**Warnings and Precautions, Adult Onset Still’s Disease (5.12)** 1/2022

**Warnings and Precautions, Autoimmunity (5.1)** 5/2022

**LEMTRADA** is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS [see Warnings and Precautions (5)]. (1)

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

**Dosage and Administration**

- Baseline laboratory tests are required prior to treatment. (2.1)
- Administer LEMTRADA by intravenous infusion over 4 hours for 2 or more treatment courses:
  - Initial treatment of 2 courses:
    - First course: 12 mg/day on 5 consecutive days. (2.3)
    - Second course: 12 mg/day on 3 consecutive days 12 months after first treatment course. (2.3)
  - Subsequent treatment courses of 12 mg per day on 3 consecutive days (36 mg total dose) may be administered, as needed, at least 12 months after the last dose of any prior treatment course. (2.3)
- Premedicate with corticosteroids prior to LEMTRADA infusion for the first 3 days of each treatment course. (2.2)

**Contraindications**

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

**Warnings and Precautions**

- Immune Thrombocytopenia: Obtain complete blood counts (CBCs) with differential prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion. (5.6)
- Glomerular Nephropathies: Obtain serum creatinine levels, urinalysis with cell counts and urine protein to creatinine ratio prior to initiation of treatment. Monitor serum creatinine levels and urinalysis with cell counts at monthly intervals thereafter until 48 months after the last infusion. (5.7)
- Thyroid Disorders: Obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion. (5.5)
- Other Autoimmune Cytopenias: Monitor CBCs monthly until 48 months after the last infusion. (2.5, 5.9)

**Adverse Reactions**

Most common adverse reactions (incidence >10% and > interferon beta-1a): rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, parotitis, dizziness, abdominal pain, flushing, and vomiting. (5.15)

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: 08/2022

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**References and Additional Information**

- LEMTRADA® (alemtuzumab) injection, for intravenous use
- LEMTRADA is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS [see Warnings and Precautions (5)]. (1)
- Baseline laboratory tests are required prior to treatment. (2.1)
- Administer LEMTRADA by intravenous infusion over 4 hours for 2 or more treatment courses:
  - Initial treatment of 2 courses:
    - First course: 12 mg/day on 5 consecutive days. (2.3)
    - Second course: 12 mg/day on 3 consecutive days 12 months after first treatment course. (2.3)
  - Subsequent treatment courses of 12 mg per day on 3 consecutive days (36 mg total dose) may be administered, as needed, at least 12 months after the last dose of any prior treatment course. (2.3)
- Premedicate with corticosteroids prior to LEMTRADA infusion for the first 3 days of each treatment course. (2.2)
- Known hypersensitivity or anaphylactic reactions to alemtuzumab or any of the excipients in LEMTRADA (4)
- Infection with Human Immunodeficiency Virus (4)
- Active infection (4)
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
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FULL PRESCRIBING INFORMATION

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, STROKE, AND MALIGNANCIES

- LEMTRADA causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-gliomerular basement membrane disease. 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 [see Warnings and Precautions (5.1)].

- LEMTRADA causes serious and life-threatening infusion reactions. LEMTRADA must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period [see Warnings and Precautions (5.2)].

- Serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported within 3 days of LEMTRADA administration. Instruct patients to seek immediate medical attention if symptoms of stroke occur [see Warnings and Precautions (5.3)].

- LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams [see Warnings and Precautions (5.4)].

- Because of the risk of autoimmunity, infusion reactions, and malignancies, LEMTRADA is available only through restricted distribution under a Risk Evaluation and Mitigation Strategy (REMS) Program. Call 1-855-676-6326 to enroll in the LEMTRADA REMS program [see Warnings and Precautions (5.5)].

1 INDICATIONS AND USAGE

LEMRADA is 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

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

2 DOSAGE AND ADMINISTRATION

2.1 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 (5.15)],

- complete any necessary immunizations 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. Postpone treatment with LEMTRADA until 6 weeks after VZV vaccination.
- perform tuberculosis screening according to local guidelines.
- instruct patients to avoid potential sources of Listeria monocytogenes.

2.2 Recommended Premedication and Concomitant Medication

Corticosteroids

Pharmacists should review the drug interactions before prescribing any corticosteroids that might affect the response to LEMTRADA treatment [see Warnings and Precautions (5.13)].

Herpes Prophylaxis

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

2.3 Recommended Dosage

- The recommended dosage of LEMTRADA is 12 mg/day administered by intravenous infusion for 2 treatment courses: First Treatment Course: 12 mg/day on 5 consecutive days (60 mg total dose).
- Second Treatment Course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course.

Following the second treatment course, subsequent treatment courses of 12 mg per day on 3 consecutive days (36 mg total dose) may be administered, as needed, at least 12 months after the last dose of any prior treatment courses.

2.4 Preparation Instructions

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

- Inspect LEMTRADA visually for particulate matter and discoloration prior to dilution and administration. Do not use if particulate matter is present or the solution is discolored. Do not freeze or shake vials prior to use.
- Withdraw 1.2 mL of LEMTRADA from the vial into a syringe using aseptic technique and inject into a 100 mL bag of sterile 0.9% Sodium Chloride, USP or 5% Dextrose in Water, USP.
- Gently invert the bag to mix the solution. Ensure the sterility of the prepared solution because it contains no antimicrobial preservatives. Each vial is for single use only.
- Prior to administration, protect diluted LEMTRADA solution from light and store for as long as 8 hours either at room temperature 15°C to 25°C (59°F to 77°F) or keep refrigerated at conditions 2°C to 8°C (36°F to 46°F).

2.5 Infusion Instructions

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

Administer LEMTRADA in a setting in which equipment and personnel to appropriately manage anaphylaxis, serious infusion reactions, myoccardial ischemia, myocardial infarction, and cerebrovascular and respiratory adverse reactions are available [see Warnings and Precautions (5.2)].

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

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

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

2.6 Laboratory Testing and Monitoring to Assess Safety

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 [see Warnings and Precautions (5.4)].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

LEMRADA is contraindicated in patients:

- with known hypersensitivity or anaphylactic reactions to alemtuzumab or any of the excipients in LEMTRADA
- who are infected with human immunodeficiency virus (HIV) because LEMTRADA causes prolonged reductions of CD4+ lymphocyte counts
- with active infection

5 WARNINGS AND PRECAUTIONS

5.1 Autoimmunity

Treatment with LEMTRADA can result in the formation of autoantibodies and increase the risk of serious autoimmune mediated conditions, which may be life threatening.

In clinical studies (controlled and open-label extension), LEMTRADA-treated patients experienced thyroid disorders (36.8%), immune thrombocytopenia (2%), and glomerular nephropathies (0.3%) [see Warnings and Precautions (5.6, 5.7, 5.8)]. Villous and autoimmune hemolytic anemia occurred in 0.3% of patients. Autoimmune pancreatitis [see Warnings and Precautions (5.9)], undifferentiated connective tissue disorders, and type 1 diabetes each occurred in 0.2% of patients. Rheumatoid arthritis, retinal pigment epithiopathy, and acquired hemophilia A (anti-Factor VIII antibodies) [see Warnings and Precautions (5.15)] occurred in 0.1% of patients. During postmarketing use, cases of vasculitis, autoimmune hepatitis [see Warnings and Precautions (5.10)], Guillain-Barré syndrome [see Adverse Reactions (5.3)], thrombotic thrombocytopenic purpura [see Warnings and Precautions (5.13)], and autoimmune encephalitis [see Warnings and Precautions (5.14)] have been reported.

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.
5.5 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, 5.4)].

Notable requirements of the LEMTRADA REMS Program include the following:

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

Further information, including a list of qualified healthcare facilities, is available at 1-855-676-6336.

5.6 Immune Thrombocytopenia

Immune thrombocytopenia (ITP) occurs in 2% of LEMTRADA-treated patients in MS clinical studies (controlled and open-label extension).

A controlled clinical study in patients with MS, one LEMTRADA-treated patient developed ITP that went unrecognized prior to the implementation of monthly blood monitoring requirements, and died from intracerebral hemorrhage. Nead platelet counts ≤50,000 cells per microliter as a result of ITP occurred in 2% of all LEMTRADA-treated patients in clinical studies in MS. Anti-platelet antibodies did not precipitate ITP onset. ITP has been diagnosed more than 3 years after the last LEMTRADA dose. Symptoms of ITP include easy bruising, petechiae, spontaneous mucocutaneous bleeding (e.g., epistaxis, hemoptysis), and heavier than normal or irregular menstrual bleeding. Hemoptysis may also be indicative of anti-glomerular basement membrane (GBM) disease [see Warnings and Precautions (5.7)], and an appropriate differential diagnosis has to be undertaken. Remind the patient to remain vigilant for symptoms they may experience and to seek immediate medical help if they have any concerns.

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

5.7 Glomerular Nephropathies Including Anti-Glomerular Basement Membrane Disease

Glomerular nephropathies occurred in 0.3% of LEMTRADA-treated patients in MS clinical studies. There were two cases of membranous glomerulonephritis and 2 cases of anti-glomerular basement membrane (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 are required because early treatment can improve the preservation of renal function. Anti-GBM disease can be life-threatening if left untreated. Alveolar hemorrhage, manifested as hemoptysis, is a common component of anti-GBM disease and has been reported in postmarketing cases. Cases of anti-GBM disease have been diagnosed up to 40 months after the last dose of LEMTRADA.

Symptoms of nephropathy may include edema, hematuria, change in urine color, decreased urine output, dysuria, proteinuria, and hemoptysis. Patients and caregivers should be instructed to seek medical advice if they have concerns.

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

For urine dipstick results of 1+ protein or greater, measure the urine protein to creatinine ratio. For urine protein to creatinine ratio greater than 200 mg/g, increase in serum creatinine greater than 30%, or creatinine level higher than 2.0 mg/dL, perform further evaluation for nephropathy. Increased serum creatinine with hematuria or signs of pulmonary involvement of anti-GBM disease (e.g., hemoptysis, exudal dyspnea) warrant immediate evaluation. Early detection and treatment of nephropathies may decrease the risk of poor outcomes.

5.8 Thyroid Disorders

Thyroid endocrine disorders, including autoimmune thyroid disorders, occurred in 36.8% of LEMTRADA-treated patients in MS clinical studies (controlled and open-label extension). Newly diagnosed thyroid disorders occurred throughout the uncontrolled clinical study follow-up period, more than 2 years after the first LEMTRADA dose. Autoimmune thyroid disorders included Graves’ disease (life-threatening hypothyroidism, hyperthyroidism, autoimmune thyroiditis, and goiter). Graves’ ophthalmopathy with decreased vision, eye pain, and exophthalmos occurred in 2% of LEMTRADA-treated patients. Seven patients required surgical orbital decompression. Serious thyroid events occurred in about 5.2% of LEMTRADA-treated patients in clinical studies and included cardiac and psychiatric events associated with thyroid disease. Of all LEMTRADA-treated patients, 3.8% underwent thyroidectomy.

Thyroid disease poses special risks in women who are pregnant [see Use in Specific Populations (8.1)]. Obtain thyroid function tests, such as TSH levels, prior to initiation of treatment and every 3 months thereafter for the first 48 months after the last infusion. Continue to test thyroid function after 48 months if clinically indicated or in case of pregnancy.

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

5.9 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 antibody (Coombs’ test). Patients with anti-glomerular basement membrane (anti-GBM) disease developed elevated serum creatinine with hematuria or signs of pulmonary involvement of anti-GBM disease. The majority of LEMTRADA-treated patients have had autoimmune cytopenias.

During postmarketing use, additional autoimmune cytopenias, including fatal autoimmune hemolytic anemia and aplastic anemia, have been reported in the treatment of patients with B-CLL, as well as other disorders, generally at higher and more frequent doses of alemtuzumab than recommended in MS.

Use CBC results to monitor for cytopenias. Prompt medical intervention is indicated if a cytopenia is confirmed.

5.10 Autoimmune Hepatitis

Autoimmune hepatitis causing clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with LEMTRADA in the postmarketing setting. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of liver disease, the drug may be stopped and the patient referred to a liver specialist.
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 interrupts or discontinues treatment with LEMTRADA, as appropriate.

5.10 Discontinuation of LEMTRADA

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

5.11 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking LEMTRADA. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme hypoferritinemia, and/or splenomegaly. HLH is associated with HLA-B27 positive patients with recent or ongoing infection and who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. LEMTRADA should be discontinued if an alternate etiology for the signs or symptoms cannot be established.

5.12 Adult Onset Still’s Disease (AOSD)

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

5.13 Thrombotic Thrombocytopenic Purpura (TTP)

TTP has been reported to be associated with LEMTRADA. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological sequelae, fever, and renal impairment. TTP is associated with high morbidity and mortality rates if not recognized and treated early. LEMTRADA should be discontinued if TTP is confirmed or an alternate etiology for the signs or symptoms cannot be established.

5.14 Autoimmune Encephalitis (AIE)

During postmarketing use, cases of AIE have been reported in patients treated with LEMTRADA. AIE can present with a variety of clinical manifestations, including subacute onset of memory impairment, alopecia, mood changes, and seizures. AIE is associated with altered immunity and may be at increased risk of infection following administration of live viral vaccines. LEMTRADA administration is contraindicated in patients with active infection (see Contraindications (4)).

5.15 Acquired Hemophilia A

Cases of acquired hemophilia A (factor VIII deficiency) have been reported in both the clinical trial and postmarketing settings. Patients typically present with spontaneous cutaneous hematomas and extensive bruising, although hematuria, epistaxis, gastrointestinal, or other types of bleeding may occur. Obtain a coagulation assay including APTT in patients who present with such symptoms. Patients should be informed about the signs and symptoms of acquired hemophilia A and be advised to seek immediate medical attention if any of these symptoms occur.

5.16 Infections

Infections occurred in 71% of LEMTRADA-treated patients compared to 53% of patients treated with interferon beta-1a in controlled clinical studies in MS up to 2 years in duration. Infections that occurred more often in LEMTRADA-treated patients than interferon beta-1a patients included nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, herpetic infections, influenza, and bronchitis. Tuberculosis, CMV infection, and PML 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, pneumonia, herpes zoster, and tooth infection. Do not administer live viral vaccines following a course of LEMTRADA. Patients treated with LEMTRADA have impaired immunity and may be at increased risk of infection following administration of live viral vaccines. LEMTRADA administration is contraindicated in patients with active infection (see Contraindications (4)) and should be discontinued if AIE is confirmed by the presence of neural autoantibodies or an alternate etiology cannot be established.

5.17 Hemorrhagic Cerebrovascular Diseases

Frequent headache, convulsions, and hemorrhagic cerebrovascular diseases have been reported in LEMTRADA-treated patients. Symptoms have included intracranial hemorrhage, subarachnoid hemorrhage, and aneurysm rupture. Hemorrhagic cerebrovascular diseases have been reported in 3% of LEMTRADA-treated patients compared to 2% of interferon beta-1a treated patients. Patients should be evaluated and monitored for clinical symptoms of hemorrhagic cerebrovascular diseases as appropriate.

5.18 Infections (see Warnings and Precautions (5.17))

Infections (e.g., meningitis, encephalitis, sepsis, and gastrointestinal) have occurred in 3% of patients treated with LEMTRADA. LEMTRADA has been associated with an increased risk of infections and opportunistic infections. LEMTRADA is contraindicated in patients with active infection, active neoplastic disease, or current or recent history of severe or opportunistic infection (see Contraindications (4)). Infections and opportunistic infections have been reported in patients treated with LEMTRADA. LEMTRADA is associated with an increased risk of serious infections and opportunistic infections.

5.19 Skin and Soft Tissue Infections

Increased rates of skin and soft tissue infections have been reported in LEMTRADA-treated patients compared to interferon beta-1a treated patients. Infections have included cellulitis, abscess, and pustule (0.1%) and cellulitis, abscess, cellulitis with lymphadenopathy, and pustule (0.8%). Infections have occurred in 5% of LEMTRADA-treated patients compared to 2% of interferon beta-1a treated patients. Patients should be monitored and instructed to seek medical evaluation if skin infections occur (see Contraindications (4)).

5.20 Hepatitis

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) reactivation has been reported in patients treated with LEMTRADA. Because patients may be at risk for HBV or HCV reactivation, patients should be evaluated for HBV and/or HCV prior to therapy with LEMTRADA. The risk of HBV and/or HCV reactivation increases with treatment duration and may persist for up to 24 months following the last dose of LEMTRADA. PML has been associated with HBV and/or HCV reactivation, and patients should be monitored and instructed to seek medical evaluation if signs or symptoms of hepatitis occur (see Contraindications (4)).

5.21 Pneumonia

Pneumonia has been reported in patients treated with LEMTRADA. Infections with pneumococci, mycoplasma, and viruses have been reported. Patients should be monitored and instructed to seek medical evaluation if signs or symptoms of pneumonia occur (see Contraindications (4)).

6. ADVERSE REACTIONS

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

- Autoimmunity (see Boxed Warning and Warnings and Precautions (5.1))
- Infusion Reactions (see Boxed Warning and Warnings and Precautions (5.2))
- Stroke and Cerebrovascular Arterial Dissection (see Warnings and Precautions (5.3))
- Malignancies (see Warnings and Precautions (5.4))
- Immune Thrombocytopenia (see Warnings and Precautions (5.5))
- Gliomathelial Malignancies Including Anti-glomerulitis Basement Membrane Disease (see Warnings and Precautions (5.7))
- Thyroid Disorders (see Warnings and Precautions (5.8))
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.

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<th>Reaction</th>
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<th>Interferon beta-1a 44 mcg (N=389) %</th>
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</tr>
<tr>
<td>Dysgeusia</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Influenza</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

6.2 Lymphopenia
Nearly all (99.9%) patients treated with LEMTRADA in MS clinical trials experienced lymphopenia. The lowest lymphocyte counts occurred approximately by 1 month after each course of treatment. The mean lymphocyte count at 1 month after LEMTRADA treatment was 0.25 x 10^9/L (range 0.02-3.6 x 10^9/L) and 0.32 (0.02-1.81 x 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, 0.6% 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 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 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.

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 63%, 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 antibody-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: Acquired hemophagocytic lymphohistiocytosis (see Warnings and Precautions (5.11))
Infections (see Warnings and Precautions (5.16))
Neoplasms (see Warnings and Precautions (5.19))

Hepatobiliary Disorders: Autoimmune hepatitis (see Warnings and Precautions (5.10))

Other Adverse Reactions
- Other Autoimmune Cytopenias (see Warnings and Precautions (5.9))
- Autoimmune Hepatitis (see Warnings and Precautions (5.10))
- Hemophagocytic Lymphohistiocytosis (see Warnings and Precautions (5.11))
- Adult Onset Still’s Disease (see Warnings and Precautions (5.12))
- Thrombotic Thrombocytopenic Purpura (see Warnings and Precautions (5.13))
- Autoimmune Encephalitis (see Warnings and Precautions (5.14))
- Acquired Hemophilia A (see Warnings and Precautions (5.15))
- Infections (see Warnings and Precautions (5.16))
- Progressive Multifocal Leuкоencephalopathy (PML) (see Warnings and Precautions (5.17))
- Acute Acalculous Cholecystitis (see Warnings and Precautions (5.18))
- Pneumonitis (see Warnings and Precautions (5.19))

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In controlled clinical trials (Study 1 and Study 2), a total of 811 patients with relapsing forms of MS received LEMTRADA. The population was 16 to 55 years of age, 65% were female, and 92% were Caucasian. A total of 811 patients received a total of 2 treatment courses and approximately 70% of patients by 12 months after each course. The overall follow-up in the controlled trials was equivalent to 1622 patient years.

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>Dermatitis</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Blood in urine</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Dyspea</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Decrease in CD4 lymphocytes</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Decrease in CD8 lymphocytes</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Aesthensia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Decrease in T-lymphocyte count</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Erythema</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Neck pain</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>
Infections and Infections: Opportunistic infections [see Warnings and Precautions (5.16)]. Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.17)].

Immune System Disorders: Autoimmune hemolytic anemia, Guillain-Barré syndrome [see Warnings and Precautions (5.1)]. Herpesviral leukoencephalitis [see Warnings and Precautions (5.11)]. Sarcoidosis

Musculoskeletal and Connective Tissue Disorders: Adult Onset Still’s Disease [see Warnings and Precautions (5.12)].

Nervous System Disorders: Autoimmune encephalitis [see Warnings and Precautions (5.14)]. Myasthenia gravis and Lambert-Eaton myasthenic syndrome

Pulmonary System Disorders: Pulmonary alveolar hemorrhage

Skin and Appendage Disorders: Porphyria cutanea tarda

Infections and Infestations: Opportunistic infections [see Warnings and Precautions (5.1)]. Untreated hypothyroidism in pregnant women increases the risk for miscarriage and may have effects on the fetus including growth retardation and death. 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-thyroid hormone receptor antibodies resulted in neonatal Graves disease with hyperthyroidism in her infant who was born 1 year after alemtuzumab dosing [see Warnings and Precautions (5.1)].

8.2 Lactation

Risk Summary

There are no adequate and well-controlled studies in pregnant women [see Warnings and Precautions (5.18)]. Alemtuzumab was detected in the milk of lactating huCD52 transgenic mice following intravenous administration. Before initiation of LEMTRADA treatment, women of childbearing potential should be counselled on the clinical need for LEMTRADA and any potential adverse effects on the breastfed child from LEMTRADA or the effects of the drug on milk production. Alemtuzumab was detected in the milk of lactating huCD52 transgenic mice following intravenous administration.

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

Infertility

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients less than 17 years of age have not been established. Use of LEMTRADA is not recommended in pediatric patients due to the risks of autoimmunity, infection, reactions, and stroke, and because it may increase the risk of malignancies (thyroid, melanoma, lymphoproliferative disorders, and lymphoma) [see Warnings and Precautions (5.3, 5.4, 5.5, 5.6, 5.7)].

8.5 Geriatric Use

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

10 OVERDOSE

Two MS patients experienced serious reactions (headache, rash, and either hypotension or sinus tachycardia) after a single accidental infusion up to 60 mg of LEMTRADA. Doses of LEMTRADA greater than those recommended may increase the intensity and/or duration of infusion reactions or its immune effects. There is no known antidote for alemtuzumab overdose.

11 DESCRIPTION

Alemtuzumab is a recombinant humanized IgG1 kappa monoclonal antibody directed against the cell surface glycoprotein, CD52. Alemtuzumab has an approximate molecular weight of 150 kDa. 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.

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

Each vial of solution contains 10 mg alemtuzumab, dibasic sodium phosphate (1.15 mg), disodium edetate dihydrate (0.0187 mg), polycarb 80 (0.1 mg), potassium chloride (0.2 mg), potassium dihydrogen phosphate (0.2 mg), sodium chloride (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 cellular cytotoxicity and complement-mediated lysis.

12.2 Pharmacodynamics

Effects of LEMTRADA on the Lymphocyte Population

In a study of 53 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 for at least 2 hours after the first but not subsequent infusions.

12.3 Pharmacokinetics

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

Elimination

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

The elimination half-life was approximately 2 weeks and was comparable between courses. The serum half-lives were generally undetectable (<80 ng/mL) within approximately 30 days following each course. Specific Populations

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the carcinogenic or genotoxic potential of LEMTRADA have not been conducted. When LEMTRADA (3 or 10 mg/kg IV) was administered to huCD52 transgenic male mice on 5 consecutive days prior to cohabitation with untreated wild-type females, no effect on fertility or reproductive performance was observed. However, adverse effects on sperm parameters (including abnormal morphology [detached head] and reduced total count and motility) were observed at all doses tested.

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

14 CLINICAL STUDIES

The efficacy of LEMTRADA was demonstrated in two studies (Study 1 and 2) that evaluated LEMTRADA 12 mg in patients with relapsing-remitting multiple sclerosis (RRMS). LEMTRADA was administered by intravenous infusion once daily over a 5-day course, followed one year later by intravenous infusion once daily over a 3-day course. Both studies included patients who had experienced at least 2 relapses in 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

Trial 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 and 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
significant difference between the treatment groups for the change in T2 lesion volume. The results of Study 1 are shown in Table 2 and Figure 1.

Table 2: Clinical and MRI Results of Study 1

<table>
<thead>
<tr>
<th></th>
<th>LEMTRADA (N=426)</th>
<th>interferon beta-1a 44 mcg (N=202)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.26</td>
<td>0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative reduction</td>
<td>49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with disability progression at Year 2</td>
<td>13%</td>
<td>21%</td>
<td>0.0084</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients remaining relapse-free at Year 2</td>
<td>66%</td>
<td>47%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MRI Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent change in T2 lesion volume from baseline</td>
<td>-1.3</td>
<td>-1.2</td>
<td>0.14</td>
</tr>
</tbody>
</table>

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

Study 2
Study 2 was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 mcg 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.

Table 3: Clinical and MRI Results of Study 2

<table>
<thead>
<tr>
<th></th>
<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>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.18</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative reduction</td>
<td>55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with disability progression at Year 2</td>
<td>8%</td>
<td>11%</td>
<td>0.22</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients remaining relapse-free at Year 2</td>
<td>78%</td>
<td>59%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MRI Outcomes</strong></td>
<td></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>
<td>0.31</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
LEMTRADA (alemtuzumab) injection is a sterile, clear and colorless to slightly yellow solution for intravenous infusion, containing no antimicrobial preservatives.

Each LEMTRADA carton (NDC 56168-0200-1) contains one single-dose vial that delivers 12 mg/1.2 mL (10 mg/mL). The vial stopper is not made with natural rubber latex.

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

17 PATIENT COUNSELING INFORMATION
Advice the patient to read the FDA-approved patient labeling (Medication Guide).

Autoimmunity
- Advise patients to contact their healthcare provider promptly if they experience any symptoms of potential autoimmune disease. Give examples of important symptoms such as bleeding, easy bruising, petechiae, purpura, hematuria, edema, jaundice, or hemoptysis [see Warnings and Precautions (5.1)].
- Advise patients that the importance of monthly blood and urine tests for 48 months following the last course of LEMTRADA to monitor for signs of autoimmunity because early detection and prompt treatment can help prevent serious and potentially fatal outcomes associated with these events. Advise patients that monitoring may need to continue past 48 months if they have signs or symptoms of autoimmunity.
- Advise patients that LEMTRADA may cause hypothyroid or hyperthyroid disorders.
- Advise patients to contact their healthcare provider if they experience symptoms reflective of a potential thyroid disorder such as unexplained weight loss or gain, fast heartbeat or palpitations, nervousness, worsening tiredness, eye swelling, constipation, or feeling cold.
- Advise women of childbearing potential of the risks of pregnancy with concomitant thyroid disease.
- Advise women of childbearing potential to discuss pregnancy planning with their doctor.
- Advise patients to contact their healthcare provider if they develop signs or symptoms suggestive of hepatic dysfunction such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and/or dark urine, or bleeding or bruising more easily than normal.
- Advise patients to contact their healthcare provider if they experience symptoms of acquired hemophilia A such as spontaneous bruising, nose bleeds, painful or swollen joints, other types of bleeding, or bleeding from a cut that may take longer than usual to stop.
- Advise patients that cases of autoimmune encephalitis may occur after receiving LEMTRADA. This condition may include symptoms such as behavior and psychiatric changes, movement disorders, short-term memory loss or seizures, as well as other symptoms that may resemble an MS relapse. Instruct patients to contact their healthcare provider immediately if they experience symptoms of autoimmunity.

Infusion Reactions
- Advise patients that infusion reactions may occur at the time of infusion or after they leave the infusion center [see Warnings and Precautions (5.3)].
- Instruct the patient to remain at the infusion center for at least 2 hours after each LEMTRADA infusion, or longer at the discretion of the healthcare provider. Advise patients that symptoms of infusion reactions may occur after they leave the infusion center and to report these symptoms to their healthcare provider.
- Advise patients that their healthcare provider will monitor vital signs, including blood pressure, before and during the infusion and to contact their healthcare provider promptly if they experience infusion reactions, which include swelling in the mouth or throat, difficulty breathing, weakness, abnormal heart rate (fast, slow, or irregular), chest pain, rash, facial drooping, sudden severe headache, weakness on one side of the body, difficulty with speech, or neck pain.
- Advise patients that there have also been reports of rare but serious infusion reactions, including bleeding in the lung, chest tightness/pain or discomfort, heart attack, and stroke or tears in blood vessels supplying the brain, which should be reported to your healthcare provider.
- Advise patients that reactions may occur following any of the doses during the treatment course. In the majority of cases, reactions occurred within 1–3 days of the infusion.

Stroke and Cerebrovascular Arterial Dissection
- Educate patients on the symptoms and instruct patients to seek immediate medical attention if symptoms of stroke or cerebrovascular arterial dissection occur (e.g., neck pain, weakness on one side, facial droop, difficulty with speech, sudden severe headache) [see Warnings and Precautions (5.3)].

Malignancies
- Advise patients that LEMTRADA may increase their risk of malignancies including thyroid cancer and melanoma [see Warnings and Precautions (5.4)].
- Advise patients to report symptoms of thyroid cancer, including a new lump or swelling in the neck, pain in the front of the neck, hoarseness or other voice changes that do not go away, trouble swallowing or breathing, or a constant cough not due to a cold.
- Advise patients that they should have baseline and yearly skin examinations.

LEMTRADA REMS Program
- LEMTRADA is available only through a restricted program called the LEMTRADA REMS Program [see Warnings and Precautions (5.5)]. Inform the patient of the following notable requirements:
  - Patients and providers must be enrolled in the program.
  - Patients must comply with the ongoing monitoring requirements.
  - Patients must report any side effects or symptoms to their doctor.
- LEMTRADA is available only at certified infusion centers participating in the program. Therefore, provide patients with information on the LEMTRADA REMS Program in order to locate an infusion center.
- Advise patients to read the LEMTRADA REMS material for patients, LEMTRADA Treatment and Infusion Reactions Patient Guide.
- Instruct patients to carry the LEMTRADA REMS Patient Safety Information Card with them in case of an emergency.

Hemophagocytic Lymphohistiocytosis
- Educate patients that treatment with LEMTRADA may increase the risk of a type of excessive immune activation (hemophagocytic lymphohistiocytosis), which can be fatal, particularly if not diagnosed and treated early.
- Advise patients to contact their healthcare provider immediately if they experience symptoms such as fever, swollen glands, skin rash, or new neurologic symptoms such as mental status changes, ataxia, or seizures.
- In cases reported with LEMTRADA, symptoms occurred within approximately thirteen months to thirty-three months following the initiation of treatment.
Infections

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

• 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 (5.16)].

• Advise patients to avoid or adequately heat foods that are potential sources of Listeria monocytogenes prior to receiving LEMTRADA and if they have had a recent course of LEMTRADA. The duration of increased risk for Listeria infection after LEMTRADA administration is not known. Inform patients that Listeria infection can lead to significant complications or death [see Warnings and Precautions (5.16)].

• Advise patients to take their prescribed medication for herpes prophylaxis as directed by their healthcare provider [see Warnings and Precautions (5.16)].

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

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 (5.17)].

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 (5.16)].

Pneumonitis

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

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 (5.20)].

Fetal Risk

• Advise 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.

• Advise patients exposed to LEMTRADA during pregnancy that there is a pregnancy safety surveillance program that monitors pregnancy outcomes [see Use in Specific Populations (8.1)]. If exposure occurs during pregnancy, healthcare providers and patients are encouraged to report pregnancies by calling 1-800-745-4447, option 2.

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US License Number: 1596

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

Tell your healthcare provider right away if you have any of the following symptoms of a serious infusion reaction during the infusion, and after you have left the healthcare facility:

- swelling in your mouth or throat
- trouble breathing
- weakness
- fast, slow, or irregular heartbeat
- chest pain
- rash

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 to reduce your chances of these reactions or to treat them after they happen.

3. **Stroke and tears in your arteries that supply blood to your brain (carotid and vertebral arteries).** Some people have had serious and sometimes deadly strokes and tears in their carotid or vertebral arteries within 3 days of receiving LEMTRADA. Get help right away if you have any of the following symptoms that may be signs of a stroke or tears in your carotid or vertebral arteries:

- drooping of parts of your face
- sudden severe headache
- neck pain

4. **Certain cancers.** Receiving LEMTRADA may increase your chance of getting some kinds of cancers, including thyroid cancer, skin cancer (melanoma), and blood cancers called lymphoproliferative disorders and lymphoma. Call your healthcare provider if you have the following symptoms that may be a sign of thyroid cancer:

- 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 “LEMTRADA Treatment and Infusion Reactions Patient Guide” after you are enrolled in the program.
- Carry your LEMTRADA REMS Patient Safety Information Card with you in case of an emergency.

**What is LEMTRADA?**

LEMTRADA is a prescription medicine used to treat relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Since treatment with LEMTRADA can increase your risk of getting certain conditions and diseases, LEMTRADA is generally prescribed for people who have tried 2 or more MS medicines that have not worked well enough.

LEMTRADA is not recommended for use in patients with clinically isolated syndrome (CIS). It is not known if LEMTRADA is safe and effective for use in children under 17 years of age.

**Who should not receive LEMTRADA?**

**Do not receive LEMTRADA if you:**

- are allergic to alemtuzumab or to any of the inactive ingredients in LEMTRADA. See the end of this Medication Guide for a complete list of ingredients in LEMTRADA.
- are infected with human immunodeficiency virus (HIV)
- have an active infection

**What should I tell my healthcare provider before receiving LEMTRADA?**

Before receiving LEMTRADA, tell your healthcare provider if you:

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

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

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

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

What are the possible side effects of LEMTRADA?
• 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

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

low blood counts (cytopenias). LEMTRADA may cause a decrease in some types of blood cells. Some people with these low blood counts have increased infections. Symptoms of cytopenias may include:

- weakness
- chest pain
- yellowing of the skin or whites of eyes (jaundice)
- dark urine
- fast heartbeat

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

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

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

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

thrombotic thrombocytopenic purpura (TTP). Thrombotic thrombocytopenic purpura (TTP) can occur with LEMTRADA. TTP is a blood clotting problem where blood clots can form in blood vessels anywhere in the body. TTP needs to be treated in a hospital right away, because it can cause death. Get medical help right away if you have any of these symptoms:

- purplish spots (called purpura) on the skin or in the mouth (mucous membranes) due to bleeding under the skin
- your skin or the whites of your eyes are yellow (jaundice)
- you feel tired or weak
- your skin looks very pale
- fever
- fast heart rate or feeling short of breath
- headache
- speech changes
- confusion
- vision changes
- seizure
- low amount of urine or dark urine, or urine that has blood in it
- stomach area (abdominal) pain
- nausea, vomiting, or diarrhea

autoimmune encephalitis (AIE). Autoimmune encephalitis (AIE), a brain disorder, can occur after receiving LEMTRADA and may include symptoms that may seem like an MS relapse. Call your healthcare provider right away if you have any of the following symptoms:

- personality changes
mood changes  
seeing things that are not there (hallucinations)  
agitation  
short term memory loss  
confusion  
movement disorders  
seizure

**bleeding disorder (acquired hemophilia A).** LEMTRADA may cause a bleeding disorder called acquired hemophilia A. Call your healthcare provider right away if you have any of the following symptoms:
- bruising
- nose bleeds
- painful or swollen joints
- bleeding from a cut that may take longer than usual to stop
- blood in urine
- dark or bloody stools

**serious infections.** LEMTRADA may cause you to have serious infections while you receive and after receiving a treatment course. Serious infections may include:
- **listeria.** People who receive LEMTRADA have an increased chance of getting an infection caused by the bacteria, listeria, which can lead to significant complications or death. Avoid foods that may be a source for listeria (for example, deli meat, unpasteurized milk and cheese products, soft cheeses, or undercooked meat, seafood or poultry) or make sure that the food you eat which may contain listeria is heated well if you receive treatment with LEMTRADA.
- **herpes viral infections.** Some people taking LEMTRADA have an increased chance of getting herpes viral infections. Your healthcare provider will prescribe medicines to reduce your chances of getting these infections. Take these medicines exactly as your healthcare provider tells you to.
- **human papilloma virus (HPV).** Females have an increased chance of getting a cervical HPV infection. If you are a female, you should have an HPV screening each year.
- **tuberculosis.** Your healthcare provider should check you for tuberculosis before you receive LEMTRADA.
- **fungal infections.**

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

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

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

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

The most common side effects of LEMTRADA include:
- rash
- headache
- thyroid problems
- fever
- swelling of your nose and throat (nasopharyngitis)
- nausea
- urinary tract infection
- feeling tired
- trouble sleeping
- upper respiratory tract infection
- herpes viral infection
- hives
- itching
- fungal infection
- joint pain
- pain in your arms or legs
- back pain
- diarrhea
- sinus infection
- mouth pain or sore throat
- tingling sensation
- dizziness
- stomach pain
- sudden redness in face, neck, or chest
- vomiting
Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of LEMTRADA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

**General information about the safe and effective use of LEMTRADA.**
This Medication Guide summarizes the most important information about LEMTRADA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LEMTRADA that is written for health professionals. For more information, go to www.LemtradaREMS.com or call Genzyme at 1-855-676-6326.

**What are the ingredients in LEMTRADA?**
**Active ingredient:** alemtuzumab
**Inactive ingredients:** dibasic sodium phosphate, disodium edetate dihydrate, polysorbate 80, potassium chloride, potassium dihydrogen phosphate, sodium chloride, and Water for Injection, USP.

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