QW), SC three times weekly (TIW), and SC every other day, respectively. Plegridy™ (peginterferon beta-1a injection) is a pegylated interferon beta-1a product that is also indicated for the treatment of relapsing forms of MS and is dosed SC every 14 days.[11] Another self-injectable MS therapy is Copaxone® (glatiramer acetate injection for SC use), which can be dosed SC either once daily (QD) or TIW.[12] Glatopa™ (glatiramer acetate injection for SC use) is the generic for Copaxone and is available in the 20 mg dose only.[13] Although some differences in efficacy have been observed in clinical trials among the interferon beta products, in general, these self-injectable MS therapies appear to reduce the annualized relapse rate (ARR) by approximately one-third.[14] Copaxone and several interferon beta products have been available for over 20 years with established efficacy and known safety.[16] Oral therapies indicated in relapsing forms of MS include Aubagio® (teriflunomide tablets),[17] Gilenya™ (fingolimod capsules),[18]and Tecfidera™ (dimethyl fumarate delayed-release capsules).[19] Compared with placebo these agents lead to reductions in the ARR of approximately 31% with Aubagio, 54% with Gilenya, and 44% to 53% with Tecfidera.[6] Therapies administered by IV infusion include Tysabri® (natalizumab for IV infusion)[20] and mitoxantrone injection,[21] which are given once every 4 weeks (over 1 hour) and once every 3 months (over 5 to 15 minutes), respectively. These therapies have also demonstrated benefits in patients with MS with the effect of ARR being reduced by approximately 67%.[6,20] However, Tysabri must be used cautiously due to the risk of progressive multifocal leukoencephalopathy (PML).[20] Due to toxicities (e.g., cardiotoxicity, increased risk of developing secondary acute myeloid leukemia) the role of mitoxantrone is limited to a carefully selected patient population who have not responded to other therapies.[21] Zinbryta™ (daclizumab injection for SC use) was approved in 2016 and is an interleukin-2 receptor blocking antibody indicated for the treatment of adult patients with relapsing forms of MS.[23] Due to its safety profile, Zinbryta therapy should be reserved for patients who have had an adequate response to two or more medications indicated for the treatment of MS. Zinbryta reduced the ARR by approximately 50%.[23] Ocrevus™ (ocrelizumab injection for IV use) is a CD20-directed cytolytic antibody indicated for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis (MS).[24] Ocrevus is given by IV infusion. The initial dose is 300 mg, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses are 600 mg by IV infusion once every 6 months. In two pivotal trials Ocrevus was superior to Rebif in reducing the ARR. Another pivotal trial found Ocrevus was superior to placebo in the proportion of patients with confirmed disability progression at 12 weeks.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

Enter all indications/criteria here.

SPECIAL CONSIDERATIONS

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

FDA-Approved Indications

1. **Multiple Sclerosis (MS), Initial Therapy (this includes patients who have started but not completed the first course of Lemtrada Therapy).**

Criteria. *The patient must meet the following criteria (A, B, C, AND D)*:

- **A)** The patient is ≥ 17 years of age; AND
- **B)** The patient has a relapsing form of MS (relapsing forms of MS are RRMS, SPMS with relapses, and PRMS); AND
- **C)** The patient has had in inadequate response, according to the prescribing physician, to two disease-modifying agents used for MS (e.g., Avonex, Rebif, Betaseron, Extavia, Copaxone, Plegridy, Gilenya, Glatopa, Aubagio, Tecfidera, Tysabri, Ocrevus, or Zinbryta); AND
- **D)** Lemtrada is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of MS.

Lemtrada is indicated for the treatment of patients with relapsing forms of MS. Due to its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS.[1] The safety and efficacy of Lemtrada in pediatric patients < 17 years of age have not been established. Lemtrada is administered by IV infusion over 4 hours for two treatment courses. The first course is 12 mg/day IV on 5 consecutive days and the second course is administered 12 months after the first treatment course. Many MS medications are available with established efficacy and a known safety profile. In the professional opinion of specialized physicians, these criteria have been adopted.

2. **Multiple Sclerosis (MS), in Patients Who Have Completed One Prior Course of Lemtrada Therapy.**

Criteria. *The patient must meet the following criteria (A, B, AND C)*:

- **A)** The patient is ≥ 17 years of age; AND
- **B)** The patient has a relapsing form of MS (relapsing forms of MS are RRMS, SPMS with relapses, and PRMS); AND
- **C)** Lemtrada is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of MS.

Lemtrada is administered by IV infusion over 4 hours for two treatment courses.[1] The first course is 12 mg/day IV on 5 consecutive days and the second course is administered is 12 mg IV on 3 consecutive days 12 months after the first treatment course. These criteria do not have the requirement of two

prior MS therapies to allow for continuation of therapy among patients who have started treatment with Lemtrada. In the professional opinion of specialized physicians, these criteria have been adopted.

Dosing in Multiple Sclerosis (MS). *Dosing must meet the following (A OR B)*:

A) First treatment course of 12 mg/day by IV infusion on 5 consecutive days (60 mg total dose); OR

B) Second treatment course of 12 mg/day by IV infusion on 3 consecutive days (36 mg total dose) administered 12 months after the first Lemtrada treatment course.

No other dosing regimens or additional treatment courses should be administered. Data from the Lemtrada prescribing information recommends only a first and second course of therapy.[1]

Initial Approval/Extended Approval.

A) *Initial Approval*. Initial approval is for five doses given on 5 consecutive days.

B) *Extended Approval*. A second Lemtrada treatment course can be administered 12 months after the first treatment course for a total of three doses on 3 consecutive days.

Duration of Therapy in Multiple Sclerosis (MS): Two treatment courses total.

Labs/Diagnostics. None required.

Waste Management for All Indications.
The Lemtrada dose is 12 mg/day IV for five consecutive days (60 mg total) for the first treatment course and 12 mg/day IV on 3 consecutive days (36 mg total dose) for the second treatment course, which is administered 12 months after the first treatment course.

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. **Children with Multiple Sclerosis (MS) aged < 17 Years.** The safety and effectiveness of Lemtrada in pediatric patients < 17 years of age have not been established. Use of Lemtrada is not recommended in pediatric patients due to the risk of autoimmunity, infusion reactions, and because it may increase the risk of malignancies (e.g., thyroid, melanoma, lymphoproliferative disorders, and lymphoma).

2. **Current Use of Lemtrada with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Lemtrada should not be given in combination with other disease-modifying agents used for MS (e.g., Betaseron/Extavia, Rebif, Copaxone, Avonex, Plegridy, Glatopa, Gilenya, Aubagio, Tecfidera, Tysabri, Ocrevus, or Zinbryta). Concomitant use of Lemtrada with immunosuppressive therapies could increase the risk of immunosuppression.[1]

3. **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.[1]

4. **Patients with Relapsing Forms of Multiple Sclerosis (MS) who are Requesting a Third (or More) Courses of Lemtrada Therapy.** The Lemtrada prescribing information only recommends two therapy courses of Lemtrada for patients with relapsing forms of MS. The dosing and timing of additional courses of Lemtrada therapy are not fully characterized. Although some data are available, addition information is needed before additional Lemtrada therapy courses beyond the currently recommended two courses can be recommended.[25-28]
5. **Primary Progressive (Chronic Progressive) Multiple Sclerosis (MS).** The safety and efficacy of Lemtrada have not been studied in patients with primary progressive (chronic progressive) MS. Lemtrada is indicated in patients with relapsing forms of MS.[1]

Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References	
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therapy: a randomized controlled phase 3 study. *Lancet*. 2012;380:1829-1839.
4. Campath® injection for intravenous use [prescribing information]. Cambridge, MA: Genzyme Corporation; September 2014.
5. Clinical bulletin. Information for health professionals. Overview of multiple sclerosis. Rosalind Kalb and Nancy Reitman. © 2012 National Multiple Sclerosis Society.
6. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. July 2014. Available at: http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf Accessed November 30, 2016.
7. Avonex® injection [prescribing information]. Cambridge, MA: Biogen Idec; March 2016.
8. Rebif® injection [prescribing information]. Rockland, MA: EMD Serono; November 2015.
9. Betaseron® injection [prescribing information]. Whippany, NJ: Bayer; April 2016.
10. Extavia® injection [prescribing information]. East Hanover, NJ: Novartis; May 2016.
11. Plegridy™ injection [prescribing information]. Cambridge, MA: Biogen, Inc.; July 2016.
12. Copaxone® injection [prescribing information]. Overland Park, KS: Teva Neuroscience; August 2016.
13. Glatiramer acetate injection 20 mg/mL [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals; February 2017.
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15. Glatopa™ injection [prescribing information]. Princeton, NJ: Sandoz; April 2016.
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19. Tecfidera® delayed-release capsules [prescribing information]. Cambridge, MA: Biogen Idec; January 2017.
20. Tysabri® injection [prescribing information]. Cambridge, MA: Biogen Idec; August 2017.
21. Mitoxantrone injection [prescribing information]. Irvine, CA: Teva Parenteral Medicines, Inc.; May 2012.
22. O'Connor PW, Oh J. Disease-modifying agents in multiple sclerosis. *Handb Clin Neurol*. 2014;122:465-501.
23. Zinbryta™ injection for subcutaneous use [prescribing information]. Cambridge, MA and North Chicago, IL: Biogen and AbbVie; August 2017.
24. Ocrevus™ injection for intravenous infusion [prescribing information]. San Francisco, CA: Genentech, Inc (a Member of the Roche Group); March 2017.
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26. Tuohy O, Costelloe L, Hill-Cawthorne G, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatry*. 2015;86:208-215.
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CFR	

WAC	WAC 284-43-2050	
RCW		
Contract Citation	☒ WAH	
	☒ IMC	
	☒ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
06/11/2018	Revised	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee