Clinical Policy Title: Alemtuzumab (Lemtrada®)

Clinical Policy Number: 00.02.15

Effective Date: June 1, 2018
Initial Review Date: April 10, 2018
Most Recent Review Date: May 1, 2018
Next Review Date: May 2019

Related policies:
None.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of alemtuzumab (Lemtrada®) for relapsing or remitting multiple sclerosis to be clinically proven and, therefore, medically necessary (Hamidi, 2018; Riera, 2016; Zhang, 2017).

Limitations:
Alemtuzumab may be prescribed for those age 17 and over.

Routine monthly monitoring is required for at least 48 months after the final infusion for early identification of adverse effects, including serious autoimmune effects.

Because of potential autoimmune side effects, alemtuzumab may not be used in persons living with human immunodeficiency virus.

Alemtuzumab may cause harm to a fetus; therefore, women who are pregnant should not take alemtuzumab. Birth control should be used for four months after treatment with alemtuzumab.
See Appendices A and B for prior authorization criteria.

Alternative covered services:

- Oral or intravenous methylprednisolone.
- Interferon treatments.

Background

Multiple sclerosis is an immune system-mediated disease affecting the central nervous system (National Institute of Neurological Disorders and Stroke, 2017). It is marked by the immune system causing damage to the myelin sheaths that insulate axons (nerve fibers), to the oligodendrocytes (myelin-producing cells), and to the underlying axons through producing lesions or scars along the axon. This process includes the activation of T cells, which cause inflammation, secrete chemicals that damage axons, and attract immune cells to the area, creating further inflammation. The results affect nerve conduction, preventing or prohibiting signals along the nerve, thereby disrupting communication between the brain and other parts of the body. The typical signs and symptoms of multiple sclerosis include fatigue; numbness or tingling of the extremities, face, or body; spasticity (often of the legs); pain; weakness; dizziness and vertigo; bladder, bowel, cognitive, hearing, sexual, and vision problems; and emotional changes and depression.

The impact of multiple sclerosis may be relatively mild, somewhat disabling, or severely devastating. The course of multiple sclerosis varies widely. Symptoms may be minor and disappear on their own, or they may worsen and become extremely disabling. For many, symptoms return spontaneously in acute episodes of declining function followed by periods of partial to full recovery, known as relapsing-remitting multiple sclerosis. For about half of those with relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis develops. There is no cure for multiple sclerosis. The course of the disease is monitored by measures of disease progression, the relapse rate, and the level of disability. The disability level often is monitored by use of the Expanded Disability Status Scale (Meyer-Moock, 2014). This ordinal scale ranges from 0 (normal clinical status) to 10 (death due to multiple sclerosis). Since symptoms spontaneously disappear for some people, and there are serious risks and uncertain benefits associated with disease-modifying treatment, not everyone takes treatment.

Several disease-modifying drugs for multiple sclerosis for cases of relapsing-remitting multiple sclerosis have been approved by the Food and Drug Administration. These include interferon drugs; ocrelizumab, a CD20-directed cytolytic antibody for adults, which is also approved for primary progressive multiple sclerosis; a synthetic form of myelin basic protein known as copolymer 1; fingolimod; glatiramer acetate; teriflunomide; dimethyl fumarate; natalizumab (accompanied by strict guidelines for treatment); and alemtuzumab (for multiple sclerosis, marketed as Lemtrada, manufactured by Sanofi Genzyme, Cambridge, Mass.). Alemtuzumab is an anti-CD52 antibody that binds to B and T cells in the immune system and destroys them. The mechanism by which this process may improve active relapsing-
remitting multiple sclerosis is not well understood. An immunosuppressant treatment, mitoxantrone, is approved by the Food and Drug Administration for the treatment of advanced or chronic multiple sclerosis. Several medications used to treat symptoms of multiple sclerosis will not be discussed here.

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- U.K. National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on February 14, 2018. Search terms were: “alemtuzumab” and “multiple sclerosis.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The policy coverage is mainly based on findings from three clinical trials examined together in systematic reviews. These are known as CAMMS223, CARE MS-I, and CARE MS-II (CAMMS223 Trial Investigators, 2008; Cohen, 2012; Coles, 2012; 2017). Two of these studies, CAMMS223 and CARE MS-II compared intravenous alemtuzumab at two levels (12 mg or 24 mg administered daily intravenously for five consecutive days during the first month, and three consecutive days during months 12 and 24) and subcutaneous interferon beta 1a (22 μg or 44 μg three times per week). CARE-MS I compared the lower 12 mg dose of alemtuzumab with the same interferon beta 1a dose, and did not include a 24-mg alemtuzumab dose. Participants were treatment naïve in CAMMS223 and CARE-MS I, but treatment experienced in CARE-MS II.

The following discussion reflects analyses based on findings of the three studies together. A 2017 Cochrane review (Zhang) included data from the above three studies (n = 1,694 participants of any age or gender) comparing intravenous alemtuzumab at two levels (12 mg or 24 mg administered daily intravenously for five consecutive days during the first month, and three consecutive days during...
months 12 and 24) and subcutaneous interferon beta 1a (22 μg or 44 μg three times per week [Rebif®]). Both levels of alemtuzumab resulted in lower levels of relapse and disease progression, with the differences between medications being statistically significant. The dose of 24 mg alemtuzumab resulted in a better score on the Expanded Disability Status Scale at a statistically significant level, while the lower dose did not. These findings confirm a previous Cochrane review, analyzing data from the same three studies (Riera, 2016).

More recently, a systematic review of 11 disease-modifying therapies prescribed for relapsing-remitting multiple sclerosis included data from the same three studies (Hamidi, 2018). The authors found that of the 11 included treatments, alemtuzumab (12 mg) was the most effective in preventing annual relapse (based on high-quality evidence). The 12-mg and 24-mg doses of alemtuzumab were the two most effective of the 11 treatments in improving scores on the Expanded Disability Status Scale. Alemtuzumab (12 mg) was associated with the fewest serious adverse events of all of the treatments. No treatment was associated with higher mortality than placebo. An included cost-effectiveness analysis showed that alemtuzumab was the most effective of the 11 treatments in terms of higher quality-adjusted life years and lower cost than the alternative treatments, over a 20-year time-horizon. For the outcome measure of disability progression, alemtuzumab was the most effective treatment, but this finding was based on low- or very-low-quality evidence. Two alternate treatments, dimethyl fumarate and fingolimod, were the most effective treatments for reducing disability progression based on high-quality evidence.

In 2014, alemtuzumab was recommended as a treatment option for relapsing-remitting multiple sclerosis by the National Guideline Clearinghouse (2014a). In the European Union, alemtuzumab is recommended for relapsing-remitting multiple sclerosis and may be considered as an initial therapy for treatment naïve patients as well as a therapy for patients who have relapsed with prior treatment (Berger, 2017). Monthly monitoring for up to four years after the final infusion is recommended to avoid serious adverse effects (Berger, 2017; Lamber, 2018a).

**Policy updates:**

None.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>Hamidi (2018)</td>
<td>A multiple treatment comparison of eleven disease-modifying drugs used for multiple sclerosis</td>
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</table>

**Key points:**

- This systematic review assessed the efficacy and cost effectiveness of 11 disease-modifying treatments for multiple sclerosis. Total sources included one health technology assessment, which included 37 pertinent randomized clinical trials, and 15 articles representing 11 unique randomized clinical trials. The latter included an unpublished report on one RCT conducted by a pharmaceutical company.
### Citation | Content, Methods, Recommendations
--- | ---
**Zhang (2017)**
Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis | **Key points:**
- This Cochrane review compares two levels of alemtuzumab with interferon beta 1a (Rebif). Three studies with 1,694 participants of all ages and genders were included.
- In the alemtuzumab 12-mg/day group, the results showed statistically significant difference in reducing relapses (RR: 0.60; CI: 0.52 – 0.70), preventing disease progression (RR: 0.60; confidence interval: CI: 0.45 – 0.79) and developing new T2 lesions on magnetic resonance imaging (RR: 0.75; CI 0.61 – 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of Expanded Disability Status Scale score (mean difference (MD): -0.35; CI -0.73 – 0.03).
- In the alemtuzumab 24-mg/day group, the results showed statistically significant differences in reducing relapses (RR 0.38; CI 0.23, 0.62), preventing disease progression (RR: 0.42; CI 0.21 - 0.84), and the changes of Expanded Disability Status Scale score (MD: -0.83; CI: -1.17, -0.49) after 36 months of follow-up.
- All three studies reported adverse and serious adverse events, but the difference between the two medications was not statistically significant. Treatment must be carefully monitored to address any adverse effects.

### References

**Professional society guidelines/other:**


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.
Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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Appendix

Keystone First Pharmacy Prior Authorization Criteria, March 6, 2018

Prior Authorization Group: LEMTRADA®

LEMTTRA®: Lemtrada®

Covered Uses: Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex (DrugPoint or DRUGDEX), American Hospital Formulary Service (AHFS – accessed via Lexicomp), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.

Exclusion Criteria: Patients that are infected with HIV (Human Immunodeficiency Virus)

Required Medical Information: See “Other Criteria”

Age Restrictions: Patients must be 17 years age or older

Prescriber Restrictions: Prescriber must be a neurologist

Coverage Duration: If all of the criteria are met, the initial request will be approved for 5 vials (60mg). For continuation of therapy, if all criteria are met, the request will be approved for 3 vials (36mg). If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Other Criteria (Review Date 1/2018):
INITIAL AUTHORIZATION:

- The patient is ≥ 17 years old with a clinical diagnosis of a relapsing form of multiple sclerosis.
- Documentation of the following lab values have been submitted within 30 days of request:
  - HIV testing
  - Thyroid function tests
  - Complete blood count with differential
  - Serum creatinine
  - Urinalysis with cell counts
  - Baseline skin exam (for melanoma)
- The member has a documented trial of glatiramer AND Aubagio or has a documented medical reason (intolerance, hypersensitivity, etc) for not utilizing these therapies.
- Documentation has been provided that the patient will be taking formulary anti-herpetic prophylaxis for a minimum of 60 days beginning day one of treatment.
- Lemtrada® is being prescribed at an FDA approved dosage

PA CRITERIA FOR REAUTHORIZATION:

- The patient is ≥ 17 years old with a clinical diagnosis of a relapsing form of multiple sclerosis.
- A period of 12 months has elapsed since previous treatment.
- Documentation of the following lab values have been submitted with request:
  - HIV testing (within 30 days of request)
  - Thyroid function tests (every 90 days of request)
  - Complete blood count with differential (within 30 days of request)
  - Serum creatinine (within 30 days of request)
  - Urinalysis with cell counts (within 30 days of request)
  - Annual skin exam (for melanoma)
- Documentation has been provided that the patient will be taking formulary anti-herpetic prophylaxis for a minimum of 60 days beginning day one of treatment.
- Lemtrada® is being prescribed at an FDA approved dosage

NOTE: Medical Director/clinical reviewer must override criteria when, in his/her professional judgment, the requested item is medically necessary.

Keystone First/Select Health of South Carolina Pennsylvania/AmeriHealth Northeast/Community Health Choices Pharmacy prior authorization criteria, March 6, 2018

Prior Authorization Group: LEMTRADA®

Drug(s): Lemtrada®

Covered Uses: Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex (DrugPoint or DRUGDEX), American Hospital Formulary Service (AHFS – accessed via Lexicomp), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.

Exclusion Criteria: Patients that are infected with HIV (Human Immunodeficiency Virus)
Required Medical Information: See “Other Criteria”

Age Restrictions: Patients must be 17 years age or older

Prescriber Restrictions: Prescriber must be a neurologist

Coverage Duration: If all of the criteria are met, the initial request will be approved for 5 vials (60mg). For continuation of therapy, if all criteria are met, the request will be approved for 3 vials (36mg). If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Other Criteria (Review Date 11/2016):

INITIAL AUTHORIZATION:
- The patient is ≥ 17 years old with a clinical diagnosis of a relapsing form of multiple sclerosis.
- Documentation of the following lab values have been submitted within 30 days of request:
  - HIV testing
  - Thyroid function tests
  - Complete blood count with differential
  - Serum creatinine
  - Urinalysis with cell counts
  - ECG (within 3 months)
  - Baseline skin exam (for melanoma)
- Clinical or diagnostic information was submitted that indicates that that patient has a documented (consistent with pharmacy claims data OR for new members to the health plan consistent with medical chart history) treatment failure after receiving an adequate trial (including dates, doses of 6 months or more of each therapy) of glatiramer acetate 40mg (Copaxone®), AND teriflunomide (Aubagio®), AND THEN Tysabri®, or has a documented medical reason (intolerance, hypersensitivity, etc) for not utilizing these therapies for a minimum of 6 months each to manage their medical condition.
- Documentation has been provided that the patient will be taking formulary anti-herpetic prophylaxis for a minimum of 60 days beginning day one of treatment.
- Lemtrada® is being prescribed at an FDA approved dosage

PA CRITERIA FOR REAUTHORIZATION:
- The patient is ≥ 17 years old with a clinical diagnosis of a relapsing form of multiple sclerosis.
- A period of 12 months has elapsed since previous treatment.
- Documentation of the following labs values have been submitted with request:
  - HIV testing (within 30 days of request)
  - Thyroid function tests (every 90 days of request)
  - Complete blood count with differential (within 30 days of request)
  - Serum creatinine (within 30 days of request)
  - Urinalysis with cell counts (within 30 days of request)
  - ECG (within 3 months)
  - Annual skin exam (for melanoma)
- Documentation has been provided that the patient will be taking formulary anti-herpetic prophylaxis for a minimum of 60 days beginning day one of treatment.
- Lemtrada® is being prescribed at an FDA approved dosage

**NOTE:** Medical Director/clinical reviewer must override criteria when, in his/her professional judgment, the requested item is medically necessary.