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Policy Number: 016.005

Title: Coverage Determination Policy for Lemtrada (Alemtuzumab)

Regions: ☒ Texas ☒ New Mexico

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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WellMed
Doctors helping patients for more than 25 years

WellMed Drug and Biologic Coverage Determination Policy

Title: Coverage Determination Policy for Lemtrada (Alemtuzumab)

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Coverage Policy Number: 016.005

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Request

WellMed Medical Management will cover **Lemtrada (Alemtuzumab)** as medically necessary when **ALL** of the following are met:

A. Diagnosis of relapsing forms of multiple sclerosis (MS) (e.g., relapsing-remitting MS, active secondary-progressive MS); and

B. Treatment-naïve to Lemtrada:

I. Patient has history of failure following a trial for at least 4 weeks or history of intolerance to at least two of the following:

a. interferon β-1a (Avonex® or Rebif®)

b. interferon β-1b (Betaseron® or Extavia®)

c. glatiramer acetate (Copaxone® or Glatopa®)

d. dimethyl fumarate (Tecfidera®)

e. teriflunomide (Aubagio®)

f. fingolimod (Gilenya®)

g. peginterferon beta-1a (Plegridy™)

h. natalizumab (Tysabri®)

i. ocrelizumab (Ocrevus®)

j. rituximab (Riabni™, Rituxan®, Ruxience®, & Truxima®))

k. siponimod (Mayzent®)

l. ozanimod (Zeposia®)

m. ofatumumab (Kesimpta®)

n. monomethyl fumarate (Bafiertam)

o. cladribine (Mavenclad)

-AND-

II. Patient has not been previously treated with Lemtrada; and

III. Patient is not receiving Lemtrada in combination with another disease modifying agent for multiple sclerosis (e.g., interferon beta preparations, glatiramer acetate, natalizumab, fingolimod, teriflunomide, ocrelizumab, etc.); and

IV. Initial dosing is administered: 12 mg intravenously daily for 5 consecutive days; and

V. Regimen is administered only once within 12 months; and

VI. Initial authorization is for no more than 12 months and no more than 5 doses

Renewal/Continuation of Therapy Requests

WellMed Medical Management will cover **Lemtrada (alemtuzumab)** as medically necessary for treatment-experienced patients when **ALL** of the following are met:

A. Patient has previously received treatment with alemtuzumab; and
B. Documentation of positive clinical response to alemtuzumab therapy;and
C. Patient is not receiving alemtuzumab in combination with another disease modifying agent for multiple sclerosis (e.g., interferon beta preparations, glatiramer acetate, natalizumab, fingolimod, teriflunomide, ocrelizumab, etc.); and
D. Retreatment dosing is administered: 12 mg intravenously daily for 3 consecutive days; and
E. Regimen is administered only once within 12 months; and
F. Authorization is for no more than 12 months and no more than 3 doses

Note:

Lemtrada (Alemtuzumab) is currently unproven and not medically necessary for the treatment of:

1. *Rheumatoid arthritis*
2. *Autoimmune neutropenia*
3. *Autoimmune hemolytic anemia*
4. *Pure red cell aplasia*
5. *Immune thrombocytopenic purpura*
6. *Evans syndrome*
7. *Autoimmune pancytopenia*

Note:

Because of its safety profile,the use of LEMTRADA 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

Baseline laboratory tests are required prior to treatment with Lemtrada: Complete blood count (CBC) with differential, Serum creatinine levels, Urinalysis with urine cell counts, thyroid function test, serum transaminases (AST, ALT and bilirubin) (prior to treatment initiation and at monthly intervals as well as baseline and yearly skin exams to monitor for melanoma

Patient should be screened for tuberculosis prior to initiation of therapy in addition to completing any immunizations 6 weeks prior to therapy; 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 those who are antibody-negative

FDA Approved Dose and Indication

FDA Approved Indication	FDA Approved Dose
Relapsing Remitting Multiple Sclerosis	**Initial doses:** 12 mg intravenously daily for 5 consecutive days (60 mg total dose) once within 12 months
	Renewal doses: 12 mg intravenously daily for 3 consecutive days (36 mg total dose) every 12 months after first treatment course

General Background

Lemtrada is a recombinant humanized IgG1 kappa monoclonal antibody directed against the cell surface glycoprotein, CD52, present on T and B lymphocytes, and on natural killer cells, monocytes, and macrophages. Following cell surface binding to T and B lymphocytes, alemtuzumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

Lemtrada causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine counts at periodic intervals for 48 months after the last dose. Lemtrada® causes serious and life-threatening infusion reactions. Lemtrada® must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period. Lemtrada® may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams. Lemtrada® is contraindicated in patients with Human Immunodeficiency Virus (HIV) because it causes prolonged reduction of CD4+ lymphocyte counts. Providers should consider delaying initiation of Lemtrada® in patients with active infections until the infection is fully controlled. Do not administer live viral vaccines following a course of Lemtrada®. Lemtrada® is available only through a restricted distribution program (REMS).

Clinical Evidence

Havrdova et al., reported the findings from alemtuzumab-treated patients who completed the CARE-MS I and continued into the extension trial, where patients could receive additional alemtuzumab courses upon evidence of MS disease activity. Eligibility criteria for re-treatment were more than 1 protocol defined relapse or more than 2 new/enlarging T2 hyperintense and/or gadolinium (Gd)-enhancing brain or spinal cord lesions on MRI. Assessments included annualized relapse rate (ARR), 6-month confirmed disability worsening (CDW), 6-month confirmed disability improvement (CDI), no evidence of disease activity (NEDA), brain volume loss (BVL), and adverse events (AEs). Most alemtuzumab-treated patients (95.1%) completing CARE-MS I enrolled in the extension, and 68.5% received no additional alemtuzumab treatment. Of the 110 patients who received alemtuzumab retreatment, 77 (70.0%), 28 (25.5%), and 5 (4.5%) received a total of 1, 2, and 3 alemtuzumab retreatment courses, respectively, over years 3–5. ARR remained low in years 3, 4, and 5 (0.19, 0.14, and 0.15, respectively). Over years 0–5, 79.7% were free of 6month CDW; 33.4% achieved 6-month CDI. Most patients (61.7%, 60.2%, and 62.4%) had NEDA in years 3, 4, and 5. Median yearly BVL improved over years 2–4, remaining low in year 5 (years 1–5: 20.59%, 20.25%, 20.19%, 20.15%, and 20.20%). Exposure-adjusted incidence rates of most AEs declined in the extension relative to the core study. Thyroid disorder incidences peaked at year 3 and subsequently declined. The authors concluded that based on the published data, alemtuzumab provides durable efficacy through 5 years in the absence of continuous treatment, with most patients not receiving additional courses.

Giovannoni et al., reported additional prespecified and post hoc disability outcomes from the CARE-MS II trial that included the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), and Sloan low contrast letter acuity (SLCLA).11,12 These outcomes focused on the improvement of preexisting disability, in addition to slowing of disability accumulation. From the CARE-MS II trial, patients were randomized to either receive subcutaneous interferon β1A (SC INF-β-1a, 202 patients) 44 mcg, or alemtuzumab 12mg (426 patients), with baseline demographics, clinical characteristics and pre-study relapse rates equivalent between groups. Alemtuzumab treated patients were more likely than SC IFN-b-1a–treated patients to show improvement in EDSS scores ($p < 0.0001$) on all 7 functional systems. Significantly more alemtuzumab patients demonstrated 6-month confirmed disability improvement (28.8% vs. 12.9%, $p = 0.0003$). The likelihood of improved vs stable/worsening MSFC scores was greater with alemtuzumab than SC IFN-b-1a ($p = 0.0300$); improvement in MSFC scores with alemtuzumab was primarily driven by the upper limb coordination and dexterity domain. Alemtuzumab-treated patients had more favorable changes from baseline in SLCLA (2.5% contrast) scores ($p = 0.0014$) and MSFC + SLCLA composite scores ($p = 0.0097$) than SC IFN-b-1a–treated patients. The authors concluded that in patients with RRMS and inadequate response to prior disease-modifying therapies, alemtuzumab provides greater benefits than SC IFN-b-1a across several disability outcomes, reflecting improvement of preexisting disabilities, and that alemtuzumab modifies disability measures favorably compared with SC IFN-b-1a.

Professional Societies

In 2018, the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology (AAN) published practice guideline recommendations for disease-modifying therapies (DMT) for adults with multiple sclerosis.15 Thirty recommendations were developed. The recommendations that specifically make reference to alemtuzumab (Lemtrada) are as follows:

Starting DMTs Recommendations: Recommendation 14: Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS (Level B).

Switching DMTs Recommendations: Recommendation 7 (Statement 7b): If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B).

Technology Assessments

A 2017 Cochrane review was published to compare the efficacy, tolerability and safety of alemtuzumab versus interferon beta 1a in the treatment of people with RRMS to prevent disease activity. The review included three trials involving 1694 participants. All trials compared alemtuzumab 12 mg per day or 24 mg per day versus IFN beta 1a for treating RRMS. The authors concluded that there is low- to moderate-quality evidence that annual intravenous cycles of alemtuzumab at a dose of 12 mg per day or 24 mg per day reduces the proportion of participants with relapses, disease progression, change of EDSS score and developing new T2 lesions on MRI over 24 to 36 months in comparison with subcutaneous IFN beta-1a 44 µg three times per week. Alemtuzumab appeared to be relatively well tolerated. The most frequently reported adverse events were infusionassociated reactions, infections and autoimmune events. The use of alemtuzumab requires careful monitoring so that potentially serious adverse effects can be treated early and effectively.14

A 2016 Cochrane review was published to assess the safety and effectiveness of alemtuzumab used alone or associated with other treatments to decrease disease activity in patients with any form of MS. The review evaluated three studies with 1713 participants. The authors concluded that in patients with relapsing-remitting MS, alemtuzumab 12 mg was better than subcutaneous interferon beta-1a for the following outcomes assessed at 24 months: relapse-free survival, sustained disease progression-free survival, number of participants with at least one adverse event and number of participants with new or enlarging T2-hyperintense lesions on MRI. The quality of the evidence for these results was low to moderate. Alemtuzumab 24 mg seemed to be better than subcutaneous interferon beta-1a for relapse-free survival and sustained disease progression-free survival, at 36 months. More randomized clinical trials are needed to evaluate the effects of alemtuzumab on other forms of MS and compared with other therapeutic options. These new studies should assess additional relevant outcomes such as the rate of participants free of clinical disease activity, quality of life, fatigue and adverse events (individual rates, serious adverse events and long-term adverse events). Moreover, these new studies should evaluate other doses and durations of alemtuzumab course.

Unproven

Miscellaneous

Alemtuzumab has been used in the treatment of other conditions including rheumatoid arthritis,5-6 autoimmune neutropenia,7 autoimmune hemolytic anemia,8-9 pure red cell aplasia,7,10 immune thrombocytopenic purpura,7-8 Evans syndrome,7 and autoimmune

pancytopenia.7 While a beneficial effect of alemtuzumab has been reported in some of these conditions, none of them have been studied in large, controlled clinical trials or studies were discontinued before completion due to alemtuzumab associated toxicity.

HCPCS Code

HCPCS Code	Description	Availability
J0202	Alemtuzumab, 1 mg Injection	12mg/1.2mL(10mg/mL) in a single-dose vial

Acronyms

NCD = National Coverage Determination

LCD = Local Coverage Determinations

FDA = Food and Drug Administration

PBO = Placebo

AE = Adverse events

SAE = Serious adverse events

MS = Multiple Sclerosis

EDSS = Expanded Disability Status Scale

CBC = Complete blood count

RRMS = Relapsing remitting multiple sclerosis

REMS = Risk Evaluation and Mitigation Strategy

ARR = Assessments included annualized relapse rate

CDW = Confirmed disability worsening

CDI = Confirmed disability improvement

NEDA = No evidence of disease activity

BVL = Brain volume loss

MSFC = Multiple Sclerosis Functional Composite

SLCLA = Sloan low contrast letter acuity

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