For Healthcare Facilities

LEMTRADA REMS Education Program for Healthcare Facilities

This Educational Piece Includes Information About:

- The LEMTRADA REMS requirements to implement in your healthcare facility
- Serious risks of autoimmune conditions, infusion reactions, stroke and malignancies
- Proper administration of LEMTRADA® (alemtuzumab)

LEMTRADA® alemtuzumab 12mg IV

What Is the LEMTRADA REMS (Risk Evaluation and Mitigation Strategy)?

A REMS is a strategy to manage known or potential risks associated with a drug and is required by the FDA to ensure that the benefits of the drug outweigh its risks. LEMTRADA is only available under a restricted program called the LEMTRADA REMS because of the risks of infusion reactions, autoimmune conditions, stroke and malignancies. The *LEMTRADA REMS Education Program for Healthcare Facilities* is designed to educate and train healthcare facilities' authorized representatives on the serious risks associated with LEMTRADA, the LEMTRADA REMS requirements, and how to properly administer LEMTRADA.

- **Prescribers** must be enrolled in the LEMTRADA REMS to be able to prescribe LEMTRADA.
- **Pharmacies** must be enrolled in the LEMTRADA REMS to be able to dispense LEMTRADA.
- **Healthcare** Facilities must be enrolled in the LEMTRADA REMS to be able to dispense and administer LEMTRADA.
- **Patients** must be certified and authorized in the LEMTRADA REMS in order to receive LEMTRADA.

STEPS FOR HEALTHCARE FACILITY CERTIFICATION	
1	Designate an authorized representative.
2	Review the *LEMTRADA REMS Education Program for Healthcare Facilities*, including the Prescribing Information.
3	Complete and sign the LEMTRADA REMS Healthcare Facility Enrollment Form. This enrollment must be renewed every 2 years.
4	Implement the necessary staff training and processes to comply with the LEMTRADA REMS requirements.

The *LEMTRADA REMS Education Program for Healthcare Facilities*, LEMTRADA REMS Healthcare Facility Enrollment Form, and other LEMTRADA REMS tools are available online at **www.LemtradaREMS.com** or by contacting the LEMTRADA REMS at 1-855-676-6326.

To enroll in the LEMTRADA REMS, call 1-855-676-6326 or enroll online at **www.LemtradaREMS.com**.

Who Can Be An Authorized Representative?

An authorized representative at the healthcare facility can be a:

- Pharmacist
- Director of infusion center
- Prescriber
- Nurse
- Or any responsible individual in the healthcare facility

Please check with your manager to ensure the appropriate person represents the healthcare facility and attests to the enrollment requirements as stated on the LEMTRADA REMS Healthcare Facility Enrollment Form.

- One representative needs to enroll per healthcare facility (the "authorized representative"). One authorized representative can manage more than one healthcare facility.
- Please note, there are no LEMTRADA REMS requirements for staff at a healthcare facility who will not be involved with dispensing or administering LEMTRADA.

Overview of Important Safety Information

INDICATION AND USAGE

LEMTRADA 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.

Limitations of Use:
LEMTRADA is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

The Prescribing Information includes a **BOXED WARNING** for LEMTRADA.

Please see the Prescribing Information for complete safety information, including BOXED WARNING.

SERIOUS RISKS ASSOCIATED WITH LEMTRADA

Infusion Reactions

Most patients treated with LEMTRADA in controlled clinical trials in MS experienced infusion reactions during or after LEMTRADA administration. Some of these reactions were serious and life-threatening. In some patients, infusion reactions were reported more than 24 hours after LEMTRADA infusion. Serious reactions occurred in 3% of patients, including cases of anaphylaxis in 2 patients (including anaphylactic shock), angioedema, bronchospasm, hypotension, chest pain, bradycardia, tachycardia (including atrial fibrillation), transient neurologic symptoms, hypertension, headache, pyrexia, and rash. Other infusion reactions included nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnea, pulmonary infiltrates, dysgeusia, dyspepsia, dizziness, and pain. In clinical studies, 0.6% of patients with infusion reactions received epinephrine or atropine. Cases of pulmonary alveolar hemorrhage and myocardial ischemia have been reported with onset within 48 hours of LEMTRADA infusion.

Premedicate patients with high-dose corticosteroids (1000 mg of methylprednisolone or equivalent) immediately prior to LEMTRADA infusion for the first 3 days of each treatment course. Consider pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration. Infusion reactions may occur in patients despite pretreatment.

Consider additional monitoring in patients with medical conditions which predispose them to cardiovascular or pulmonary compromise. Physicians should alert patients that an infusion reaction could occur within 48 hours of infusion.

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

Patients must be observed for infusion reactions during and for at least 2 hours after each LEMTRADA infusion. Consider longer periods of observation if clinically indicated. Vital signs should be monitored before and periodically during the infusion. If an infusion reaction occurs, appropriate symptomatic treatment should be provided as needed. If the infusion is not well tolerated, the duration of the infusion may be extended. If severe infusion reactions occur, immediate discontinuation of the infusion should be considered.

Stroke and Cervicocephalic Arterial Dissection

Stroke

In the postmarketing setting, serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported within 3 days of LEMTRADA administration, with most cases occurring within 1 day.

Cervicocephalic Arterial Dissection

In the postmarketing setting, cases of cervicocephalic (e.g., vertebral, carotid) arterial dissection involving multiple arteries have been reported within 3 days of LEMTRADA administration. Ischemic stroke was reported in one of these cases.

Educate patients on the symptoms of stroke and cervicocephalic (e.g., carotid, vertebral) arterial dissection. Instruct patients to seek immediate medical attention if symptoms of stroke or cervicocephalic arterial dissection occur.

Autoimmune Conditions

LEMTRADA has been associated with risk of autoimmune conditions, including immune thrombocytopenia, other cytopenias (including neutropenia, hemolytic anemia, and pancytopenia), thyroid disorders, and glomerular nephropathies, which may occur many years after treatment and may be serious or life-threatening. Early detection and prompt treatment can help prevent serious and potentially fatal outcomes associated with these events.

Please review the sections that follow to gain a better understanding of the risks of autoimmune conditions.

Immune Thrombocytopenia (ITP)

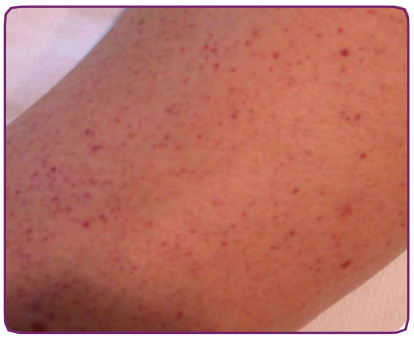
Immune thrombocytopenia (ITP) is an autoimmune disorder usually associated with anti-platelet antibodies. Platelet depletion reduces the ability of the blood to clot.

ITP was reported in 2% of patients in clinical trials in MS. ITP can be a serious condition leading to morbidity and mortality, and may occur several years after dosing. Prescribers are required to monitor all patients for ITP by obtaining complete blood counts with differential ≤30 days prior to initiation of treatment and at monthly intervals thereafter until 48 months after the patient's last infusion of LEMTRADA. After this period of time, testing should be performed based on clinical findings suggestive of ITP. Patients should also be monitored for clinical symptoms of ITP. Symptoms of ITP could include (but are not limited to) easy bruising, petechiae, spontaneous mucocutaneous bleeding (epistaxis, hemoptysis), and heavier than normal or

irregular menstrual bleeding. These clinical signs of ITP may be apparent before serious bleeding develops.

POTENTIAL CLINICAL PRESENTATIONS OF ITP

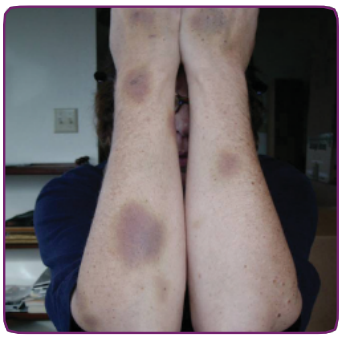
Note: These pictures are only a guide in order to show examples of bruises or petechiae.
The patient may have a less severe type of bruise or petechiae than these pictures and still have ITP.



This is an example of a leg with petechiae.

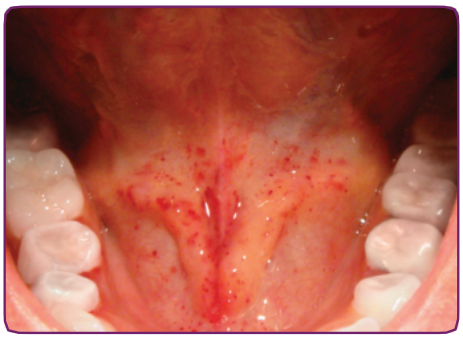
Petechiae are small, scattered, "pinprick" spots under the skin that are red, pink, or purple.

Petechiae can occur anywhere on the patient's body, not just the legs.



This is an example of easy or excessive bruising.

This could occur anywhere on the patient's body.



This is an example of purpura under the tongue.

Purpura could occur on any mucous membrane, including anywhere in the mouth (under the tongue, roof of the mouth, inner cheeks, tongue, gums).

Other Autoimmune Cytopenias (including neutropenia, hemolytic anemia, and pancytopenia)

Autoimmune cytopenias such as neutropenia, hemolytic anemia, and pancytopenia have been reported in clinical studies in MS. One LEMTRADA-treated patient with autoimmune pancytopenia died from sepsis. Symptoms of autoimmune hemolytic anemia may include weakness, chest pain, jaundice, dark urine, and tachycardia. Monthly CBC results will also be used to monitor for cytopenias. If a cytopenia is confirmed, appropriate medical intervention should be promptly initiated.

Glomerular Nephropathies

Glomerular nephropathies, including anti-glomerular basement membrane (anti-GBM) disease, have been reported after treatment with LEMTRADA in MS patients in clinical trials.

In postmarketing cases, some LEMTRADA-treated patients with anti-GBM disease developed end-stage renal disease requiring dialysis or renal transplantation. Urgent evaluation and treatment is required, because early treatment can improve the preservation of renal function. Anti-GBM disease can be life-threatening if left untreated. Cases of anti-GBM disease have been diagnosed up to 40 months after the last dose of LEMTRADA.

Clinical manifestations of nephropathy may include elevation in serum creatinine, hematuria, and/or proteinuria. While not observed in clinical trials, alveolar hemorrhage manifested as hemoptysis may occur with anti-GBM disease. Since patients may be asymptomatic, prescribers are required to monitor patients by obtaining 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 patient's last infusion. After this period of time, testing should be performed based on clinical findings suggestive of nephropathies.

Thyroid Disorders

Thyroid endocrine disorders, including autoimmune thyroid disorders occurred in 36.8% of LEMTRADA-treated patients in clinical studies (controlled and open-label extension). Newly diagnosed thyroid disorders occurred throughout the uncontrolled clinical study follow-up period, more than 7 years after the first LEMTRADA dose. Serious thyroid events occurred in 5.2% of patients. Prescribers are required to monitor all patients for thyroid disorders by obtaining thyroid function tests, such as thyroid-stimulating hormone (TSH) levels ≤30 days prior to the first infusion of LEMTRADA, and then every 3 months thereafter continuing until 48 months following the last infusion. Continue to test thyroid function after 48 months if clinically indicated. Prescribers should also monitor for signs and symptoms of thyroid disorders, which may include excessive sweating, unexplained weight loss, eye swelling, nervousness and fast heartbeat (hyperthyroidism), or unexplained weight gain, feeling cold, worsening tiredness, and newly occurring constipation (hypothyroidism).

Autoimmune Hepatitis

Autoimmune hepatitis causing clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with LEMTRADA in the postmarketing setting. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), prescribers should promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with LEMTRADA, as appropriate.

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

Malignancies

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

LEMTRADA may increase the risk of melanoma. Prescribers should perform baseline and yearly skin examinations to monitor for melanoma in patients receiving LEMTRADA. Cases of lymphoproliferative disorders and lymphoma have occurred in LEMTRADA-treated patients with MS.

Strategies to Implement in Your Healthcare Facility to Mitigate Risk of Infusion Reactions

- Ensure the infusion site is equipped with the necessary equipment and personnel to manage infusion reactions (including anaphylaxis and cardiac and respiratory emergencies).
- Premedicate patients with high-dose corticosteroids (1000 mg of methylprednisolone or equivalent) immediately prior to LEMTRADA infusion for the first 3 days of each LEMTRADA treatment course. Consider pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration. Infusion reactions may occur despite pretreatment.
- Observe patients for infusion reactions during and for at least 2 hours after each LEMTRADA infusion.
- Consider longer periods of observation if clinically indicated. Monitor vital signs before and periodically during the infusion.
- Provide appropriate symptomatic treatment as needed if an infusion reaction occurs.
- Consider extending the duration of the infusion if the infusion is not well tolerated.
- Consider immediate discontinuation of the infusion if severe infusion reactions occur.
- Do not administer LEMTRADA outside of the authorized representative's certified healthcare facility.

Proper Storage and Administration

STORAGE OF LEMTRADA

- LEMTRADA is packaged in 12 mg/1.2 mL (10 mg/mL) single-dose vials.
- LEMTRADA vials should be stored at 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light.

PRIOR TO EACH TREATMENT COURSE OF LEMTRADA

- Confirm prescriber is certified and patient is enrolled and authorized to receive LEMTRADA.
- Counsel each patient about the risk for infusion reactions.
- Provide the patient with *What You Need to Know About LEMTRADA Treatment and Infusion Reactions: A Patient Guide* prior to dispensing LEMTRADA.
- Administer corticosteroids immediately prior to LEMTRADA administration for the first 3 days of each treatment course.
- Ensure oral prophylaxis for herpes infection is available or has been prescribed to start on the first day of each treatment course. Consider pretreating patients with antihistamines and/or antipyretics prior to LEMTRADA administration as needed.
- Monitor vital signs before and periodically during the infusion.

ADMINISTRATION OF LEMTRADA

1. Inspect vial for particulate matter/discoloration prior to use.
2. Withdraw 1.2 mL of LEMTRADA from the vial into a syringe using aseptic technique.
3. Inject into 100 mL sterile 0.9% Sodium Chloride, USP or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution.
4. Cover IV solution bag to protect from light.
5. Administer 12 mg/day over approximately 4 hours.
6. Do not administer as IV push or bolus.
7. If infusion is not well tolerated, infusion duration may be extended.
8. Use the LEMTRADA diluted product within 8 hours after dilution. LEMTRADA diluted product may be stored at room temperature (15° to 25°C) or refrigerated conditions (2° to 8°C). Protect from light. Do not administer as IV push or bolus.
9. Monitor patient vital signs before and periodically during the infusion, and provide appropriate symptomatic treatment for infusion reactions as needed.
10. Monitor patients for at least 2 hours after each LEMTRADA infusion or longer if clinically indicated.

FOLLOWING THE CONCLUSION OF EACH LEMTRADA TREATMENT COURSE

- Complete a LEMTRADA REMS Infusion Checklist for each patient at the conclusion of each treatment course and fax (1-855-557-2478) to the LEMTRADA REMS or submit online at **www.LemtradaREMS.com** within 5 business days of the last infusion.
- Return unused vials of LEMTRADA to Genzyme within 50 days of receipt of the LEMTRADA REMS Patient Authorization and Baseline Lab Form.

Adverse Event Reporting

Report suspected adverse events to Genzyme Medical Information at **1-800-745-4447** (option 2) or to FDA at 1-800-FDA-1088 or **www.FDA.gov/medwatch**.

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LEMTRADA® alemtuzumab 12mg IV