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

WARNING: AUTOINMUNITY, INFUSION REACTIONS, STROKE, 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)

• 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)

Recent Major Changes

Boxed Warning

Indications and Usage (1)

Dosage and Administration (2.3)

Dosage and Administration (2.6)

Warnings and Precautions (5.1, 5.2, 5.3, 5.7)

Warnings and Precautions (5.2)

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Recent Major Changes

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)]. 

Limitations of Use:

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

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

Revised: 10/2019

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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
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.

- 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. Informed patients that they should report symptoms that occur during and after each infusion because they may indicate a need for prompt medical intervention.

2.6 Laboratory Testing and Monitoring to Assess Safety
Measure the urine protein to creatinine ratio prior to initiation of treatment. Conduct the following laboratory tests at baseline and at periodic intervals until 48 months after 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)
- Serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and total bilirubin levels (prior to treatment initiation and periodically thereafter)

Conduct baseline and yearly skin exams to monitor for melanoma.

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*Sections or subsections omitted from the full prescribing information are not listed
patients. During postmarketing use, cases of vasculitis, autoimmune hepatitis [see Warnings and Precautions (5.7)], and Guillain-Barré syndrome have been reported [see Adverse Reactions (6.5)].

Chronic inflammatory demyelinating polyradiculoneuropathy has been reported in the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL), as well as other autoimmune 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 autoimmunity formation with LEMTRADA.

Measure the uric acid to creatinine ratio prior to initiation of treatment. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts before starting treatment and then at monthly intervals until 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 (5.5)].

5.2 Infusion Reactions

Infusion reactions may occur despite pretreatment. During postmarketing use, cases of pulmonary alveolar hemorrhage and myocardial ischemia have been reported with onset within 48 hours of LEMTRADA infusion. Cases of severe (including fatal) neutropenia have been reported with 2 months of LEMTRADA infusion. Some cases resolved with receiving granulocyte-colony stimulating factor treatment. Mild to moderate decreases in platelet counts, starting at the time of alemtuzumab infusion and often resolving without treatment, have been reported. Other serious and sometimes fatal infusion reactions (e.g., hypoxia, syncope, acute cardiac distress syndrome, respiratory arrest, myocardial infarction, acute cardiac insufficiency, 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.

5.3 Stroke and Cervicocephalic 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 1 day [see Warnings and Precautions (5.3)]. Premedicate patients with corticosteroids immediately prior to LEMTRADA infusion 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. 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 treatment for treatment emergencies.

5.4 Lymphoproliferative Disorders and Lymphoma

EMTRADA 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 alpha-treated group. However, patients with thyroid disorders are treated 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 consider the risk of thyroid cancer in patients with 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. In postmarketing cases, some LEMTRADA-treated patients with anti-GBM disease developed end-stage renal disease requiring dialysis or renal transplantation. Urgent evaluation and treatment is required, because early treatment can improve the preser-

5.7 Glomerular Nephropathies Including Anti-Glomerular Basement Membrane Disease

Glanular nephropathies occurred in 0.3% of LEMTRADA-treated patients in MS clinical studies. There were 3 cases of membranous glomerulonephritis and 2 cases of anti-GBM disease. In postmarketing cases, some LEMTRADA-treated patients with anti-GBM disease developed end-stage renal disease requiring dialysis or renal transplantation. Urgent evaluation and treatment is required, because early treatment can improve the preser-

5.8 Thyroid Disorders

Thyroid 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, and goiter. Graves’ ophthalmopathy with decreased vision, eye pain, and exophthalmos occurred in 2% of LEMTRADA-treated patients. 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 thyroid disease. LEMTRADA-treated patients, 5.8% 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.

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

5.9 Other Autoimmune Cytopenias

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.

In postmarketing studies, 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 the postmarketing setting. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with LEMTRADA as appropriate.

Prior to starting treatment with LEMTRADA, obtain serum transaminases (ALT and AST) and total bilirubin levels. Obtain transaminase levels and total bilirubin levels periodically until 48 months after the last dose.

5.11 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, sinusitis, herpetic infections, influenza, and bronchitis. Serious infections occurred in 3% 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, pneumonitis, meningitis, and tooth infection.

Do not administer live viral vaccines following 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.

Consider delaying LEMTRADA administration in patients with active infection until the infection is fully controlled.

Concomitant use of LEMTRADA with antineoplastic or immunosuppressive therapies could increase the risk of immunosuppression.

Opportunistic Infections

In the postmarketing setting, serious, sometimes fatal, opportunistic infections have been reported in patients taking LEMTRADA, including aspergillosis, coccidioidomycosis, histoplasmosis, Pneumocystis jiroveci pneumonia, nocardiosis and cytomegalovirus infections.

Listeria Monocytogenes Infections

Listeria monocytogenes infections (e.g., meningitis, encephalitis, sepsis, and gastrointes-
tinal) including fulminant Listeria meningencephalitis, have occurred in LEMTRADA-treated patients. Listeria infections have occurred as early as 3 days after treatment and up to 8 months after the last LEMTRADA dose. The duration of increased risk for Listeria infection of LEMTRADA treatment is unknown.

Advise patients to avoid or eat adequately heated foods that are potential sources of Listeria monocytogenes (e.g., deli meat, dairy products made with unpasteurized milk, soft cheeses, or undercooked meat, seafood, or poultry). Instruct these patients to take preventive action to avoid infections in the treatment of patients with LEMTRADA.

Infections in Non-MS Patients

The rates of infections were generally higher in LEMTRADA-treated patients compared to patients treated with interferon beta-1a (5% or higher) in controlled clinical studies in MS.

Infections in Non-MS Patients

During postmarketing use, serious and sometimes fatal viral, bacterial, protozoan, and fungal infections, including infections with latent infections, 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.

Hepatitis B vaccines are available on the association of LEMTRADA with Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) reactivation because patients with evidence of active or chronic infections were excluded from the clinical studies. Consider screening patients at high risk of HBV and/or HCV infection before initiation of LEMTRADA and exercise caution in patients treated with LEMTRADA to patients receiving HBV or HCV. As these patients may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status.

5.12 Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) has occurred in a patient with MS 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 treatment of 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 immuno-modulatory 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.

Toxicity may be less than expected, as a first sign or symptom suggestive of PML, withholding LEMTRADA and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress 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 perception leading to confusion. In addition, focal neurological signs and symptoms of increased intracranial pressure may occur. MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to an early diagnosis of PML, if present. Following discontinuation of another MS medication associated with PML, lower PML-related mortality and morbidity have been reported in patients who were initially asymptomatic at diagnosis compared to patients who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

5.13 Acute Acalculous Cholecystitis

LEMTARA may increase the risk of acute acalculous cholecystitis. In controlled clinical studies, 2.0% of LEMTRADA-treated MS patients developed acute acalculous cholecystiti-
tis, compared to 0% of patients treated with interferon beta-1a. During postmarketing use, 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 the last LEMTRADA dose. In most cases, signs and symptoms of cholecystitis started within 1 month of exposure to LEMTRADA monocytogenes infections. Symptoms of Listeria infection include fever, chills, diarrhea, nausea, vomiting, headache, pains in joints and muscles, neck stiffness, difficulty walking, mental status changes, coma, and other neurologic changes. As is the case with many infections, treatment cannot always prevent mortality and morbidity related to Listeria infections. Therefore, advise patients to watch for symptoms of Listeria infection and seek prompt medical help if symptoms occur.

Herpes Viral Infections

Herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections can occur at any time during LEMTRADA treatment. Both HSV and VZV infections can cause serious clinical syndromes, including atypical dissemination to internal organ systems, and can occasionally be fatal. Herpes zoster typically occurs in patients who have had a prior history of herpes zoster. Herpes zoster can cause severe pain for months to years after the acute episode. Herpes zoster infection is an example of a condition in which the risk of delayed, recurrent disease may be increased in patients treated with LEMTRADA.

Prevention of Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) Infections

For patients treated with LEMTRADA and herpes zoster, prophylaxis with acyclovir or valacyclovir may be considered. Prophylaxis with acyclovir should begin within 72 hours of zoster rash onset and continue at least 2 months after rash onset. Prophylaxis with acyclovir should begin when dermatomal skin symptoms first appear for patients without a prior history of herpes zoster. Prophylaxis with valacyclovir should begin when zoster rash onset and continue for at least 2 months after rash onset. Prophylaxis with valacyclovir should begin when skin symptoms first appear for patients without a prior history of herpes zoster. Prophylaxis should be considered for patients with a prior history of herpes zoster who develop new dermatomal skin symptoms during LEMTRADA treatment.

Prevention of Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) Infections

Herpes zoster prophylaxis should begin within 72 hours of rash onset and continue at least 2 months after rash onset.

5.15 Infections

In clinical studies, 6 of 1217 (0.5%) LEMTRADA-treated patients had pneumonias of varying severity, including cases of hyper-expanded or cavity-forming pneumonias. Although both fibrosis occurred in clinical studies. Patients should be advised to report symptoms of pneumonias, which may include shortness of breath, cough, wheezing, chest pain or tightness, and hemo-

5.16 Drug-Product Interactions

5.16.1 Drug Products with Same Active Ingredient

LEMTARA contains the same active ingredient (alemtuzumab) found in CAMPATH®. If LEMTRADA is considered for use in a patient who has previously received CAMPATH, exercise increased vigilance for additive and long-lasting effects on the immune system. Unlike CAMPATH, LEMTRADA has a shorter half-life and a lower systemic exposure than CAMPATH.

5.17 Adverse Drug Reactions

5.17.1 General Considerations

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

- Autoimmune enteritis [see Boxed Warning and Warnings and Precautions (5.1)]
- Infection Reactions [see Boxed Warning and Warnings and Precautions (5.2)]
- Stroke and Cerebrovascular Arterial Dissection [see Warnings and Precautions (5.3)]
- Malignancies [see Warnings and Precautions (5.4)]
- Immune Thrombocytopenia [see Warnings and Precautions (5.5)]
- Autoimmune Hemolytic Anemia [see Warnings and Precautions (5.6)]
- Hypogammaglobulinemia [see Warnings and Precautions (5.7)]
- Thyroid Disorders [see Warnings and Precautions (5.8)]
- Other Autoimmune Cytopenias [see Warnings and Precautions (5.9)]
- Autoimmune Hepatitis [see Warnings and Precautions (5.10)]
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), overall, 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 in interferon beta-1a) were 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.

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>LEMTRADA (N=811)</th>
<th>interferon beta-1a 44 mcg (N=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>53%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>52%</td>
<td>23%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29%</td>
<td>9%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>Nausea</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Herpes viral infection</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Thyroid gland disorders</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12%</td>
<td>9%</td>
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<tr>
<td>Pain in extremity</td>
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<td>9%</td>
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<tr>
<td>Back pain</td>
<td>12%</td>
<td>8%</td>
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<tr>
<td>Diarrhea</td>
<td>12%</td>
<td>6%</td>
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<tr>
<td>Sinusitis</td>
<td>11%</td>
<td>8%</td>
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<tr>
<td>Oropharyngeal pain</td>
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<td>5%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Chills</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<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>
</tbody>
</table>

6.2 Lymphopenia

Nearly all (99.9%) patients treated with LEMTRADA in MS clinical trials experienced lymphopenia. The lowest lymphocyte count 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 (range 0.02-2.30 × 10^9/L) and 0.32 (0.02-1.81 × 10^9/L) 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, 0.8% of patients in both the LEMTRADA and interferon beta-1a groups had events of attempted suicide or suicidal ideation. There were no completed suicides in either clinical study treatment group. Suicidal behavior or ideation occurred in patients with or without a history of a psychiatric or thyroid disorder. Advise patients to report immediately any symptoms of depression or suicidal ideation to the prescribing physician.

6.4 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The incidence of antibodies is highly dependent on the specificity and sensitivity of the assay. Additionally, the observed incidence of antibody (including inhibitory antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to LEMTRADA with the incidence of antibodies to other products may be misleading.

Using an enzyme-linked immunosorbent assay (ELISA) and a competitive binding assay, anti-alemtuzumab binding antibodies were detected in 62%, 67%, and 29% of LEMTRADA-treated patients, at months 1, 3, and 12 (Course 1) as well as 83%, 83%, and 75% of LEMTRADA-treated patients at months 13, 15, and 24 (Course 2). Samples that tested positive for binding antibodies were further evaluated for evidence of in vitro inhibition using a flow cytometry assay. Neutralizing antibodies were detected in 87%, 46%, and 5% of positive binding antibody patients at months 1, 3, and 12 (Course 1) as well as 94%, 86%, and 42% of positive binding antibody patients at months 13, 15, and 24 (Course 2). Anti-alemtuzumab antibodies were associated with decreased alemtuzumab concentration during Course 2, but not Course 1. Through 2 treatment courses, 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 adverse events. High titer anti-alemtuzumab antibodies, which were observed in 13 patients, were associated with incomplete lymphocyte depletion following a third or fourth treatment course, but there was no clear effect of anti-alemtuzumab antibodies on the clinical efficacy or safety profile of LEMTRADA.

6.5 Postmarketing Experience

The following adverse reactions have been identified during post approval use of alemtuzumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing Experience with LEMTRADA

Blood and Lymphatic System Disorders: Neutropenia, thrombocytopenia [see Warnings and Precautions (5.2)]
Cerebrovascular Disorders: Stroke, including hemorrhagic and ischemic stroke and coccidioidomycotic arterial dissection [see Warnings and Precautions (5.3)]
Gastrointestinal System Disorders: Cholelithiasis, including acalculous cholecystitis and acute acalculous cholecystitis [see Warnings and Precautions (5.13)]
Hepatobiliary Disorders: Autoimmune hepatitis [see Warnings and Precautions (5.10)]
Infections: Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.12)]
Immune System Disorders: Autoimmune hepatitis, vasculitis, Guillain-Barré syndrome [see Warnings and Precautions (5.1)], hemophagocytic lymphohistiocytosis
Pulmonary System Disorders: Pulmonary alveolar hemorrhage [see Warnings and Precautions (5.2)]

Postmarketing Experience with CAMPATH

CAMPATH is approved for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) and is generally given at higher and more frequent doses (e.g., 30 mg) than recommended in the treatment of MS.

Cardiac Disorders: Congestive heart failure, cardiomyopathy, and decreased ejection fraction in non-MS patients previously treated with potentially cardiotoxic agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LEManualTRA during pregnancy. Physicians are encouraged to register patients by calling 1-866-758-2990.

Risk Summary

There are no adequate data on the developmental risk associated with the use of LEManualTRA in pregnant women. LEManualTRA was embryolthal in pregnant huCD52 transgenic mice when administered during organogenesis [see Animal Data]. Auto- antibodies may develop after administration of LEManualTRA. Placental transfer of anti-thyroid antibodies resulting in neonatal Graves' disease has been reported. In the U.S., a general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown. Clinical Considerations

LEManualTRA induces persistent thyroid disorders [see Warnings and Precautions (5.8)]. Untreated hypothyroidism in pregnant women increases the risk for miscarriage and may have effects on the fetus including mental retardation and dwarfism. In mothers with Graves' disease, maternal thyroid stimulating hormone receptor antibodies can be transferred to a developing fetus and can cause neonatal Graves' disease. In a patient who developed Graves' disease after treatment with alemtuzumab, placental transfer of anti-thyrotropin receptor antibodies resulted in neonatal Graves' Disease with thyroid storm in her infant who was born 1 year after alemtuzumab dosing [see Warnings and Precautions (5.11)].

Data

Animal Data

When LEManualTRA was administered to pregnant huCD52 transgenic mice during organogenesis (gestation days [GD] 6-10 or GD 11-15) at doses of 3 or 10 mg/kg IV, no teratogenic effects were observed. However, there was an increase in embryolthaleness (increased postimplantation loss and the number of dams with all fetuses dead or resorbed) in pregnant animals dosed during GD 11-15. In a separate study in pregnant huCD52 transgenic mice administered LEManualTRA during organogenesis (GD 6-10 or GD 11-15) at doses of 3 or 10 mg/kg IV, decreases in B- and T-lymphocyte populations were observed in the offspring at both doses tested. In pregnant huCD52 transgenic mice administered LEManualTRA at doses of 3 or 10 mg/kg/day during organogenesis and lactation: 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. 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.

8.2 Lactation

Risk Summary

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. Alemtuzumab was detected in the milk of huCD52 transgenic mice administered LEManualTRA [see Animal Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEManualTRA and any potential adverse effects on the breastfed child from LEManualTRA or from the underlying maternal conditions.

Data

Animal Data

Alemtuzumab was detected in the milk of lactating huCD52 transgenic mice following intravenous administration of LEManualTRA at a dose of 10 mg/kg on postpartum days 8-12. Serum levels of alemtuzumab were similar in lactating mice and offspring on postpartum Day 12, and were associated with evidence of pharmacological activity (decrease in lymphocyte counts) in the offspring.

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

In huCD52 transgenic mice, administration of LEManualTRA 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. Use of LEManualTRA is not recommended in pediatric patients due to the risks of autoimmunity, infusion reactions, and stroke, and because it may increase the risk of malignancies (thyroid, melanoma, lymphoproliferative disorders, and lymphoma) [see Warnings and Precautions (5.1), (5.2), (5.3), (5.4)].

8.5 Geriatric Use

Clinical studies of LEManualTRA 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 sinus tachycardia) after a single accidental infusion up to 60 mg of LEManualTRA. Doses of LEManualTRA 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.

11 DESCRIPTION

Alemtuzumab is a recombinant humanized IgG1 kappa monoclonal antibody directed against the CD52 antigen on lymphocytes and certain natural killer cells. CD52 is a cell surface glycoprotein found on most hematopoietic cells. Alemtuzumab has an approximate molecular weight of 150 kD. Alemtuzumab is produced in mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium containing neomycin. Neomycin is not detectable in the final product.

LEManualTRA (alemtuzumab) injection is a sterile, clear and colorless to slightly yellow, solution (pH 7.2 ± 0.2) for intravenous infusion. Each mL of solution contains 10 mg alemtuzumab, dibasic sodium phosphate (1.15 mg), disodium edetate dihydrate (0.0187 mg), polysorbate 80 (0.1 mg), potassium chloride (0.2 mg), potassium dihydrogen phosphate (0.2 mg), sodium chloride (0.8 mg), and Water for Injection USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which alemtuzumab 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, alemtuzumab results in antibody-dependent cell-mediated cytotoxicity and complement-mediated lysis.

12.2 Pharmacodynamics

Effects of LEManualTRA on the Lymphocyte Population

LEManualTRA 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 12 mg course (the first treatment course). During the first treatment course, lymphocyte counts decreased over time: T cell counts usually recovered within 6 months; T cell counts increased more slowly and usually remained below baseline 12 months after treatment. Approximately 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, 270 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 33 MS patients, alemtuzumab 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 from baseline on day 1 for at least 2 hours after the first but not subsequent infusions.

12.3 Pharmacokinetics

The pharmacokinetics of LEManualTRA 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 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 3014 ng/mL on Day 5 of the first treatment course, and 2276 ng/mL on Day 3 of the second treatment course. Distribution

LEManualTRA 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 LEManualTRA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

When LEManualTRA (3 or 10 mg/kg IV) was administered to huCD52 transgenic male mice or female mice during the reproductive period 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 LEManualTRA (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 STUDY

The efficacy of LEManualTRA was demonstrated in two studies (Study 1 and 2) that evaluated LEManualTRA 12 mg in patients with relapsing-remitting multiple sclerosis (RRMS). LEManualTRA 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 extended lymphoma 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 while on interferon beta or glatiramer acetate therapy.

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

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.
MEDICATION GUIDE
LEMTTRA® (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.

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, What You Need to Know About LEMTRADA Treatment: A Patient Guide and What You Need to Know About LEMTRADA Treatment and Infusion Reactions: A Patient Guide.

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

Advise patients to contact their healthcare provider if they develop symptoms of serious infection such as fever or swollen glands [see Warnings and Precautions (5.11)].

Advise patients to complete any necessary immunizations at least 6 weeks prior to treatment with LEMTRADA [see Dosage and Administration (2.1)]. Advise patients that they should talk to their healthcare provider before taking any vaccine after recent treatment with LEMTRADA [see Warnings and Precautions (5.1)].

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. Inform patients that Listeria infection can lead to significant complications or death [see Warnings and Precautions (5.11)].

Advise patients to take their prescribed medication for herpes prophylaxis as directed by their healthcare provider [see Warnings and Precautions (5.11)].

Advise patients that yearly HPV screening is recommended [see Warnings and Precautions (5.11)].

Progressive Multifocal leukoencephalopathy
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 of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress 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 (5.12)].

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 (5.13)].

Pneumonitis
Advise patients that pneumonitis has been reported in patients treated with LEMTRADA [see Warnings and Precautions (5.14)]. Advise patients to report symptoms of lung disease such as shortness of breath, cough, wheezing, chest pain or tightness, and hemoptysis.

Concomitant Use of CAMPATH
Advise patients that alemtuzumab is the same drug as CAMPATH for use in B-CLL. Patients should inform their healthcare provider if they have taken CAMPATH [see Warnings and Precautions (5.15)].

Pregnancy Exposure Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LEMTRADA during pregnancy [see Use in Specific Populations (8.1)].

Fetal Risk
Inform patients that LEMTRADA may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing age of the need for effective contraception during LEMTRADA treatment and for 4 months after a treatment course of LEMTRADA. Advise the patient that if she should nevertheless become pregnant, she should immediately inform her physician.

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Genzyme Corporation
Cambridge, MA 02142

US License Number: 1596

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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 lymphomas. Call your healthcare provider if you have the following symptoms that may be a sign of thyroid cancer:

- new lump
- swelling in your neck
- pain in the front of your neck
- hoarseness or other voice changes that do not go away

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 REMS “What You Need to Know About LEMTRADA Treatment: A Patient Guide” and “What You Need to Know About LEMTRADA Treatment and Infusion Reactions: A 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 infected with human immunodeficiency virus (HIV).

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.

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) 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
    - eye swelling
    - unexplained weight loss
    - nervousness
    - fast heartbeat
  - Symptoms of hypothyroidism may include:
    - unexplained weight gain
    - worsening tiredness
    - feeling cold
    - 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
  - dark urine
  - fast heartbeat
  - yellowing of the skin or whites of eyes (jaundice)
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.

- **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

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, polydextrose 80, potassium chloride, potassium dihydrogen phosphate, sodium chloride, and Water for Injection, USP.

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