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.
LEMTTRA® (alemtuzumab) injection, for intravenous use
Initial U.S. Approval: 2001

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, STROKE, AND MALIG-
NANCIES

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 cell counts monthly until 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)
- Serious and life-threatening stroke has been reported within 3 days of LEMTRADA administration. Instruct patients to seek immediate medical attention if symptoms of stroke occur. (5.3)
- LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams. (5.4)
- LEMTRADA is available only through a restricted distribution program. (5.5)

INDICATIONS AND USAGE

- LEMTRADA is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-
remitting disease and active secondary progressive disease, in adults. 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 [see Warnings and Precautions (5)]. (1)

Limitations of Use:

- LEMTRADA is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile [see Warnings and Precautions (5)]. (1)

DOSEAGE AND ADMINISTRATION

- Baseline laboratory tests are required prior to treatment. (2.1)
- Administer LEMTRADA by intravenous infusion over 4 hours for 2 or more treatment courses:
- Initial treatment of 2 courses:
  - First course: 12 mg/day on 5 consecutive days. (2.3)
  - Second course: 12 mg/day on 3 consecutive days 12 months after first treatment course. (2.3)
- 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. (2.3)
- Premedicate with corticosteroids prior to LEMTRADA infusion for the first 3 days of each treatment course. (2.2)
- 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. (2.2)

FULL PRESCRIBING INFORMATION: CONTENTS’
WARNING: AUTOIMMUNITY, INFUSION REACTIONS, STROKE, AND MALIG-
NANCIES

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CONTRAINDICATIONS

- Must be diluted prior to administration. (2.4)

DOSEAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Known hypersensitivity or anaphylactic reactions to alemtuzumab or any of the excipients in LEMTRADA (4)
- Infection with Human Immunodeficiency Virus (4)
- Active infection (4)

WARNINGS AND PRECAUTIONS

- Immune Thrombocytopenia: Obtain complete blood counts (CBCs) with differential prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. (5.6)
- 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. (5.7)
- Thyroid Disorders: Obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion. (5.8)
- Other Autoimmune Cytopenias: Monitor CBCs monthly until 48 months after the last infusion. (5.9)
- Autimmune Hepatitis: If signs of hepatic dysfunction occur, promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment. (5.10)
- Hemophagocytic Lymphohistiocytosis: Consider this diagnosis and evaluate pa-

patients immediately if they develop signs or symptoms of systemic inflammation. Discontinue LEMTRADA if an alternative etiology is not established. (5.11)
- Adult Onset Still’s Disease (AOSD): If a patient develops AOSD, they require prompt evaluation and treatment. (5.12)
- Thorbotic Thrombotic Purpura (TTP): Evaluate patients immediately if they develop clinical symptoms or laboratory findings consistent with TTP. Discontinue LEMTRADA if TTP is confirmed or if an alternative etiology is not established. (5.13)
- Autoimmune Encephalitis (AIE): Evaluate patients if they develop signs and symptoms suggestive of AIE, such as subacute onset of memory impairment, altered mental status, psychiatric symptoms, neurological findings, and seizures. (5.14)
- Acquired Hemophilia A: Obtain a coagulopathy panel including aPTT in patients who present with signs such as spontaneous subcutaneous hematomas, extensive bruising, hematuria, epistaxis, or gastrointestinal or other types of bleeding. (5.15)
- Infections: Administration is contraindicated in patients with active infection. Do not administer live viral vaccines following a course of LEMTRADA. (4, 5.16)
- Progressive Multifocal Leukoencephalopathy (PML): Withhold LEMTRADA at the first sign or symptom suggestive of PML. (5.17)

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 1-800-745-4447, option 2 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm. (8.1)
Women of childbearing potential should use effective contraception during and for 4 months after a course of treatment with LEMTRADA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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2.2 Recommended Premedication and Concomitant Medication

Corticosteroids

Prepare the diluted solution of LEMTRADA for intravenous infusion. Do not administer as an intravenous push or bolus. Obtain a baseline ECG. Monitor vital signs before the infusion and periodically during the infusion. Provide appropriate symptomatic treatment for infusion reactions as needed.

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.

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, serious infusion reactions, myocardial ischemia, myocardial infarction, and cerebrovascular and respiratory adverse reactions are available [see Warnings and Precautions (5.2)].

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

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

1. Administer antiviral prophylaxis for herpetic viral infections starting on the first day of each treatment course and continue for a minimum of 2 months following treatment with LEMTRADA or until the CD4+ lymphocyte count is at least 200 cells per microliter, whichever occurs later [see Warnings and Precautions (5.15)].

2.3 Recommended Dosage

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.

Following the second 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 courses.

2.4 Preparation Instructions

Perform baseline laboratory tests at least 6 weeks prior to treatment. Conduct the following laboratory tests at baseline and at periodic intervals until 48 months after the last dose of any prior treatment courses.

Following the second 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 courses.

Conduct baseline and yearly skin exams [see Warnings and Precautions (5.4)].

6.5 Postmarketing Experience

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed
who are infected with human immunodeficiency virus (HIV) because LEMTRADA causes prolonged reductions of CD+ lymphocyte counts.

5.2 Autoimmunity

Treatment with LEMTRADA can result in the formation of autoantibodies and increase the risk of serious autoimmune mediated conditions, which may be life threatening. In clinical studies (controlled and open-label extension), LEMTRADA-treated patients experienced thyroid disorders (36.8%), immune thrombocytopenia (2%), and glomerular nephropathies (0.3%) [see Warnings and Precautions (5.5)]. In clinical trials of LEMTRADA, the incidence of autoimmune conditions was comparable in patients receiving LEMTRADA and placebo. Patients and healthcare providers should monitor for symptoms of thyroid cancer including neck mass, hoarseness of voice, change in voice, and weight loss [see Warnings and Precautions (5.1)]. Further information, including a list of qualified healthcare facilities, is available at the REMS website: www.LemtradaREMS.com or by calling 1-855-676-6326.

5.3 Stroke and Cerebrovascular Arterial Dissection

In the postmarketing setting, serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported within 3 days of LEMTRADA administration, with most cases occurring within the first 48 hours of treatment. Consider pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration. Infusion reactions may occur despite pretreatment.

In clinical studies, patients who received LEMTRADA for a short course of treatment (2 doses) and 3 more doses of IBETE were monitored by cervical ultrasound before and after the first dose. Cerebrovascular dissections were reported in 3 of 30 patients (1%). In clinical studies, patients with a history of cerebrovascular disease were excluded. Patients with contraindications to cervical dissection scans were not enrolled in clinical studies. Consider pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration. Infusion reactions may occur despite pretreatment.

In the postmarketing setting, serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported within 3 days of LEMTRADA administration, with most cases occurring within the first 48 hours of treatment. 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. Physicians should alert patients that an infusion reaction could occur within 48 hours of infusion. 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, cerebrovascular, cardiac and respiratory emergencies) [see Dosage and Administration (2.5)].

LEMTRADA is available only through a restricted program under a REMS [see Warnings and Precautions (5.5)].

5.4 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 conditions. Two additional cases of thyroid cancer in LEMTRADA-treated patients occurred in uncontrolled studies.

In postmarketing studies, cases of lymphoproliferative disorders and lymphoma have been reported 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 preexisting or ongoing malignancies.

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 thyroid cancer. Further information, including a list of qualified healthcare facilities, is available at the REMS website: www.LemtradaREMS.com or by calling 1-855-676-6326.
8.5 Thyroid Disorders

Thyroid endocrine disorders, including autoimmune thyroid disorders, occurred in 36.8% of LEMTRADA-treated patients in MS clinical studies (controlled and open-label extension). 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, hypothyroidism, autoimmune thyroiditis, or thyroid hormone abnormalities with decreased free T3 and T4, thyrotoxicosis, or hypothyroidism. One LEMTRADA-treated patient with autoimmune thyroiditis and hypothyroidism had several signs of the exophthalmos occurred in 2% of LEMTRADA-treated patients. Seven patients required surgical orbital decompression. Serious thyroid events occurred in about 5.2% of LEMTRADA-treated patients in clinical studies and included cardiac and psychiatric events associated with primary thyroid disease. Of all LEMTRADA-treated patients, 3.8% 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 or in case of pregnancy. In patients with ongoing thyroid disorder, LEMTRADA should be administered only if the potential benefit justifies the potential risks.

8.9 Other Autoimmune Cytoptenias

Autoimmune cytopenias such as neutropenia (0.1%), hemolytic anemia (0.3%), and pancytopenia (0.2%) occurred in LEMTRADA-treated patients in MS clinical studies (controlled and open-label extension). In cases of autoimmune hemolytic anemia, patients tested positive for direct antiglobulin antibodies, and nadir hemoglobin levels ranged from 2.9–8.6 g/dL. Symptoms of autoimmune hemolytic anemia include weakness, chest pain, jaundice, dark urine, and tachycardia. One LEMTRADA-treated patient with autoimmune pancytopenia died from sepsis.

During postmarketing use, additional autoimmune cytopenias, including fatal autoimmune hemolytic anemia and aplastic anemia, have been reported in the treatment of patients with B-CLL, as well as other disorders, generally at higher and more frequent doses of alemtuzumab than recommended in MS. Use CBC results to monitor for cytopenias. Prompt medical intervention is indicated if a cytopenia is confirmed.

5.10 Autoimmune Hepatitis

Autoimmune hepatitis causing clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with LEMTRADA in postmarketing use. Patients presenting with elevated liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice) and/or liver dysfunction should be evaluated immediately, and a diagnosis of ESLD should be considered. LEMTRADA should be discontinued if an alternate etiology for the signs or symptoms cannot be established.

5.11 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking LEMTRADA. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality. HLH has been reported early and late in LEMTRADA treatment. Common manifestations include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms (e.g., mental status changes, ataxia, or seizures), cytopenias, high serum ferritin, hypertriglyceridemia, and liver function and coagulation abnormalities. Hemophagocytosis may be seen on histologic examination of bone marrow, spleen, or lymph nodes. In cases of HLH reported with LEMTRADA, most patients presented with fever, elevated ferritin, transaminases, hypertriglyceridemia, and all patients required hospitalization. Although the small number of cases limits the ability to draw conclusions pertaining to mean or range of latency for HLH, symptoms have been reported to occur within approximately thirteen months to thirty-three months following the initiation of treatment. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. LEMTRADA should be discontinued if an alternate etiology for the signs or symptoms cannot be established.

5.12 Adult Onset Still’s Disease (AOSD)

During postmarketing use, Adult Onset Still’s Disease (AOSD) has been reported in patients treated with LEMTRADA. AOSD is a rare inflammatory condition that requires urgent evaluation and treatment. Patients presenting with high fever, a combination of the following signs and symptoms: fever, arthritis, rash, and leukocytosis in the absence of infections, malignancies, and other rheumatic conditions. Patients with manifestations of AOSD should be evaluated immediately and LEMTRADA should be discontinued if an alternate etiology for the signs or symptoms cannot be established.

5.13 Thrombotic Thrombocytopenic Purpura (TTP)

TTP has been reported in patients treated with LEMTRADA. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological sequelae, fever, and renal impairment associated with high creatinine and low urine output. Thrombotic microangiopathy (TMA) characterized by small vessel occlusion by a fibrin thrombus has been reported in 2% of patients treated with LEMTRADA. During postmarketing use, cases of AIE have been reported in patients treated with LEMTRADA compared to 3% of patients treated with interferon beta-1a in controlled clinical studies in MS up to 2 years in duration. Infections that occurred more often in LEMTRADA-treated patients than interferon beta-1a patients included nasopharyngitis, urinary tract infection, upper respiratory tract infection, skin infections, sinusitis, pneumonia, bronchia, and infections of the lower respiratory tract. In 2% of patients treated with LEMTRADA as compared to 1% of patients treated with interferon beta-1a. Serious infections in the LEMTRADA group included: appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection.

Do not administer live viral vaccines as a course of LEMTRADA. Patients treated with LEMTRADA have altered immunity and may be at increased risk of infection following administration of live viral vaccines.

LEMTRADA administration is contraindicated in patients with active infection [see Contraindications (4)]. Concomitant use of LEMTRADA with antineoplastic or immunosuppressive therapies could increase the risk of immunosuppression.

5.16 Infections

Infections occurred in 71% of LEMTRADA-treated patients compared to 53% of patients treated with interferon beta-1a in controlled clinical studies in MS up to 2 years in duration. Infections that occurred more often in LEMTRADA-treated patients than interferon beta-1a patients included nasopharyngitis, urinary tract infection, upper respiratory tract infection, skin infections, sinusitis, pneumonia, bronchia, and infections of the lower respiratory tract. In 2% of patients treated with LEMTRADA as compared to 1% of patients treated with interferon beta-1a. Serious infections in the LEMTRADA group included: appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection.

5.15 Acquired Hemophilia A

Cases of acquired hemophilia A (anti-Factor VIII antibodies) have been reported in both the clinical trial and postmarketing settings. Patients typically present with spontaneous subcutaneous hematomas and extensive bruising, although hematuria, epistaxis, gastrointestinal, or other types of bleeding may occur. Obtain a coagulopathy panel including aPTT in patients who present with bleeding symptoms. Patients should be informed about the signs and symptoms of acquired hemophilia A and advised to seek immediate medical attention if any of these symptoms occur.

5.17 Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) has occurred in a patient treated with LEMTRADA. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and...
that usually leads to death or severe disability. PML was diagnosed two months after the second course of LEMTRADA. The patient had previously received multiple MS therapies, but had not received other drugs for MS for more than one year. The patient had no other identified systemic medical conditions resulting in compromised immune system function and had not previously been treated with natalizumab, which has a known association with PML. The patient was not taking any immunosuppressive or immunomodulatory medications concomitantly. After the diagnosis of PML, the patient developed immune reconstitution inflammatory syndrome (IRIS). The patient’s condition improved, but mild residual neurologic sequelae remained at last follow-up.

5.18 Acute Acalculous Cholecystitis

LEMTRADA may increase the risk of acute acalculous cholecystitis. In controlled clinical studies, 0.2% of LEMTRADA-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with interferon beta-1a. During postmarketing, additional cases of acute acalculous cholecystitis have been reported in LEMTRADA-treated patients. Time to onset of symptoms ranged from less than 24 hours to 2 months after LEMTRADA infusion. Typical risk or predisposing factors such as concurrent critical illness was not reported. Abdominal ultrasound or computed tomography was used to support the diagnosis of acute acalculous cholecystitis in some cases. Some patients were treated conservatively with antibiotics and recovered without surgical intervention, whereas others underwent cholecystectomy. Symptoms of acute acalculous cholecystitis include abdominal pain, abdominal tenderness, fever, nausea, and vomiting. Leukocytosis and abnormal liver enzymes are also commonly observed. Acute acalculous cholecystitis is a condition that is associated with high morbidity and mortality rates if not diagnosed early and treated. If acute acalculous cholecystitis is suspected, evaluate and treat promptly.

5.19 Pneumonitis

In clinical studies, 8 of 1217 (0.5%) LEMTRADA-treated patients had pneumonitis of varying severity. Cases of hypersensitivity pneumonitis and pneumonitis with fibrosis occurred in clinical studies. Patients should be advised to report symptoms of pneumonitis, which may include shortness of breath, cough, wheezing, chest pain or tightness, and hemoptysis.

5.20 Drug Products with Same Active Ingredient

LEMTRADA contains the same active ingredient (alemtuzumab) found in CAMPATH®. If LEMTRADA is used for a patient who has previously received CAMPATH, exercise increased vigilance for additive and long-lasting effects on the immune system.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Autoimmunity [see Boxed Warning and Warnings and Precautions (5.1)]
- Infusion Reactions [see Boxed Warning and Warnings and Precautions (5.2)]
- Stroke and Cervicofacial Arterial Dissection [see Warnings and Precautions (5.3)]
- Malignancies [see Warnings and Precautions (5.4)]
- Immune Thrombocytopenia [see Warnings and Precautions (5.5)]
- Glomerular Nephropathies Including Anti-glomerular Basement Membrane Disease [see Warnings and Precautions (5.6)]
- Thyroid Disorders [see Warnings and Precautions (5.7)]
- Other Autoimmune Cytopenias [see Warnings and Precautions (5.8)]
- Autoimmune Hepatitis [see Warnings and Precautions (5.10)]
- Hemophagocytic Lymphohistiocytosis [see Warnings and Precautions (5.11)]
- Adult Onset Still’s Disease [see Warnings and Precautions (5.12)]
- Thrombotic Thrombocytopenic Purpura (TTP) [see Warnings and Precautions (5.13)]
- Autoimmune Encephalitis (AIE) [see Warnings and Precautions (5.14)]
- Acquired Hemophagocytic Syndrome [see Warnings and Precautions (5.15)]
- Progressive Multifocal Leukoencephalopathy (PML) [see Warnings and Precautions (5.17)]
- Acute Acalculous Cholecystitis [see Warnings and Precautions (5.18)]
- Pneumonitis [see Warnings and Precautions (5.19)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical trials (Study 1 and Study 2), a total of 811 patients with relapsing forms of MS received LEMTRADA. The population was 18 to 55 years of age, 65% were female, and 92% were Caucasian. A total of 811 patients received 1 course of therapy, and 789 patients received a second course of therapy at 12 months. The overall follow-up in the controlled trials was equivalent to 1622 patient-years. In MS clinical studies (controlled and open-label extension), a total of 1217 patients received LEMTRADA. Approximately 60% of patients received a total of 2 treatment courses and approximately 24% of patients received a total of 3 treatment courses; others received a total of 4 or more treatment courses, although data beyond 3 treatment courses are limited. The overall follow-up was 6858 person-years. Patients had a median of 6 years of follow-up from the first LEMTRADA dose, with approximately 14% having at least 7 years of follow-up.

Most Common Adverse Reactions

In controlled clinical trials, the most common adverse reactions with LEMTRADA (in at least 10% of patients and more frequently than with interferon beta-1a) were rash, headache, pyrexia, nasopharyngitis, 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, diarrea, sinustitis, oropharyngeal pain, gastritis, dizziness, abdominal pain, flushing, and vomiting.

Table 1 lists adverse reactions occurring in ≥5% of LEMTRADA-treated patients in Study 1 and 2 and at the same or at a higher rate than interferon beta-1a.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEMTRADA (N=811)</th>
<th>Interferon beta-1a 44 mcg (N=389)</th>
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<tbody>
<tr>
<td>Rash</td>
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<td>Headache</td>
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<tr>
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<td>Thyroid gland disorders</td>
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<td>Dysgeusia</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Influenza</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Blood in urine</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Decrease in CD4 lymphocytes</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>
6.2 Lymphopenia

Nearly all (99.9%) patients treated with LEMTRADA in MS clinical trials experienced lymphopenia. The lowest lymphocyte counts occurred approximately by 1 month after each course of treatment. The mean lymphocyte count at 1 month after LEMTRADA treatment was 0.25 × 10^9 L^-1 (range 0.02–2.30 × 10^9 L^-1) and 0.32 (0.02–1.81 × 10^9 L^-1) for treatment courses 1 and 2, respectively. Total lymphocyte counts increased to reach the lower limit of normal in approximately 40% of patients by 6 months after each LEMTRADA treatment course and approximately 80% of patients by 12 months after each course [see Clinical Pharmacology (12.2)].

6.3 Suicidal Behavior or Ideation

In clinical studies, 0.6% of patients in both the LEMTRADA and interferon beta-1a groups had events of suicidal ideation or attempted suicide. Of these patients, two (0.02%) patients treated with LEMTRADA die by suicide during the course of treatment were associated with decreased T-lymphocyte populations and decreased CD8 lymphocyte count. There was no evidence from clinical trials that the presence of binding or inhibitory anti-alemtuzumab antibodies had a significant effect on clinical outcomes, total lymphocyte count, or other laboratory values. However, there was an increase in antibody response were observed in offspring at both doses tested.

8.2 Lactation

There are no data on the presence of alemtuzumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. No adverse effects on breastfed infants were observed. However, there was an increase in antibody response were observed in offspring at both doses tested. In pregnant huCD52 transgenic mice administered LEMTRADA at a dose of 3 or 10 mg/kg/day IV throughout gestation and lactation, there was an increase in pup deaths during the lactation period at 10 mg/kg. Decreases in T- and B-lymphocyte populations and in antibody response were observed in offspring at both doses tested.

8.3 Females and Males of Reproductive Potential

Contraception

Before initiation of LEMTRADA treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus. To avoid in utero exposure to LEMTRADA, women of childbearing potential should use effective contraceptive measures when receiving a course of treatment with LEMTRADA and for 4 months following that course of treatment [see Use in Specific Populations (8.1)].

Infertility

In huCD52 transgenic mice, administration of LEMTRADA prior to and during the mating period resulted in adverse effects on sperm parameters in males and reduced number of corpora lutea and implantations in females [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients less than 17 years of age have not been established. LEMTRADA administration should not be used in pediatric patients due to the risks of autoimmune, infusion reactions, and stroke, and because it may increase the risk of malignancies (thymus, melanoma, lymphoproliferative disorders, and lymphoma) [see Warnings and Precautions (5.1), (5.2), (5.4)].

8.5 Geriatric Use

Clinical studies of LEMTRADA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

10 OVERDOSAGE

Two MS patients experienced serious reactions (headache, rash, and either hypotension or tachycardia) after a single accidental infusion up to 80 mg of LEMTRADA. Dosages of LEMTRADA greater than those recommended may increase the intensity and/or duration of infusion reactions or its immune effects. There is no known antidote for alemtuzumab overdosage.

Table 1: Adverse Reactions in the Pooled 2-Year Active-Controlled Studies in Patients with Relapsing-Remitting Multiple Sclerosis (continued)

<table>
<thead>
<tr>
<th></th>
<th>LEMTRADA (N=811)</th>
<th>Interferon beta-1a 44 mcg (N=289)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in CD8 lymphocytes</td>
<td>6 2</td>
<td>6 6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 4</td>
<td>5 4</td>
</tr>
<tr>
<td>Decrease in T-lymphocyte count</td>
<td>5 3</td>
<td>5 2</td>
</tr>
<tr>
<td>Erythema</td>
<td>5 2</td>
<td>5 2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5 2</td>
<td>5 2</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5 2</td>
<td>5 2</td>
</tr>
<tr>
<td>Neck pain</td>
<td>5 2</td>
<td>5 2</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>5 1</td>
<td>5 1</td>
</tr>
</tbody>
</table>
Alectuzumab is a recombinant humanized IgG1 kappa monoclonal antibody directed against the cell surface glycoprotein, CD52. Alectuzumab has an approximate molecular weight of 150 kD. Alectuzumab is produced in mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium containing neomycin. Neomycin is not detectable in the final product.

Lemtrada (alemtuzumab) injection is a sterile, clear and colorless to slightly yellow, solution (pH 7.2 ± 0.2) for intravenous infusion.

Each 1 mL of solution contains 10 mg alectuzumab, dibasic sodium phosphate (1.15 mg), disodium edetate dihydrate (0.0187 mg), polyborate 80 (0.1 mg), potassium chloride (0.2 mg), potassium oxalate potassium (0.2 mg), sodium chloride (6 mg), and Water for Injection, USP.

11 DESCRIPTION

11.1 Mechanism of Action

The precise mechanism by which alectuzumab exerts its therapeutic effects in multiple sclerosis is unknown but is presumed to involve binding to CD52, a cell surface antigen present on T and B lymphocytes, and on natural killer cells, monocytes, and macrophages. Following cell surface binding to T and B lymphocytes, alectuzumab results in antibody-dependent cellular cytosis and complement-mediated lysis.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lemtrada depletes circulating T and B lymphocytes after each treatment course. In clinical trials, the lowest cell counts occurred 1 month after a course of treatment at the time of the first post-treatment blood count. Lymphocyte counts then increased over time; B cell counts usually recovered within 6 months; T cell counts increased more slowly and usually remained below baseline 12 months after treatment. Approximating 60% of patients had total lymphocyte counts below the lower limit of normal 6 months after each treatment course and 20% had counts below the lower limit of normal after 12 months. Reconstitution of the lymphocyte population varies for the different lymphocyte subtypes. At Month 1 in clinical trials, the mean CD4+ lymphocyte count was 40 cells per microliter and, at Month 12, 278 cells per microliter. At 30 months, approximately half of patients had CD4+ lymphocyte counts that remained below the lower limit of normal.

Cardiac Electrophysiology

In a study of 53 MS patients, alectuzumab 12 mg per day for 5 days caused no changes in the QTc interval greater than 20 ms. An average 22 to 26 beats-per-minute increase in heart rate was observed for at least 2 hours after the first but not subsequent infusions.

12.2 Pharmacodynamics

Effects of Lemtrada on the Lymphocyte Population

Lemtrada depletes circulating T and B lymphocytes after each treatment course. In clinical trials, the lowest cell counts occurred 1 month after a course of treatment. The clinical outcome measures were the annualized relapse rate over 2 years and the time to confirmed disability progression, as defined in Study 1. The MRI outcome measure was the change in T2 lesion volume.

Study 1 was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously three times a week) controlled study in patients with RRMS. Patients entering Study 1 had EDSS scores of 3 or less and no prior treatment for multiple sclerosis.

Patients were randomized to receive Lemtrada (n=426) or interferon beta-1a (n=202). At baseline, the mean age was 35 years, the mean disease duration was 4.5 years, and the mean EDSS score was 2.7.

The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression. Confirmed disability progression was defined as at least a 1-point increase above baseline EDSS (1.5 point increase for patients with baseline EDSS of 0) sustained for 6 months. The MRI outcome measure was the change in T2 lesion volume.

The annualized relapse rate was significantly lower in patients treated with Lemtrada than in patients who received interferon beta-1a. Time to onset of 6-month confirmed disability progression was significantly delayed with Lemtrada treatment compared to interferon beta-1a. There was no significant difference between the treatment groups for the change in T2 lesion volume. The results of Study 1 are shown in Table 2 and Figure 1.

Study 2 was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously three times a week) controlled study in patients with RRMS. Patients entering Study 2 had EDSS scores of 3 or less and no prior treatment for multiple sclerosis.

Patients were randomized to receive Lemtrada (n=376) or interferon beta-1a (n=187). At baseline, the mean age was 33 years, the mean disease duration was 2 years, and the mean EDSS score was 2.

The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression, as defined in Study 1. The MRI outcome measure was the change in T2 lesion volume. The annualized relapse rate was significantly lower in patients treated with Lemtrada than in patients who received interferon beta-1a. There was no significant difference between the treatment groups for the time to confirmed disability progression and for the primary MRI endpoint (change in T2 lesion volume). The results for Study 2 are shown in Table 3.

12.3 Pharmacokinetics

The pharmacokinetics of Lemtrada were evaluated in a total of 148 patients with relapsing forms of MS who received 12 mg/day on 5 consecutive days, followed by 12 mg/day on 3 consecutive days 12 months following the first treatment course.

Absorption

Serum concentrations increased with each consecutive dose within a treatment course, with the highest observed concentrations occurring following the last infusion of a treatment course. The mean maximum concentration was 304 ng/mL on Day 5 of the first treatment course, and 2276 ng/mL on Day 3 of the second treatment course.

Distribution

Lemtrada is largely confined to the blood and interstitial space with a central volume of distribution of 14.1 L.

Elimination

The elimination half-life was approximately 2 weeks and was comparable between courses. The serum concentrations were generally undetectable (<60 ng/mL) within approximately 30 days following each treatment course.

Specific Populations

Age, race, or gender had no effect on the pharmacokinetics of Lemtrada.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the carcinogenic or genotoxic potential of Lemtrada have not been conducted.

When Lemtrada (3 or 10 mg/kg IV) was administered to huCD52 transgenic male mice on 5 consecutive days prior to cohabitation with untreated wild-type females, no effect on fertility or reproductive performance was observed. However, adverse effects on sperm parameters (including abnormal morphology [detached/no head] and reduced total count and motility) were observed at both doses tested.

When Lemtrada (3 or 10 mg/kg IV) was administered to huCD52 transgenic female mice for 5 consecutive days prior to cohabitation with untreated wild-type males, there was a decrease in the average number of corpora lutea and implantation sites and an increase in postimplantation loss, resulting in fewer viable embryos at the higher dose tested.

14 CLINICAL STUDIES

The efficacy of Lemtrada was demonstrated in two studies (Study 1 and 2) that evaluated Lemtrada 12 mg in patients with relapsing-remitting multiple sclerosis (RRMS). Lemtrada was administered by intravenous infusion once daily over a 5-day course, followed one year later by intravenous infusion once daily over a 3-day course. Both studies included patients who had experienced at least 2 relapses during the 2 years prior to trial entry and at least 1 relapse during the year prior to trial entry. Neurological examinations were performed every 12 weeks and at the time of suspected relapse. Magnetic resonance imaging (MRI) evaluations were performed annually.

Study 1

Study 1 was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously three times a week) controlled study in patients with RRMS. Patients entering Study 1 had Expanded Disability Status Scale (EDSS) scores of 5 or less and had to have experienced at least one relapse during the year prior to trial entry. Neurological examinations were performed every 12 weeks and at the time of suspected relapse. Magnetic resonance imaging (MRI) evaluations were performed annually.

Patients were randomized to receive Lemtrada (n=426) or interferon beta-1a (n=202). At baseline, the mean age was 35 years, the mean disease duration was 4.5 years, and the mean EDSS score was 2.7.

The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression. Confirmed disability progression was defined as at least a 1-point increase above baseline EDSS (1.5 point increase for patients with baseline EDSS of 0) sustained for 6 months. The MRI outcome measure was the change in T2 lesion volume.

The annualized relapse rate was significantly lower in patients treated with Lemtrada than in patients who received interferon beta-1a. Time to onset of 6-month confirmed disability progression was significantly delayed with Lemtrada treatment compared to interferon beta-1a. There was no significant difference between the treatment groups for the change in T2 lesion volume. The results of Study 1 are shown in Table 2 and Figure 1.

Table 2: Clinical and MRI Results of Study 1

<table>
<thead>
<tr>
<th></th>
<th>Lemtrada</th>
<th>Interferon beta-1a 44 mcg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.26</td>
<td>0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative reduction</td>
<td>49%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with disability progression at Year 2</td>
<td>13%</td>
<td>21%</td>
<td>0.0084</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>42%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Percent of patients remaining relapse-free at Year 2</td>
<td>65%</td>
<td>47%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 1: Time to 6-month Confirmed Disability Progression (Study 1)

Table 3: Clinical and MRI Results of Study 2

<table>
<thead>
<tr>
<th></th>
<th>Lemtrada</th>
<th>Interferon beta-1a 44 mcg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.18</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative reduction</td>
<td>55%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with disability progression at Year 2</td>
<td>8%</td>
<td>11%</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table 3: Clinical and MRI Results of Study 2

<table>
<thead>
<tr>
<th></th>
<th>Lemtrada</th>
<th>Interferon beta-1a 44 mcg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.18</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative reduction</td>
<td>55%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with disability progression at Year 2</td>
<td>8%</td>
<td>11%</td>
<td>0.22</td>
</tr>
</tbody>
</table>
 Contains one single-dose vial that delivers 12 mg/1.2 mL (10 mg/mL). The vial stopper is not made with natural rubber latex.

16.2 Storage and Handling

Store LEMTRADA vials at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Store in original carton to protect from light.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Autoimmunity

- Advise patients to contact their healthcare provider promptly if they experience any symptoms of potential autoimmune disease. Give examples of important symptoms such as bleeding, easy bruising, petechiae, purpura, hematoma, edema, jaundice, or hemoptysis [see Warnings and Precautions (5.1)].

- Advise patients of the importance of monthly blood and urine tests for 48 months following the last course of LEMTRADA to monitor for signs of autoimmunity because early detection and prompt treatment can help prevent serious and potentially fatal outcomes associated with these events. Advise patients that monitoring may need to continue past 48 months if they have signs or symptoms of autoimmunity.

- Advise patients that LEMTRADA may cause hyperthyroidy or hypothyroidy disorders.

- Advise patients to contact their healthcare provider if they experience symptoms reflective of a potential thyroid disorder such as unexplained weight loss or gain, fast heartbeat or palpitations, nervousness, worsening tremor, eye swelling, constipa-

- Advise patients of childhood potential of the risks of pregnancy with concomitant

- Advise patients of childhood potential of the risks of pregnancy with concomitant

- Advise patients that yearly HPV screening is recommended

- Advise patients that they should talk to their healthcare provider before taking any vaccine after recent treatment with LEMTRADA [see Warnings and Precautions (5.16)].

- Inform patients that there have been reports of TTP in patients treated with LEMTRADA and that this is a potentially life-threatening condition [see Warnings and Precautions (5.13)].

Infusion Reactions

- Advise patients that infusion reactions can occur at the time of infusion or after they leave the infusion center [see Warnings and Precautions (5.1)].

- Instruct the patient to remain at the infusion center for at least 2 hours after each LEMTRADA infusion, or longer at the discretion of the healthcare provider. Advise patients that symptoms of infusion reactions may occur after they leave the infusion center and to report these symptoms to their healthcare provider.

- Advise patients that their healthcare provider will monitor vital signs, including blood pressure, before and during the infusion and to contact their healthcare provider promptly if they experience infusion reactions, which include swelling in the mouth or throat, difficulty breathing, weakness, abnormal heart rate (fast, slow, or irregular), chest pain, rash, facial drooping, sudden severe headache, weakness on one side of the body, difficulty with speech, or neck pain.

- Instruct patients that there have also been reports of rare but serious infusion reactions, including bleeding in the lung, chest tightness/pain or discomfort, heart attack, or stroke caused by blood vessels supplying the brain, which should be reported to your healthcare provider.

- Advise patients that reactions may occur following any of the doses during the treatment course. In the majority of cases, reactions occurred within 1–3 days of the infusion.

- Advise patients that LEMTRADA may increase the risk of a type of serious infection such as fever, sepsis, blood clots, organ failure, and death [see Warnings and Precautions (5.16)].

- Advise patients to contact their healthcare provider immediately if they experience symptoms such as fever, swollen glands, skin rash, or new neurologic symptoms such as mental status changes, ataxia, or seizures.

- Advise patients to complete any necessary immunizations at least 6 weeks prior to treatment with LEMTRADA [see Dosage and Administration (2.1)].

- Advise patients exposed to LEMTRADA during pregnancy that there is a pregnancy risk of LEMTRADA. The duration of increased risk for pregnancy with LEMTRADA is not known and continues for at least 6 months following the last dose of LEMTRADA, which may be life-threatening. Instruct the patient to contact their healthcare provider if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML and Aicardi, progression over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes [see Warnings and Precautions (5.17)].

- Advise patients to yearly HPV screening is recommended [see Warnings and Precautions (5.16)].

- Advise patients that acute acalculous cholecystitis.

- Advise patients to report symptoms of acute acalculous cholecystitis. These include abdominal pain, abdominal tenderness, fever, nausea, and vomiting [see Warnings and Precautions (5.18)].

- Advise patients that acupuncture has been reported in patients treated with LEMTRADA [see Warnings and Precautions (5.19)]. Advise patients to report symptoms of lung disease such as shortness of breath, cough, wheezing, chest pain or tightness, and hemoptysis [see Warnings and Precautions (5.18)].

- Advise patients that LEMTRADA may cause stress, illness, or fever, or they should immediately inform their physician.

- Advise patients exposed to LEMTRADA during pregnancy that there is a pregnancy safety surveillance program that monitors pregnancy outcomes [see Use in Specific

**LEMTRADA REMS Program**

- **LEMTRADA is available only through a restricted program called the LEMTRADA REMS Program [see Warnings and Precautions (5.5)]. Inform the patient of the following notable requirements:**
  - Patients and providers must be enrolled in the program.
  - Patients must comply with ongoing monitoring requirements.
  - Patients must report any side effects or symptoms to their doctor.

- **LEMTRADA is available only at certified infusion centers participating in the program. Therefore, provide patients with information on the LEMTRADA REMS Program in order to locate an infusion center.**

- **Advise patients to read the LEMTRADA REMS material for patients, LEMTRADA Treatment and Infusion Reactions Patient Guide.**

- **Instruct patients to carry the LEMTRADA REMS Patient Safety Information Card with them in case of an emergency.**

**Hemophagocytic Lymphohistiocytosis**

- **Inform patients that treatment with LEMTRADA may increase the risk of a type of excessive immune activation (hemophagocytic lymphohistiocytosis), which can be fatal if untreated, particularly if not diagnosed and treated early.**

- **Advise patients to contact their healthcare provider immediately if they experience symptoms such as fever, swollen glands, skin rash, or new neurologic symptoms such as mental status changes, ataxia, or seizures.**

- **In cases reported with LEMTRADA, treatment occurred within approximately thirteen months to thirty-three months following the initiation of treatment.**

**Thrombotic Thrombocytopenic Purpura**

- **Inform patients that there have been reports of TTP in patients treated with LEMTRADA and that this is a potentially life-threatening condition [see Warnings and Precautions (5.13)].**

- **Advise patients to get prompt medical attention if they experience symptoms of TTP such as fever, fatigue, pallor, purpura, jaundice, tachycardia, dyspnea, hematuria, dark-colored urine, decreased urine volume, abdominal pain, nausea, vomiting, or new neurological symptoms such as confusion, altered mental status, vision or speech changes, or seizures.**

**Infections**

- **Advise patients to contact their healthcare provider if they develop symptoms of severe infection such as fatigue, fever, or swollen glands [see Warnings and Precautions (5.16)].**

- **Advise patients to avoid or adequately heat foods that are potential sources of Listeria monocytogenes prior to receiving LEMTRADA and if they have had a recent course of LEMTRADA. The duration of increased risk for Listeria infection after LEMTRADA administration is not known and may continue for at least 6 months following the last infusion of LEMTRADA. Instruct the patient to contact their healthcare provider if they develop symptoms suggestive of Listia monocytogenes.**

- **Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in a patient who received LEMTRADA. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient to contact their healthcare provider if they develop any symptoms suggestive of PML.**

- **Advise patients to report symptoms of lung disease such as shortness of breath, cough, wheezing, chest pain or tightness, and hemoptysis [see Warnings and Precautions (5.18)].**

- **Inform patients that treatment with LEMTRADA may increase the risk of a type of serious infection such as fever, sepsis, blood clots, organ failure, and death [see Warnings and Precautions (5.16)].**

**Potentially Life-Threatening Use of CAMPATH**

- **Advise patients that LEMTRADA interferon

**Table 3: Clinical and MRI Results of Study 2 (continued)**

<table>
<thead>
<tr>
<th>LEMTRADA</th>
<th>interferon beta-1a 44 mcg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=376)</td>
<td>(N=187)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients remaining relapse-free at Year 2</td>
<td>78%</td>
<td>59%</td>
</tr>
<tr>
<td>MRI Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent change in T2 lesion volume from baseline</td>
<td>-9.3</td>
<td>-6.5</td>
</tr>
</tbody>
</table>
MEDICATION GUIDE
LEMTRADA® (lem-TRA-da)
(alemtuzumab), injection for intravenous infusion

Read this Medication Guide before you start receiving LEMTRADA and before you begin each treatment course. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about LEMTRADA?

1. Serious autoimmune problems. Some people receiving LEMTRADA develop a condition where the immune cells in your body attack other cells or organs in the body (autoimmunity) which can be serious and may cause death. Serious autoimmune problems may include:
   - **immune thrombocytopenic purpura (ITP).** LEMTRADA may cause the number of platelets in your blood to be reduced (ITP). ITP can cause severe bleeding that may cause life-threatening problems. Call your healthcare provider right away if you have any of the following symptoms:
     o easy bruising
     o bleeding from a cut that is hard to stop
     o coughing up blood
     o heavier menstrual periods than normal
     o bleeding from your gums or nose that is new or takes longer than usual to stop
     o small, scattered spots on your skin that are red, pink, or purple
   - **kidney problems.** LEMTRADA may cause a serious kidney problem called anti-glomerular basement membrane disease. If this happens and you do not get treated, anti-glomerular basement membrane disease can lead to severe kidney damage, kidney failure that needs dialysis, a kidney transplant, or death. Call your healthcare provider right away if you have any of the following symptoms:
     o swelling of your legs or feet
     o blood in the urine (red or tea-colored urine)
     o decrease in urine
     o fatigue
     o coughing up blood
   Side effects may happen while you receive LEMTRADA and for 4 years after you stop receiving LEMTRADA. Your healthcare provider will order blood and urine tests before you receive, while you are receiving, and every month for 4 years after you receive your last LEMTRADA infusion. You may need to continue these blood and urine tests after 4 years if you have any autoimmune signs or symptoms. The blood and urine tests will help your healthcare provider watch for signs and symptoms of serious autoimmune problems.
   It is important to have your blood and urine tested, even if you are feeling well and do not have any symptoms from LEMTRADA and your multiple sclerosis. This may help your healthcare provider find any problems early.

2. Serious infusion reactions. LEMTRADA can cause serious infusion reactions that may cause death. Serious infusion reactions may happen while you receive, or up to 24 hours or longer after you receive LEMTRADA.

   You will receive your infusion at a healthcare facility with equipment and staff trained to manage infusion reactions. You will be watched while you receive and for at least 2 hours after you receive LEMTRADA. It is important that you stay at the infusion center for at least 2 hours after your infusion is finished or longer if your healthcare provider decides you need to stay longer. If a serious infusion reaction happens while you are receiving LEMTRADA, your infusion may be stopped.

   Tell your healthcare provider right away if you have any of the following symptoms of a serious infusion reaction during the infusion, and after you have left the healthcare facility:
   - swelling in your mouth or throat
   - trouble breathing
   - weakness
   - fast, slow, or irregular heartbeat
   - chest pain
   - rash

   Side effects may happen while you receive LEMTRADA and for 4 years after you stop receiving LEMTRADA. Your healthcare provider will order blood and urine tests before you receive, while you are receiving, and every month for 4 years after you receive your last LEMTRADA infusion. You may need to continue these blood and urine tests after 4 years if you have any autoimmune signs or symptoms. The blood and urine tests will help your healthcare provider watch for signs and symptoms of serious autoimmune problems.

3. Stroke and tears in your arteries that supply blood to your brain (carotid and vertebral arteries). Some people have had serious and sometimes deadly strokes and tears in their carotid or vertebral arteries within 3 days of receiving LEMTRADA. Get help right away if you have any of the following symptoms that may be signs of a stroke or tears in your carotid or vertebral arteries:
   - drooping of parts of your face
   - sudden severe headache
   - neck pain
   - weakness on one side
   - difficulty with speech

4. Certain cancers. Receiving LEMTRADA may increase your chance of getting some kinds of cancers, including thyroid cancer, skin cancer (melanoma), and blood cancers called lymphoproliferative disorders and lymphoma. Call your healthcare provider if you have the following symptoms that may be a sign of thyroid cancer:
You should have your skin checked before you start receiving LEMTRADA and each year while you are receiving treatment to monitor symptoms of skin cancer.

**Because of your risk of autoimmunity, infusion reactions, and the risk of some kinds of cancers, LEMTRADA is only available through a restricted program called the LEMTRADA Risk Evaluation and Mitigation Strategy (REMS) Program.** Call 1-855-676-6326 to enroll in the LEMTRADA REMS Program.

- You and your healthcare provider must be enrolled in the LEMTRADA REMS Program.
- LEMTRADA can only be given at a certified healthcare facility that participates in the LEMTRADA REMS Program. Your healthcare provider can give you information on how to find a certified healthcare facility.
- Read the **LEMTRADA Treatment and Infusion Reactions Patient Guide** after you are enrolled in the program.
- Carry your LEMTRADA REMS Patient Safety Information Card with you in case of an emergency.

**What is LEMTRADA?**
LEMTRADA is a prescription medicine used to treat relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Since treatment with LEMTRADA can increase your risk of getting certain conditions and diseases, LEMTRADA is generally prescribed for people who have tried 2 or more MS medicines that have not worked well enough. LEMTRADA is not recommended for use in patients with clinically isolated syndrome (CIS). It is not known if LEMTRADA is safe and effective for use in children under 17 years of age.

**Who should not receive LEMTRADA?**

**Do not receive LEMTRADA if you:**
- are allergic to alemtuzumab or to any of the inactive ingredients in LEMTRADA. See the end of this Medication Guide for a complete list of ingredients in LEMTRADA.
- are infected with human immunodeficiency virus (HIV)
- have an active infection

**What should I tell my healthcare provider before receiving LEMTRADA?**
Before receiving LEMTRADA, tell your healthcare provider if you:
- have bleeding problems.
- have thyroid problems.
- have kidney problems.
- have a recent history of infection.
- are taking a medicine called CAMPATH®. Alemtuzumab, the active ingredient in LEMTRADA, is the same drug as CAMPATH.
- have received a live vaccine in the past 6 weeks before receiving LEMTRADA or plan to receive any live vaccines. Ask your healthcare provider if you are not sure if your vaccine is a live vaccine.
- are pregnant or plan to become pregnant. LEMTRADA may harm your unborn baby.
  - There is a pregnancy surveillance program for people who are exposed to LEMTRADA during pregnancy. The purpose of the program is to collect information about the health of pregnant people exposed to LEMTRADA and their babies. If you become pregnant, inform your healthcare provider.
- you should use birth control while receiving LEMTRADA and for 4 months after your course of treatment.
- are breastfeeding or plan to breastfeed. It is not known if LEMTRADA passes into your breast milk. You and your healthcare provider should decide if you should receive LEMTRADA or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. LEMTRADA and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take medicines that increase your chance of getting infections, including medicines used to treat cancer or to control your immune system.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

**How will I receive LEMTRADA?**
- LEMTRADA is given through a needle placed in your vein (IV infusion).
- It takes about 4 hours to receive a full dose of LEMTRADA each day.
- You will receive LEMTRADA over 2 or more treatment courses.
- You will receive LEMTRADA for 5 days in a row (consecutive) for the first treatment course and then for 3 days in a row (consecutive) about 1 year later for your second treatment course.
- Additional LEMTRADA treatment courses, if needed, may be given for 3 days in a row (consecutive) at least 1 year after the prior treatment course.

**What are the possible side effects of LEMTRADA?** LEMTRADA may cause serious side effects including:

- see “What is the most important information I should know about LEMTRADA?”
- thyroid problems. Some people who receive LEMTRADA may get thyroid problems including an overactive thyroid (hyperthyroidism) or an underactive thyroid (hypothyroidism). Your healthcare provider will do blood tests to check how your thyroid is working. Call your healthcare provider if you have any of the symptoms of thyroid problems.
  - Symptoms of hyperthyroidism may include:
    - excessive sweating
    - unexplained weight loss
    - fast heartbeat
    - eye swelling
    - nervousness

- other infections including pneumonia, and meningitis.

- other side effects including:
  - skin cancer.
  - symptoms of skin cancer.
  - pain in the front of your neck
  - hoarseness or other voice changes that do not go away

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Symptoms of hypothyroidism may include:
- unexplained weight gain
- feeling cold
- worsening tiredness
- constipation

**low blood counts (cytopenias).** LEMTRADA may cause a decrease in some types of blood cells. Some people with these low blood counts have increased infections. Symptoms of cytopenias may include:
- weakness
- chest pain
- yellowing of the skin or whites of eyes (jaundice)
- dark urine
- fast heartbeat

Your healthcare provider will do blood tests to check for cytopenias. Call your healthcare provider right away if you have symptoms listed above.

**inflammation of the liver.** Call your healthcare provider right away if you have symptoms such as unexplained nausea, stomach pain, tiredness, loss of appetite, yellowing of skin or whites of eyes, or bleeding or bruising more easily than normal.

**hemophagocytic lymphohistiocytosis (HLH).** LEMTRADA may increase the risk of a type of overactivity of the immune system (hemophagocytic lymphohistiocytosis) that can be fatal, especially if not diagnosed and treated early. Call your healthcare provider right away if you have symptoms such as fever, swollen glands, skin rash, or new nervous system problems, such as seizures, changes in your thinking or level of alertness, or new or worsening unsteadiness or trouble walking. These symptoms have happened in people taking LEMTRADA about 13 months to 33 months after they started taking LEMTRADA.

**adult onset still’s disease (AOSD).** Adult onset still’s disease (AOSD) is a rare condition that can cause a high fever lasting more than 1 week, pain, stiffness with or without swelling in multiple joints, and/or a skin rash. If you experience a combination of these symptoms, contact your healthcare provider immediately.

**thrombotic thrombocytopenic purpura (TTP).** Thrombotic thrombocytopenic purpura (TTP) can occur with LEMTRADA. TTP is a blood clotting problem where blood clots can form in blood vessels anywhere in the body. TTP needs to be treated in a hospital right away, because it can cause death. Get medical help right away if you have any of these symptoms:
- purplish spots (called purpura) on the skin or in the mouth (mucous membranes) due to bleeding under the skin
- your skin or the whites of your eyes are yellow (jaundice)
- you feel tired or weak
- your skin looks very pale
- fever
- fast heart rate or feeling short of breath
- headache
- speech changes
- confusion
- vision changes
- seizure
- low amount of urine or dark urine, or urine that has blood in it
- stomach area (abdominal) pain
- nausea, vomiting, or diarrhea

**autoimmune encephalitis (AIE).** Autoimmune encephalitis (AIE), a brain disorder, can occur after receiving LEMTRADA and may include symptoms that may seem like an MS relapse. Call your healthcare provider right away if you have any of the following symptoms:
- personality changes
- mood changes
- seeing things that are not there (hallucinations)
- agitation
- short term memory loss
- confusion
- movement disorders
- seizure

**bleeding disorder (acquired hemophilia A).** LEMTRADA may cause a bleeding disorder called acquired hemophilia A. Call your healthcare provider right away if you have any of the following symptoms:
- bruising
- nose bleeds
- painful or swollen joints
- bleeding from a cut that may take longer than usual to stop
- blood in urine
- dark or bloody stools
• **serious infections.** LEMTRADA may cause you to have serious infections while you receive and after receiving a treatment course. Serious infections may include:
  - **listeria.** People who receive LEMTRADA have an increased chance of getting an infection caused by the bacteria, *listeria*, which can lead to significant complications or death. Avoid foods that may be a source for *listeria* (for example, deli meat, unpasteurized milk and cheese products, soft cheeses, or undercooked meat, seafood or poultry) or make sure that the food you eat which may contain *listeria* is heated well if you receive treatment with LEMTRADA.
  - **herpes viral infections.** Some people taking LEMTRADA have an increased chance of getting herpes viral infections. Your healthcare provider will prescribe medicines to reduce your chances of getting these infections. Take these medicines exactly as your healthcare provider tells you to.
  - **human papilloma virus (HPV).** Females have an increased chance of getting a cervical HPV infection. If you are a female, you should have an HPV screening each year.
  - **tuberculosis.** Your healthcare provider should check you for tuberculosis before you receive LEMTRADA.
  - **fungal infections.**

Call your healthcare provider right away if you have symptoms of a serious infection, such as fever or swollen glands. You may need to go to the hospital for treatment if you get a serious infection. It is important to tell the healthcare providers that you have received LEMTRADA. Talk to your healthcare provider before you get vaccinations after receiving LEMTRADA. Certain vaccinations may increase your chances of getting infections.

• **Progressive multifocal leukoencephalopathy (PML).** A rare brain infection that usually leads to death or severe disability has been reported with LEMTRADA. Symptoms of PML get worse over days to weeks. It is important that you call your doctor right away if you have any new or worsening medical problems that have lasted several days, including problems with:
  - thinking
  - eyesight
  - strength
  - balance
  - weakness on 1 side of your body
  - using your arms or legs

• **Inflammation of the gallbladder without gallstones (acalculous cholecystitis).** LEMTRADA may increase your chance of getting inflammation of the gallbladder without gallstones, a serious medical condition that can be life-threatening. Call your healthcare provider right away if you have any of the following symptoms of acalculous cholecystitis, which may include:
  - stomach pain or discomfort
  - fever
  - nausea or vomiting

• **swelling of lung tissue (pneumonitis).** Some people have had swelling of the lung tissue while receiving LEMTRADA. Call your healthcare provider right away if you have the following symptoms:
  - shortness of breath
  - cough
  - wheezing
  - chest pain or tightness
  - coughing up blood

The most common side effects of LEMTRADA include:

- rash
- headache
- thyroid problems
- fever
- swelling of your nose and throat (nasopharyngitis)
- nausea
- urinary tract infection
- feeling tired
- trouble sleeping
- upper respiratory tract infection
- herpes viral infection
- hives
- itching
- fungal infection
- joint pain
- pain in your arms or legs
- back pain
- diarrhea
- sinus infection
- mouth pain or sore throat
- tingling sensation
- dizziness
- stomach pain
- sudden redness in face, neck, or chest
- vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of LEMTRADA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

**General information about the safe and effective use of LEMTRADA.**

This Medication Guide summarizes the most important information about LEMTRADA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LEMTRADA that is written for health professionals.

For more information, go to www.LemtradaREMS.com or call Genzyme at 1-855-676-6326.

**What are the ingredients in LEMTRADA?**

**Active ingredient:** alemtuzumab

**Inactive ingredients:** dibasic sodium phosphate, disodium edetate dihydrate, polysorbate 80, potassium chloride, potassium dihydrogen phosphate, sodium chloride, and Water for Injection, USP.