SUPERSEDED BY CURRENT VERSION

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Subject: Alemtuzumab (Lemtrada™) IV

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Alemtuzumab (Lemtrada) was approved by the U.S. Food and Drug Administration (FDA) in November 2014 for the treatment of relapsing forms of multiple sclerosis. Due to the potential for serious adverse effects, it should be reserved for patients who have had an inadequate response to at least 2 drugs for the treatment of multiple sclerosis.

In two randomized trials, the rate of multiple sclerosis (MS) relapse was significantly reduced with alemtuzumab (rate of relapse, 22% and 35%) compared with interferon beta-1a (rate of relapse, 40% and 53%) in untreated (CARE-MS I; N=581) and previously treated (CARE-MS II; N=840) patients with relapsing-remitting MS. Alemtuzumab significantly improved the sustained accumulation of disability over 6 months compared with interferon beta-1a among previously treated patients (12.71% vs 21.13%); however, significance was not reached among previously untreated patients. In both studies alemtuzumab was associated with a higher incidence of serious infections, immune thrombocytopenia, autoimmunity, and thyroid papillary carcinoma, as well as a significantly higher incidence of herpes viral infections despite prophylaxis with acyclovir.

The FDA has required a Risk Evaluation and Mitigation Strategy for alemtuzumab.

POSITION STATEMENT:

NOTE: Aubagio, Avonex, Betaseron, Gilenya, glatiramer acetate (generic by Mylan), Mavenclad, Mayzent, Plegridy, Rebif and Tecfidera are preferred products for treatment of relapsing forms of multiple sclerosis.

Initiation of alemtuzumab (Lemtrada) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with a relapsing form of multiple sclerosis
2. Member has an inadequate response or contraindication to at least two of the following agents:
    a. Cladribine (Mavenclad)
    b. Dimethyl fumarate (Tecfidera)
    c. Fingolimod (Gilenya)
    d. Glatiramer acetate (Copaxone, Glatopa)
    e. Interferon beta-1a (Avonex, Rebif)
    f. Interferon beta-1b (Betaseron, Extavia)
    g. Mitoxantrone (Novantrone)
    h. Natalizumab (Tysabri)
    i. Ocrelizumab (Ocrevus)
    j. Peg-interferon beta-1a (Plegridy)
    k. Siponimod (Mayzent)
    l. Teriflunomide (Aubagio)
3. Member has not previously been treated with alemtuzumab
4. Member has tested negative for HIV infection
5. Member will receive antiviral prophylaxis for at least 2 months from the start of each treatment course to prevent herpetic viral infection
6. Alemtuzumab is not administered in combination with **ANY** of the following:
    a. Cladribine (Mavenclad)
    a. Dimethyl fumarate (Tecfidera)
    b. Fingolimod (Gilenya)
    c. Glatiramer acetate (Copaxone, Glatopa)
    d. Interferon beta-1a (Avonex, Rebif)
    e. Interferon beta-1b (Betaseron, Extavia)
    f. Mitoxantrone (Novantrone)
    g. Natalizumab (Tysabri)
    h. Ocrelizumab (Ocrevus)
    i. Peg-interferon beta-1a (Plegridy)
    a. Siponimod (Mayzent)
    j. Teriflunomide (Aubagio)

7. Dose does not exceed 12 mg/day

Duration of approval: 5 doses

Continuation of alemtuzumab (Lemtrada) **meets the definition of medical necessity** for a relapsing form of MS when **ALL** of the following criteria are met:

1. The member was previously approved by Florida Blue or another healthplan OR the member previously met all indication-specific criteria for coverage
2. Member has demonstrated a beneficial response associated with alemtuzumab
3. Member will receive antiviral prophylaxis for at least 2 months from the start of each treatment course to prevent herpetic viral infection
4. Use is **NOT** in combination with any of the following:
    a. Cladribine (Mavenclad)
    b. Dimethyl fumarate (Tecfidera)
    c. Fingolimod (Gilenya)
    d. Glatiramer acetate (Copaxone, Glatopa)
    e. Interferon beta-1a (Avonex, Rebif)
    f. Interferon beta-1b (Betaseron, Extavia)
    g. Mitoxantrone (Novantrone)
    h. Natalizumab (Tysabri)
    i. Ocrelizumab (Ocrevus)
    j. Peg-interferon beta-1a (Plegridy)
    k. Siponimod (Mayzent)
    l. Teriflunomide (Aubagio)
5. Member has not utilized any of the following agents since initiating treatment with alemtuzumab:
    a. Cladribine (Mavenclad)
    b. Dimethyl fumarate (Tecfidera)
    c. Fingolimod (Gilenya)
    d. Glatiramer acetate (Copaxone, Glatopa)
    e. Interferon beta-1a (Avonex, Rebif)
    f. Interferon beta-1b (Betaseron, Extavia)
    g. Mitoxantrone (Novantrone)
    h. Natalizumab (Tysabri)
    i. Ocrelizumab (Ocrevus)
    j. Peg-interferon beta-1a (Plegridy)
    k. Siponimod (Mayzent)
    l. Teriflunomide (Aubagio)
6. **ONE** of the following:
    a. Member has received fewer than two treatment courses of alemtuzumab

b. Member has received fewer than three treatment courses of alemtuzumab and experienced relapse, 2 or more new or enlarging T2 hyperintense lesions, or any new gadolinium-enhancing T1 brain or spinal cord lesions on MRI after the second course of treatment

7. Member has not received alemtuzumab in the previous 12 months
8. Dose does not exceed 12 mg/day

Duration of approval: 3 doses

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Administer by intravenous infusion over 4 hours for 2 or more treatment courses:
  - First course: 12 mg/day on 5 consecutive days
  - Second course: 12 mg/day on 3 consecutive days 12 months after first 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 course
- Premedicate with corticosteroids prior to infusion for the first 3 days of each treatment course
- Administer antiviral agents for herpetic prophylaxis starting on the first day of dosing and continuing for a minimum of two months after completion of dosing or until CD4+ lymphocyte count is more than 200 cells per microliter, whichever occurs later
- Dilute prior to administration
- Baseline lab tests are required prior to treatment. See prescribing information.

Drug Availability

- Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial

PRECAUTIONS:

Boxed Warning

- Serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease may occur. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine counts at periodic intervals for 48 months after the last dose.
- Serious and life-threatening infusion reactions can occur. Administer in a setting with personnel and equipment to manage anaphylaxis or serious infusion reaction. Monitor for 2 hours after each infusion.
- Serious and life-threatening stroke has been reported within 3 days of administration. Seek immediate medical attention if symptoms of stroke occur.
- May cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams.

- Available only through a restricted distribution program

Contraindications

- Infection with Human Immunodeficiency Virus

Precautions/Warnings

- Thyroid Disorders: obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion
- Immune thrombocytopenia and other autoimmune cytopenia: Monitor complete blood counts with differential prior to initiation and monthly until 48 months after the last infusion for autoimmune cytopenias
- Glomerular nephropathies: Obtain serum creatinine levels, urinalysis with cell counts and urine protein to creatinine ratio prior to initiation of treatment. Monitor serum creatinine levels and urinalysis with cell counts at monthly intervals thereafter until 48 months after the last infusion.
- Autoimmune Hepatitis: if signs of hepatic dysfunction occur, measure serum transaminases and total bilirubin and interrupt or discontinue treatment.
- Progressive Multifocal Leukoencephalopathy (PML): Withhold at the first sign or symptom suggestive of PML.
- Consider delaying initiation in patients with active infections until the infection is fully controlled. Fatal infections have occurred.
- Cases of hypersensitivity pneumonitis and pneumonitis with fibrosis may occur
- Do not administer live viral vaccines following a course of treatment

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0202	Injection, alemtuzumab, 1 mg

Do **NOT** use code J9010 (injection, alemtuzumab, 10 mg). This is a retired code for Campath.

ICD-10 Diagnosis Codes That Support Medical Necessity

G35	Multiple sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

Clinically isolated syndrome (CIS): the first clinical presentation of disease that shows characteristics of inflammatory demyelination that could be MS but has yet to fulfill criteria of dissemination in time.

Primary-progressive multiple sclerosis (PPMS): Steadily progressive course from onset; occurs in 10-15% of patients with MS.

Relapsing-remitting multiple sclerosis (RRMS): Characterized by acute attacks followed by periods of remission; primary form of MS that occurs in approximately 85% of patients.

Secondary-progressive multiple sclerosis (SPMS): An initial period of RRMS, followed by a steadily progressive course, with acute relapses (active disease) or without acute relapses (not active disease); 75-85% of patients diagnosed with RRMS will transition to SPMS.

RELATED GUIDELINES:

Botulinum Toxins, 09-J0000-29
Cladribine (Mavenclad), 09-J3000-34
Diagnosis and Treatment of Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis, 02-35000-01
Dimethyl Fumarate (Tecfidera), 09-J1000-96
Fingolimod (Gilenya™), 09-J1000-30
Functional Neuromuscular Stimulation, 09-E0000-54
Immune Globulin Therapy, 09-J0000-06
Magnetic Resonance Imaging (MRI) Brain and Head, 04-70540-11
Multiple Sclerosis Self Injectable Therapy, 09-J1000-39
Natalizumab (Tysabri®) IV, 09-J0000-73
Ocrelizumab (Ocrevus®), 09-J2000-78
Siponimod (Mayzent), 09-J3000-35
Teriflunomide (Aubagio), 09-J1000-82

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 10/09/19.

GUIDELINE UPDATE INFORMATION:

03/15/15	New Medical Coverage Guideline.
10/01/15	Revision to guideline consisting of HCPCS code update.
10/15/15	Review and revision to guideline; consisting of updating position statement.
01/01/16	Annual HCPCS coding update: added code J0202 and deleted codes C9399 and C9979.
01/01/17	Review and revision to guideline; consisting of updating position statement, precautions and references.
10/15/17	Review and revision to guideline; consisting of updating position statement and references.
12/15/18	Review and revision to guideline; consisting of updating position statement and references.
01/15/19	Revision to guideline; consisting of updating position statement and references.
11/15/19	Review and revision to guideline; consisting of updating position statement and references.