HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEMTRADA safely and effectively. See full prescribing information for LEMTRADA.

LEMTRADA™ (alemtuzumab) injection, for intravenous use
Initial U.S. Approval: 2001

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, AND MALIGNANCIES

See full prescribing information for complete boxed warning.

- **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. (5.1)**
- **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. (5.2)**
- **LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams. (5.3)**
- **LEMTRADA is available only through a restricted distribution program. (5.4)**

----------INDICATIONS AND USAGE----------

- LEMTRADA is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). 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. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer LEMTRADA by intravenous infusion over 4 hours for 2 treatment courses:
  - First course: 12 mg/day on 5 consecutive days. (2 1)
  - Second course: 12 mg/day on 3 consecutive days 12 months after first treatment course. (2.1)
- Premedicate with corticosteroids prior to LEMTRADA infusion for the first 3 days of each treatment course. (2.3)
- Administer antiviral agents for herpetic prophylaxis starting on the first day of LEMTRADA dosing and continuing for a minimum of two months after completion of LEMTRADA dosing or until CD4+ lymphocyte count is more than 200 cells per microliter, whichever occurs later. (2.3)
- Must be diluted prior to administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial. (3)

----------CONTRAINDICATIONS----------

Infection with Human Immunodeficiency Virus. (4)

----------WARNINGS AND PRECAUTIONS----------

- Thyroid Disorders: Obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion. (5.7)
- Other Autoimmune Cytopenias: Monitor complete blood counts monthly until 48 months after the last infusion. (5.8)
- 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. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 10% and > interferon beta-1a): rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1- (option 2) or FDA at 1-800-FDA-1088 or *h.*

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, AND MALIGNANCIES

- **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 cell counts at periodic intervals for 48 months after the last dose of LEMTRADA *[see Warnings and Precautions (5.1)]*.**
- **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 *[see Warnings and Precautions (5.2)]*.**
- **LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams *[see Warnings and Precautions (5.3)]*.**
- **Because of the risk of autoimmunity, infusion reactions, and malignancies, LEMTRADA is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) Program. Call 1- to enroll in the LEMTRADA REMS program *[see Warnings and Precautions (5.4)]*.**

1 INDICATIONS AND USAGE

LEMTRADA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

The recommended dosage of LEMTRADA is 12 mg/day administered by intravenous infusion for 2 treatment courses:

- First Treatment Course: 12 mg/day on 5 consecutive days (60 mg total dose)

- Second Treatment Course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course.

2.2 Vaccinations

Patients should complete any necessary immunizations at least 6 weeks prior to treatment with LEMTRADA *[see Warnings and Precautions (5.9)]*.

Prior to 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 those who are antibody-negative. Postpone treatment with LEMTRADA until 6 weeks after VZV vaccination.

.3 Recommended Premedication and Concomitant Medication

Corticosteroids

Premedicate patients with high dose corticosteroids (1,000 mg methylprednisolone or equivalent) immediately prior to LEMTRADA infusion and for the first 3 days of each treatment course *[see Warnings and Precautions (5.2)]*.

Herpes Prophylaxis

Administer anti-viral prophylaxis for herpetic viral infections starting on the first day of each treatment course and continue for a minimum of two months following treatment with LEMTRADA or until the CD4+ lymphocyte count is $\geq$ 200 cells per microliter, whichever occurs later *[*see *Warnings and Precautions (5.9)]*.

2.4 Preparation Instructions

Follow the steps below to prepare the diluted solution of LEMTRADA for intravenous infusion:

- Inspect LEMTRADA visually for particulate matter and discoloration prior to administration. Do not use if particulate matter is present or the solution is discolored. Do not freeze or shake vials prior to use.
- Withdraw 1.2 mL of LEMTRADA from the vial into a syringe using aseptic technique and inject into a 100 mL bag of sterile 0.9% Sodium Chloride, USP or 5% Dextrose in Water, USP.

- Gently invert the bag to mix the solution. Ensure the sterility of the prepared solution, because it contains no antimicrobial preservatives. Each vial is for single use only.

Prior to administration, protect diluted LEMTRADA solution from light and store for as long as 8 hours either at room temperature 15°C to 25°C (59°F to 77°F) or keep refrigerated at conditions 2°C to 8°C (36°F to 46°F).

2.5 Infusion Instructions

Infuse LEMTRADA over 4 hours starting within 8 hours after dilution. Extend the duration of the infusion if clinically indicated.

Administer LEMTRADA in a setting in which equipment and personnel to appropriately manage anaphylaxis or serious infusion reactions are available *[see Warnings and Precautions (5.4)]*.

Do not add or simultaneously infuse other drug substances through the same intravenous line. Do not administer as an intravenous push or bolus.

Monitor vital signs before the infusion and periodically during the infusion. Provide appropriate symptomatic treatment for infusion reactions as needed. Consider immediate discontinuation of the intravenous infusion if severe infusion reactions occur.

Observe patients for infusion reactions during and for at least 2 hours after each LEMTRADA infusion. Consider longer periods of observation if clinically indicated. Inform patients that they should report symptoms that occur during and after each infusion because they may indicate a need for prompt medical intervention *[see Warnings and Precautions (5.2)]*.

2.6 Laboratory Testing and Monitoring to Assess Safety

Conduct the following laboratory tests at baseline and at periodic intervals for 48 months following the last treatment course of LEMTRADA in order to monitor for early signs of potentially serious adverse effects:

- Complete blood count (CBC) with differential (prior to treatment initiation and at monthly intervals thereafter)
- Serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter)

- Urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter)
- A test of thyroid function, such as thyroid stimulating hormone (TSH) level (prior to treatment initiation and every 3 months thereafter)

Conduct baseline and yearly skin exams to monitor for melanoma *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial. LEMTRADA is a clear and colorless to slightly yellow solution that requires dilution prior to intravenous infusion.

4 CONTRAINDICATIONS

LEMTRADA is contraindicated in patients who are infected with Human Immunodeficiency Virus (HIV) because LEMTRADA causes prolonged reductions of CD4+ lymphocyte counts.

5 WARNINGS AND PRECAUTIONS

5.1 Autoimmunity

Treatment with LEMTRADA can result in the formation of autoantibodies and increase the risk of serious autoimmune mediated conditions. In clinical studies LEMTRADA-treated patients experienced thyroid disorders (34%), immune thrombocytopenia (2%), and glomerular nephropathies (0.3%) *[see Warnings and Precautions (5.5, 5.6, 5.7)]*. Autoimmune hemolytic anemia and autoimmune pancytopenia *[see Warnings and Precautions (5.8)]*, undifferentiated connective tissue disorders, and acquired hemophilia A (anti-Factor VIII antibodies) each occurred in 0.2% of patients. Rheumatoid arthritis, type I diabetes, vitiligo, and retinal pigment epitheliopathy occurred in 0.1% of patients.

During postmarketing use, additional autoimmune events including Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy have been reported in the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL), as well as other disorders, generally at higher and more frequent doses than recommended in MS. An oncology patient treated with alemtuzumab had fatal transfusion-associated graft-versus-host disease.

Autoantibodies may be transferred from the mother to the fetus during pregnancy. A case of transplacental transfer of anti-thyrotropin receptor antibodies resulting in neonatal Graves' disease occurred after alemtuzumab treatment in the mother *[see Use in Specific Populations (8.1)]*.

LEMTRADA may increase the risk of other autoimmune conditions because of the broad range of autoantibody formation with LEMTRADA.

Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts before starting treatment and then at monthly intervals for 48 months after the last dose of LEMTRADA to allow for early detection and treatment of autoimmune adverse reactions *[see Dosage and Administration (2.6)]*. After 48 months, testing should be performed based on clinical findings suggestive of autoimmunity.

LEMTRADA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.4)]*.

5.2 Infusion Reactions

LEMTRADA causes cytokine release syndrome resulting in infusion reactions, some of which may be serious and life threatening. In clinical studies, 92% of LEMTRADA-treated patients experienced infusion reactions. In some patients, infusion reactions were reported more than 24 hours after LEMTRADA infusion. Serious reactions occurred in 3% of patients and included anaphylaxis in 2 patients (including anaphylactic shock), angioedema, bronchospasm, hypotension, chest pain, bradycardia, tachycardia (including atrial fibrillation), transient neurologic symptoms, hypertension, headache, pyrexia, and rash. Other infusion reactions included nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnea, pulmonary infiltrates, dysgeusia, dyspepsia, dizziness, and pain. In clinical studies, 0.6% of patients with infusion reactions received epinephrine or atropine.

During postmarketing use, other serious and sometimes fatal infusion reactions included hypoxia, syncope, acute respiratory distress syndrome, respiratory arrest, myocardial infarction, acute cardiac insufficiency, and cardiac arrest have been reported in the treatment of patients with B-CLL, as well as other disorders, generally at higher and more frequent doses than recommended in MS.

Premedicate patients with corticosteroids immediately prior to LEMTRADA infusion for the first 3 days of each treatment course. In clinical trials, patients received 1,000 mg of

methylprednisolone for the first 3 days of each LEMTRADA treatment course. Consider pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration. Infusion reactions may occur despite pretreatment.

Consider additional monitoring in patients with medical conditions which predispose them to cardiovascular or pulmonary compromise.

LEMTRADA can only be administered in certified healthcare settings that have on-site access to equipment and personnel trained to manage infusion reactions (including anaphylaxis and cardiac and respiratory emergencies).

LEMTRADA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.4)]*.

5.3 Malignancies

Thyroid cancer

LEMTRADA may increase the risk of thyroid cancer. In controlled clinical studies, 3 of 919 (0.3%) LEMTRADA-treated patients developed thyroid cancer, compared to none in the interferon beta-1a-treated group. However, screening for thyroid cancer was performed more frequently in the LEMTRADA-treated group, because of the higher incidence of autoimmune thyroid disorders in those patients. Two additional cases of thyroid cancer in LEMTRADA-treated patients occurred in uncontrolled studies.

Patients and healthcare providers should monitor for symptoms of thyroid cancer including a new lump or swelling in the neck, pain in the front of the neck, persistent hoarseness or other voice changes, trouble swallowing or breathing, or a constant cough not due to an upper respiratory tract infection.

Melanoma

LEMTRADA may increase the risk of melanoma. In uncontrolled studies, 4 of 1486 (0.3%) LEMTRADA-treated patients developed melanoma or melanoma *in situ*. One of those patients had evidence of locally advanced disease.

Perform baseline and yearly skin examinations to monitor for melanoma in patients receiving LEMTRADA.

Lymphoproliferative disorders and lymphoma

Cases of lymphoproliferative disorders and lymphoma have occurred in LEMTRADA-treated patients with MS, including a MALT lymphoma, Castleman's Disease, and a fatality following treatment of non-Epstein Barr Virus-associated Burkitt's lymphoma. There are postmarketing reports of Epstein Barr Virus-associated lymphoproliferative disorders in non-MS patients.

Because LEMTRADA is an immunomodulatory therapy, caution should also be exercised in initiating LEMTRADA in patients with pre-existing or ongoing malignancies.

LEMTRADA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.4)]*.

5.4 LEMTRADA REMS Program

LEMTRADA is available only through a restricted program under a REMS called the LEMTRADA REMS Program, because of the risks of autoimmunity, infusion reactions, and malignancies *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Notable requirements of the LEMTRADA REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Patients must enroll in the program and comply with ongoing monitoring requirements *[see Dosage and Administration (2.6)]*.
- Pharmacies must be certified with the program and must only dispense to certified healthcare facilities that are authorized to receive LEMTRADA.
- Healthcare facilities must 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.

Further information, including a list of qualified healthcare facilities, is available at 1- .

5.5 Immune Thrombocytopenia

Immune thrombocytopenia (ITP) occurred in 2% of LEMTRADA-treated patients in clinical studies in MS.

In a controlled clinical trial in patients with MS, one LEMTRADA-treated patient developed ITP that went unrecognized prior to the implementation of monthly blood monitoring requirements, and died from intracerebral hemorrhage. Nadir platelet counts ≤20,000 cells per microliter as a result of ITP occurred in 2% of all LEMTRADA-treated patients in clinical studies in MS. Anti-platelet antibodies did not precede ITP onset. ITP has been diagnosed more than 3 years after the last LEMTRADA dose.

Symptoms of ITP include easy bruising, petechiae, spontaneous mucocutaneous bleeding (e.g., epistaxis, hemoptysis), and heavier than normal or irregular menstrual bleeding. Hemoptysis may also be indicative of anti-glomerular basement membrane (GBM) disease *[see Warnings and Precautions (5.6)]*, and an appropriate differential diagnosis has to be undertaken. Remind the patient to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns.

Obtain complete blood counts (CBCs) with differential prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion *[see Dosage and Administration (2.6)]*. After this period of time, testing should be performed based on clinical findings suggestive of ITP. If ITP is suspected, a complete blood count should be obtained immediately. If ITP onset is confirmed, promptly initiate appropriate medical intervention.

5.6 Glomerular Nephropathies

Glomerular nephropathies occurred in 0.3% of LEMTRADA-treated patients in MS clinical trials. There were 3 cases of membranous glomerulonephritis and 2 cases of anti-glomerular basement membrane (anti-GBM) disease. There are published and post-marketing cases of MS patients treated with alemtuzumab who developed anti-GBM disease and subsequently developed end stage renal disease requiring renal transplantation. Cases of anti-GBM disease have been diagnosed up to 40 months after the last dose of LEMTRADA. Urgent evaluation and treatment is required because anti-GBM disease can lead to renal failure requiring dialysis or transplantation and can be life-threatening if left untreated.

Clinical manifestations of nephropathy may include elevated serum creatinine levels, hematuria, or proteinuria. Alveolar hemorrhage manifested as hemoptysis is a common component of anti-GBM disease but did not occur in clinical trials.

Obtain serum creatinine levels and urinalysis with cell counts prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of nephropathies.

If clinically significant changes from baseline in serum creatinine, unexplained hematuria, or proteinuria are observed, perform further evaluation for nephropathies. Early detection and treatment of nephropathies may decrease the risk of poor outcomes.

5.7 Thyroid Disorders

Autoimmune thyroid disorders occurred in 34% of LEMTRADA-treated patients in clinical studies. Newly diagnosed thyroid disorders occurred throughout the uncontrolled clinical study follow-up period, more than 7 years after the first LEMTRADA dose. Autoimmune thyroid disorders included Graves' disease, hyperthyroidism and hypothyroidism. Graves' ophthalmopathy with decreased vision, eye pain, and exophthalmos occurred in 1% of LEMTRADA-treated patients. Two patients required surgical orbital decompression. Serious thyroid events occurred in about 2% of LEMTRADA-treated patients in clinical studies and included cardiac and psychiatric events associated with thyroid disease. Of all LEMTRADA-treated patients, 3% underwent thyroidectomy.

Thyroid disease poses special risks in women who are pregnant *[see Use in Specific Populations (8.1)]*.

Obtain thyroid function tests, such as TSH levels, prior to initiation of treatment and every 3 months thereafter until 48 months after the last infusion. Continue to test thyroid function after 48 months if clinically indicated.

In patients with ongoing thyroid disorder, LEMTRADA should be administered only if the potential benefit justifies the potential risks.

5.8 Other Autoimmune Cytopenias

Autoimmune cytopenias such as neutropenia (0.1%), hemolytic anemia (0.2%), and pancytopenia (0.2%) occurred in LEMTRADA-treated patients in clinical studies in MS.