FULL PRESCRIBING INFORMATION

1 INDICTIONS AND USAGE
LEMTRADA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

2 DOSAGE AND ADMINISTRATION

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

- First Treatment Course: 12 mg/day on 5 consecutive days (60 mg total dose)
- Second Treatment Course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course.

2.2 Testing and Procedures Prior to Treatment
Baseline laboratory tests are required prior to treatment with LEMTRADA [see Dosage and Administration (2.6)]. In addition, prior to starting treatment with LEMTRADA [see Warnings and Precautions (5.9)]:

- Complete any necessary vaccinations at least 6 weeks prior to treatment
- Determine whether patients have a history of varicella or have been vaccinated for varicella zoster virus (VZV). If not, test the patient for antibodies to VZV and consider vaccination for those who are antibody-negative. Administer treatment with LEMTRADA until 6 weeks after VZV vaccination.
- Perform tuberculin testing according to local guidelines.
- Instruct patients to avoid potential sources of Listeria monocytogenes.

2.3 Recommended Premedication and Concomitant Medication

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

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

2.4 Preparation Instructions

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

- Inspect LEMTRADA visually for particulate matter and discoloration prior to administration. Do not use if particulate matter is present or the solution is discolored. Do not freeze or shake vials prior to use.
- Withdraw 1.2 mL of LEMTRADA from the vial into a syringe using aseptic technique and inject into a 100 mL bag of sterile 0.9% Sodium Chloride, USP or 5% Dextrose in Water, USP.
- Gently invert the bag to mix the solution. Ensure the sterility of the prepared solution, because it contains no antimicrobial preservatives. Each vial is for single use only.

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

2.5 Infusion Instructions

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

Administer LEMTRADA in a setting in which equipment and personnel to appropriately manage anaphylaxis or serious infusion reactions are available [see Warnings and Precautions (5.4)]. Do not add or simultaneously infuse other drug substances through the same intravenous line. Do not administer as an intravenous push or bolus.

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

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

2.6 Laboratory Testing and Monitoring to Assess Safety

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Autoimmunity

Treatment with LEMTRADA can result in the formation of autoantibodies and increase the risk of serious autoimmunity mediated conditions. In clinical studies, LEMTRADA-treated patients experienced thyroid disorders (34%), immune thrombocytopenia (2%), and glomerular nephropathies (0.3%) [see Warnings and Precautions (5.5, 5.6, 5.7)]. Autoimmune hemolytic anemia and autoimmune pancytopenia, antibodies, and autoantibody formation with LEMTRADA. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts before starting treatment and then at monthly intervals for 48 months after the last dose of LEMTRADA to allow for early detection and treatment of autoimmune adverse reactions [see Dosage and Administration (2.6)]. After 48 months, testing should be performed based on clinical findings suggestive of autoimmunity.

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

5.2 Infusion Reactions

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

During postmarketing use, other serious and sometimes fatal infusion reactions included hypoxia, syncope, acute respiratory distress syndrome, respiratory arrest, myoccardial infarction, acute cardiac insufficiency, and cardiac arrest have been reported in the treatment of patients with B-CLL, as well as other disorders, generally at higher and more frequent doses than recommended in MS. An oncology patient treated with altemuzumab had fatal transfusion-associated graft-versus-host disease.

Infusion reactions 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. Screening for thyroid malignancies is recommended after the last treatment course of LEMTRADA.

5.3 Thyroid Cancer

During postmarketing use, additional autoimmune events including Guillain-Barré syndrome and crystalline demyelinating polyradiculoneuropathy have been reported in the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL), as well as other disorders, generally at higher and more frequent doses than recommended in MS. In B-CLL, the incidence rate of thyroid cancer was higher than expected, and some patients had severe hyperthyroidism.

5.4 Lymphoproliferative Disorders and Lymphoma

Cases of lymphoproliferative disorders and lymphoma have occurred in LEMTRADA-treated patients with MS, including a MALT lymphoma, Castleman’s Disease, and a fatality following treatment of non-Epstein Barr Virus-associated Burkitt’s lymphoma. There are postmarketing reports of Epstein Barr Virus-associated lymphoproliferative disorders, and malignancies (5.5, 5.6, 5.7). LEMTRADA may increase the risk of lymphoma, or lymphoid cells in the treatment of patients with LEMTRADA.

5.5 Autoimmune Hemolytic Anemia and Autoimmune Pancytopenia

Autoantibodies may be transferred from the mother to the fetus during pregnancy. A case of autoimmune hemolytic anemia and autoimmune pancytopenia, 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, and malignancies (5.5, 5.6, 5.7). LEMTRADA may increase the risk of lymphoma, or lymphoid cells in the treatment of patients with LEMTRADA.

5.6 Laboratory Testing and Monitoring to Assess Safety

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5.7 Malignancies

Thyroid Cancer

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6 WARNINGS AND PRECAUTIONS

Lymphoproliferative Disorders and Lymphoma

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LEMTRADA is available only through a restricted program under a REMS [see Warnings and Precautions (5.4)].
5.4 LEMTRADA REMS Program
LEMTRADA is available only through a restricted program under a REMS called the LEMTRADA REMS Program because of the risks of autoimmunity, infusion reactions, and malignancies [see Warnings and Precautions (5.1, 5.2, 5.3)]. Notable requirements of the LEMTRADA REMS Program include the following:

• Prescribers must be certified with the program by enrolling and completing training.
• Patients must enroll in the program and comply with ongoing monitoring requirements [see Dosage and Administration (2.6)].
• Pharmacies must be certified with the program and must only dispense to certified healthcare facilities. Pharmacies must be authorized to receive LEMTRADA.
• Healthcare facilities must enroll in the program and verify that patients are authorized before infusion of LEMTRADA. Healthcare facilities have on-site access to equipment and personnel trained to manage infusion reactions.

Further information, including a list of qualified healthcare facilities, is available at 1-855-676-9236.

5.5 Immune Thrombocytopenia
Immune thrombocytopenia (ITP) occurred in 2% of LEMTRADA-treated patients in clinical studies in MS. Patients treated with interferon beta-1a have a higher incidence of ITP compared to LEMTRADA-treated patients. Patients treated with interferon beta-1a should be closely monitored for development of ITP. If the patient develops ITP, prompt medical help should be sought.

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

Clinical manifestations of nephropathy may include elevated serum creatinine levels, hematuria, or proteinuria. Alveolar hemorraga manifested as hemoptysis is a common component of anti-GBM disease in published case reports. Obtain serum creatinine levels and urinalysis with cell counts prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of nephropathy. If clinically significant changes from baseline in serum creatinine, unexplained hematuria, or proteinuria are observed, perform further evaluation for nephropathies. Early detection and treatment of nephropathies may decrease the risk of poor outcomes.

5.7 Thyroid Disorders
Autoimmune thyroid disorders occurred in 34% of LEMTRADA-treated patients in clinical studies. Newly diagnosed thyroid disorders occurred throughout the uncontrolled clinical study follow-up period more than 7 years after the first LEMTRADA dose. Autoimmune thyroid disorders included Graves’ disease, hyperthyroidism and hypothyroidism. Graves’ ophthalmopathy with increased vision, eye pain, and eye symptoms was reported in 0.3% of LEMTRADA-treated patients. Two patients treated with LEMTRADA developed hypothyroidism and subsequently developed end-stage renal disease requiring renal transplantation. For patients testing positive in tuberculosis screening, treat by standard medical practice.

5.8 Other Autoimmune Cytophenias
Autoimmune cytophenias such as neutropenia (0.1%), thrombocytopenia (0.2%), and pancytopenia (0.2%) occurred in patients in clinical studies in MS. Severe neutropenia, thrombocytopenia, and 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 septic shock.

During postmarketing use, additional autoimmune cytophenias 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 than recommended in MS. Use CBC results to monitor for cytophenias. Prompt medical intervention is indicated if a cytophenia is confirmed.

5.9 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, sinustis, 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, gastritis, sepsis, pneumonia, hemorrhage, and ischemic stroke.

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 antineoplastics or immunosuppressive therapies could increase the risk of immunosuppression.

Herpes Viral Infections
No data 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 prescribing LEMTRADA to patients identified as carriers of HBV and/or HCV as these patients may be at risk of irreversible liver damage relative to a potential viral reactivation as a consequence of their pre-existing status.

5.10 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. In clinical 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 LEMTRADA infusion. Typical risk or predisposing factors such as concurrent critical illness were often 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.

5.11 Pneumonitis
No data are available on the association of LEMTRADA with pneumonitis 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 prescribing LEMTRADA to patients identified as carriers of HBV and/or HCV as these patients may be at risk of irreversible liver damage relative to a potential viral reactivation as a consequence of their pre-existing status.

5.12 Drug Products with Same Active Ingredient
LEMTRADA 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.
Most Common Adverse Reactions

In 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 (continued)

<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>
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<tr>
<td>Urinary tract infection</td>
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<td>8</td>
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<tr>
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<td>13</td>
</tr>
<tr>
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<td>15</td>
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<tr>
<td>Upper respiratory tract infection</td>
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</tr>
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<td>3</td>
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<tr>
<td>Urticaria</td>
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<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
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<td>2</td>
</tr>
<tr>
<td>Thyroid gland disorders</td>
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<td>3</td>
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<tr>
<td>Pain in extremity</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Abdominal pain</td>
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<td>Flushing</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Chest discomfort</td>
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</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 (range 0.22-0.30 × 10^9/L) and 0.32 (0.02-1.81 × 10^9/L) for treatment courses 1 and 2, respectively. Total lymphocyte counts reached 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 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. Using an enzyme-linked immunosorbent assay (ELISA) and a competitive binding assay, anti-alemtuzumab binding antibodies were detected in 62%, 67%, and 23% of LEMTRADA-treated patients, at months 1, 3, 12 (Course 1) as well as 85%, 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, 12 (Course 1) as well as 94%, 88%, 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. 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. The incidence of antibodies is highly dependent on the sensitivity and specificity 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.

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

Gastrointestinal System Disorders: Acute acalculous cholecystitis.

Postmarketing Experience with CAMPATH

CAMPATH is approved for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) and is generally administered 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 Category C

There are no adequate and well-controlled studies in pregnant women. LEMTRADA was embryolethal in pregnant huCD52 transgenic mice when administered during organogenesis. Auto-antibodies may develop after administration of LEMTRADA. Placental transfer of anti-thyroid antibodies resulting in neonatal Graves’ disease has been reported. LEMTRADA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

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, 12 (Course 1) as well as 94%, 88%, 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. 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. The incidence of antibodies is highly dependent on the sensitivity and specificity 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.

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Animal Data

When LEMTRADA 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, decreases in B-lymphocytes and T-lymphocyte populations were observed in the offspring at both doses tested. The effects of LEMTRADA, administered during organogenesis, on postnatal development have not been adequately assessed.
LEMTRADA (alemtuzumab) is a recombinant humanized IgG1 kappa monoclonal antibody directed against the cell surface glycoprotein, CD52. Alectuzumab has an approximate molecular weight of 150 kD. LEMTRADA 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 is a sterile, clear and colorless to slightly yellow, solution (pH 7.2 ± 0.2) for infusion.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients less than 17 years of age have not been established. Use of LEMTRADA is not recommended in pediatric patients due to the risks of autoimmunity, infusion reactions, 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)].

9 NONCLINICAL TOXICOLOGY

Reproductive Toxicology

When LEMTRADA (3 or 10 mg/kg IV) was administered to hCD52 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 head] and reduced total count and motility) were observed at doses tested.

When LEMTRADA (3 or 10 mg/kg IV) was administered to hCD52 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 post-implantation loss, resulting in fewer viable embryos at the higher dose tested.

10 DOSAGE AND ADMINISTRATION

Each 1 mL of solution contains alemtuzumab 10 mg, dibasic sodium phosphate (1.15 mg), disodium hydrogen carbonate (0.88 mg), polysorbate 80 (0.1 mg), potassium chloride (0.2 mg), potassium edetate dihydrate (0.0187 mg), polysorbate 80 (0.1 mg), potassium chloride (0.2 mg), polysorbate 80 (0.1 mg), potassium chloride (0.2 mg), polysorbate 80 (0.1 mg), potassium chloride (0.2 mg), and water for injection.

10.1 Nursing Mothers

Alemtuzumab was detected in the milk of lactating mice administered 10 mg/kg LEMTRADA on Days 8 through 12 postpartum. Serum levels of alectuzumab were similar in lactating mice and offspring on Day 13 postpartum, and were associated with evidence of pharmacological activity (decrease in lymphocyte counts) in the offspring.

It is not known whether alectuzumab is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from LEMTRADA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

11 DESCRIPTION

LEMTRADA (alemtuzumab) is a recombinant humanized IgG1 kappa monoclonal antibody directed against the cell surface glycoprotein, CD52. Alemtuzumab has an approximate molecular weight of 150 kD. LEMTRADA 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 is a sterile, clear and colorless to slightly yellow, solution (pH 7.2 ± 0.2) for infusion.

11.2 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 at the time of the first post-treatment blood count. The lowest lymphocyte counts were observed 31 days 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 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 CLINICAL PHARMACOLOGY

12.1 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, alemtuzumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

12.2 Pharmacokinetics

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

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

### Table 3: Clinical and MRI Results of Study 2

<table>
<thead>
<tr>
<th>LEMTRADA (N=376)</th>
<th>interferon beta-1a 44 mcg (N=187)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.18</td>
<td>0.39</td>
</tr>
<tr>
<td>Proportion of patients with disability progression at Year 2</td>
<td>8%</td>
<td>30%</td>
</tr>
<tr>
<td>Percent of patients remaining relapse-free at Year 2</td>
<td>78%</td>
<td>59%</td>
</tr>
<tr>
<td><strong>MRI Outcomes</strong></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>

### Infusions
- Advise patients to contact their healthcare provider if they develop symptoms of serious infection such as fever or swollen glands [see Warnings and Precautions (5.9)].
- Advise patients to complete any necessary immunizations at least 6 weeks prior to treatment with LEMTRADA [see Dosage and Administration (2.2)].
- Advise patients that they should talk to their healthcare provider before taking any vaccine after recent treatment with LEMTRADA [see Warnings and Precautions (5.9)].
- Advise patients to take their prescribed medication for herpes prophylaxis as directed by their healthcare provider [see Warnings and Precautions (5.9)].
- Advise patients that yearly HPV screening is recommended [see Warnings and Precautions (5.9)].
- 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 (5.9)].

### 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 (5.10)].

### Pneumonitis
- Advise patients that pneumonitis has been reported in patients treated with LEMTRADA [see Warnings and Precautions (5.11)].
- 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 (5.12)].

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### MEDICATION GUIDE

**LEMTTRADA® (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?**

LEMTTRADA can cause serious side effects, including:

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, if not treated, may cause life-threatening problems. Call your healthcare provider right away if you have any of the following symptoms:
     - easy bruising
     - bleeding from a cut that is hard to stop
     - heavier menstrual periods than normal
     - bleeding from your gums or nose that is new or takes longer than usual to stop
     - 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:
     - blood in the urine (red or tea-colored urine)
     - swelling in your legs or feet
     - 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 and will increase your chances of getting better.

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 2 hours after you receive LEMTRADA. It is important that you stay at the infusion center for 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 heart beat
- chest pain
- rash

To lower your chances of getting a serious infusion reaction, your healthcare provider will give you a medicine called corticosteroids before your first 3 infusions of a treatment course. You may also be given other medicines before or after the infusion to try reduce your chances of these reactions or to treat them after they happen.

3. 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:
- new lump
- swelling in your neck
- pain in the front of your neck
- hoarseness or other voice changes that do not go away
- trouble swallowing or breathing
- cough that is not caused by a cold

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 adults with relapsing forms of multiple sclerosis (MS). Because of its risks, LEMTRADA is generally used in people who have tried 2 or more MS medicines that have not worked well enough. 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:
- are taking a medicine called Campath\textsuperscript{®}, Alemtuzumab, the active ingredient in LEMTRADA, is the same drug as Campath.
- have bleeding problems
- have thyroid problems
- have kidney problems
- have a recent history of infection
- have HIV
- 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. You should use birth control while receiving LEMTRADA and for 4 months after your course of treatment.
- are breastfeeding. 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. You should not do both.

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 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.

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

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
  - 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.

• serious infections. LEMTRADA may cause you to have serious infections while you receive and after receiving a treatment course. Serious infections may include:
  - 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.
  - 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.

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.

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. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LEMTRADA for a condition for which it was not prescribed. Do not give LEMTRADA to other people, even if they have the same symptoms that you have. It may harm them. 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: sodium chloride, dibasic sodium phosphate, potassium chloride, potassium dihydrogen phosphate, polysorbate 80, disodium edetate dihydrate, and water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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