

LEMTRADA REMS Education Program

Included within this educational piece, LEMTRADA prescribers, healthcare facilities, and pharmacies will find information related to:

- The LEMTRADA REMS overview and requirements
- Certification and enrollment
- Drug storage and administration
- Overview of important safety information and required monitoring
- Patient counseling and management

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. It is required by the FDA to ensure that the benefits of the drug outweigh its risks. Due to serious risks of autoimmune conditions, infusion reactions, stroke and malignancies, LEMTRADA is only available through a restricted program called the LEMTRADA REMS.

LEMTRADA REMS requirements

- **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 certification and enrollment in the LEMTRADA REMS

PRESCRIBER ENROLLMENT INSTRUCTIONS

1. Complete the training programs, which includes reviewing the following materials:
 - LEMTRADA Prescribing Information
 - LEMTRADA REMS Education Program
2. Successfully complete the 8-question LEMTRADA REMS Prescriber Knowledge Assessment.
3. Enroll in the program by completing a LEMTRADA REMS Prescriber Enrollment Form.
4. Submit the completed and signed forms to the LEMTRADA REMS.

PHARMACY ENROLLMENT INSTRUCTIONS

1. An authorized representative must enroll on behalf of the pharmacy by reviewing the LEMTRADA REMS Education Program and completing the LEMTRADA REMS Pharmacy Enrollment Form, which acknowledges that the pharmacy agrees to follow the procedures outlined in the LEMTRADA REMS, including:
 - All relevant staff at the pharmacy who will be involved with the dispensing of LEMTRADA must be educated and trained.
 - The pharmacy will verify that a LEMTRADA REMS Patient Enrollment and Prescription Ordering Form is received for each prescription.
 - The pharmacy will verify that prescribers and healthcare facilities are certified and patients are authorized to receive LEMTRADA prior to dispensing LEMTRADA.
 - Enrollment in the LEMTRADA REMS must be renewed every 2 years from initial enrollment.
2. Submit the completed and signed LEMTRADA REMS Pharmacy Enrollment Form to the LEMTRADA REMS.

HEALTHCARE FACILITY ENROLLMENT INSTRUCTIONS

1. An authorized representative (i.e., a Pharmacist, Director of Infusion Center, Prescriber, Nurse, or any responsible individual) must enroll on behalf of the healthcare facility by reviewing the LEMTRADA REMS Education Program and completing the LEMTRADA REMS Healthcare Facility Enrollment Form, which acknowledges that the healthcare facility agrees to follow the procedures outlined in the LEMTRADA REMS, including:
 - All staff at the facility who will be involved with the dispensing and administration of LEMTRADA must be trained, and a written record of all staff REMS trainings must be kept on file.
 - Please note, there are no LEMTRADA REMS requirements for staff at a healthcare facility who will not be involved with dispensing or administering LEMTRADA.
 - Managers should ensure that the appropriate person(s) 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.
 - The healthcare facility will verify that prescribers are certified and patients are authorized to receive LEMTRADA prior to dispensing or administering LEMTRADA.
 - The healthcare facility will provide a copy of *LEMTRADA Treatment and Infusion Reactions Patient Guide* to the patient on the first day of each treatment course when LEMTRADA is dispensed.
 - The healthcare facility will complete a LEMTRADA REMS Infusion Checklist for each patient at the conclusion of each treatment course and submit it to the LEMTRADA REMS within 5 business days.
 - Enrollment in the LEMTRADA REMS must be renewed every 2 years from initial enrollment.
2. Submit the completed and signed LEMTRADA REMS Healthcare Facility Enrollment Form to the LEMTRADA REMS.

PATIENT ENROLLMENT INSTRUCTIONS

1. Complete the LEMTRADA REMS Patient Enrollment and Prescription Ordering Form, which contains information to be completed by both the prescriber and the patient.
2. Provide a copy of *LEMTRADA Treatment and Infusion Reactions Patient Guide* and a LEMTRADA Patient Safety Information Card to each patient who will receive LEMTRADA. You must use *LEMTRADA Treatment and Infusion Reactions Patient Guide* to inform your patients on the serious risks and REMS requirements with the use of LEMTRADA.
3. Submit the completed and signed LEMTRADA REMS Patient Enrollment and Prescription Ordering Form to the LEMTRADA REMS.
4. Provide the patient with a copy of the LEMTRADA REMS Patient Enrollment and Prescription Ordering Form and keep a copy in the patient’s medical record.

Where to find REMS information and resources

The LEMTRADA Prescribing Information, LEMTRADA REMS Prescriber Knowledge Assessment, and other REMS materials 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.

Sanofi will send confirmation of a prescriber's enrollment in the LEMTRADA REMS, including the prescriber's assigned LEMTRADA REMS identification number.

Prescribers will not be able to prescribe LEMTRADA without completing their certification in the LEMTRADA REMS.

You should understand that if you fail to comply with the LEMTRADA REMS requirements, you may no longer be able to participate in the LEMTRADA REMS.

Proper storage and administration of LEMTRADA

Ordering and storage of LEMTRADA

- LEMTRADA is ordered by submitting a LEMTRADA REMS Patient Enrollment and Prescription Ordering Form for each LEMTRADA prescription to the LEMTRADA REMS. The ordering form can be obtained online (www.LemtradaREMS.com) or by phone (1-855-676-6326). Completed forms should be faxed to 1-855-557-2478.
- 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.
- Inform each patient about the risk of infusion reactions.
- Provide the patient with *LEMTRADA Treatment and Infusion Reactions Patient Guide* prior to dispensing LEMTRADA.
- Administer corticosteroids (1000 mg methylprednisolone or equivalent) immediately prior to LEMTRADA administration for the first 3 days of each treatment course.
- Administer anti-viral prophylaxis for herpetic viral infection starting on the first day of each treatment course and continuing for a minimum of 2 months following treatment with LEMTRADA or until the CD4+ lymphocyte count is ≥ 200 cells per microliter, whichever occurs later.
- Consider pretreating patients with antihistamines and/or antipyretics prior to LEMTRADA administration as needed.
- Monitor vital signs before and periodically during the infusion.
- Submit the LEMTRADA REMS Patient Authorization and Baseline Lab Form to the LEMTRADA REMS indicating completion of each patient's baseline labs within 30 days of the infusion date.

OVERVIEW OF LEMTRADA TREATMENT

1st Course:	ON 5 CONSECUTIVE DAYS
2nd Course: (12 months later)	ON 3 CONSECUTIVE DAYS
Additional Courses: (Administered as needed \geq 12 months after prior course)	ON 3 CONSECUTIVE DAYS
Monitoring: (Start blood and urine testing before treatment)	CONTINUE UNTIL 4 YEARS AFTER LAST TREATMENT COURSE

Mandatory monthly laboratory testing is required until 4 years after the last infusion with LEMTRADA. If more than 2 courses are deemed necessary, administer subsequent course(s) at least 1 year after the prior treatment course. Mandatory monthly monitoring may extend beyond 5 years, until at least 3 years after the last 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 an 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).
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 Sanofi within 75-business days of submission of the LEMTRADA REMS Patient Authorization and Baseline Lab Form.

Adverse event reporting

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



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 accompanying Prescribing Information for complete safety information, including BOXED WARNING.

Serious risks associated with LEMTRADA

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 treatment of these conditions may decrease the risk of poor outcomes.

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

Immune thrombocytopenia (ITP)

Immune thrombocytopenia (ITP) occurred in 2% of LEMTRADA-treated patients in clinical studies (controlled and open-label extension) in MS. Immune thrombocytopenia is an autoimmune disorder usually associated with anti-platelet antibodies. Platelet depletion reduces the ability of the blood to clot. 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.

ITP can be a serious condition leading to morbidity and mortality and may occur several years after dosing. It is important to monitor all patients for ITP as follows:

- Complete blood counts with differential should be obtained ≤ 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.
- Check the patient for clinical symptoms of ITP.
- Counsel the patient on the importance of complying with monthly monitoring of their blood and the need to continue for 48 months after their last infusion.
- Educate the patient on how to recognize ITP-related symptoms and emphasize the need to remain vigilant for them.
- If ITP is suspected, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. Severe or widespread bleeding is life-threatening and demands immediate care.

The potential risk associated with retreatment with LEMTRADA following the occurrence of ITP is unknown.

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).

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Other autoimmune cytopenias (including neutropenia, hemolytic anemia, and pancytopenia)

Autoimmune cytopenias such as neutropenia, hemolytic anemia, and pancytopenia have been reported in clinical studies (controlled and open-label extension) 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. Use the monthly CBC results 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 (GBM) disease, have been reported after treatment with LEMTRADA in multiple sclerosis patients in clinical trials. Cases of anti-GBM disease have been diagnosed up to 40 months after the last dose of LEMTRADA.

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.

Clinical manifestations of nephropathy may include elevation in serum creatinine, edema, hematuria, change in urine color, decreased urine output, fatigue, dyspnea, and/or proteinuria. While not observed in clinical trials, alveolar hemorrhage manifested as hemoptysis is a common component of anti-GBM disease. Since patients may be asymptomatic, it is important that the monthly tests are conducted.

- Serum creatinine levels, urinalysis with cell counts, and urine protein to creatinine ratio should be obtained ≤ 30 days prior to the first infusion of LEMTRADA. Serum creatinine and urinalysis with cell counts should be obtained 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.
- In menstruating females, consider the timing of urinalysis to avoid false positives. The observation of clinically significant changes from baseline in serum creatinine, unexplained hematuria, and/or proteinuria, should prompt further evaluation for nephropathies, including referral to a specialist.
- Early detection and treatment of nephropathies may decrease the risk of poor outcomes.
- Immediate referral to a specialist for further assessment for patients with suspected nephropathy is strongly recommended.

Thyroid disorders

During clinical trials, autoimmune thyroid disorders including Graves' disease, hyperthyroidism, hypothyroidism, autoimmune thyroiditis, and goiter were reported. 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. Of all LEMTRADA-treated patients, 3.8% underwent thyroidectomy.

It is important to monitor all patients for thyroid disorders as follows:

- Thyroid function tests such as thyroid-stimulating hormone (TSH) levels should be obtained ≤ 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.
- Additionally, watch out 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).
- Thyroid disease poses special risks in women who become pregnant. Untreated thyroid disease can cause harm to the unborn and newborn baby. Special caution should be taken for pregnant women with Graves' disease, as maternal thyroid-stimulating hormone receptor antibodies can be transferred to a developing fetus and can cause transient neonatal Graves' disease. The HCP responsible for managing the patient's pregnancy must be made aware of the increased risk of thyroid disorders due to the patient's LEMTRADA treatment, and the need for these to be appropriately treated.

Autoimmune hepatitis

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

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

Strategies to mitigate the risk of autoimmune conditions

In order to minimize possible risks and side effects of LEMTRADA, prescribers and patients must commit to 48 months of follow-up after the last infusion of LEMTRADA. It is important that patients understand that they should continue with the monitoring, even if they are feeling well.

Creating a partnership between you and your patient, along with careful review of the patient education tool (*LEMTRADA Treatment and Infusion Reactions Patient Guide*) with your patient, will help patients to:

- Comply with periodic tests
- Identify and report symptoms early
- Receive prompt and appropriate treatment if needed

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 with high-dose corticosteroids (1000 mg of methylprednisolone or equivalent) immediately prior to LEMTRADA infusion and 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 the infusion and periodically during the infusion. If an infusion reaction occurs, appropriate symptomatic treatment should be provided as needed. The duration of the infusion may be extended if clinically indicated. If severe infusion reactions occur, immediate discontinuation of the infusion should be considered. Do not administer LEMTRADA outside of the authorized representative's certified healthcare facility.

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.

Malignancies

LEMTRADA is an immunomodulatory therapy, and caution should be exercised in initiating LEMTRADA in patients with pre-existing or ongoing malignancies.

Thyroid cancer

LEMTRADA may increase the risk of thyroid cancer. In controlled clinical studies, 0.3% of LEMTRADA-treated patients developed thyroid cancer, compared to none in the interferon beta-1a-treated group. However, screening for thyroid cancer was performed more frequently in the LEMTRADA-treated group because of the higher incidence of autoimmune thyroid disorders in those patients. Two additional cases of thyroid cancer in LEMTRADA-treated patients occurred in uncontrolled studies.

Melanoma

LEMTRADA may increase the risk of melanoma. In clinical studies, including extension data, 0.3% of LEMTRADA-treated patients developed melanoma or melanoma in situ. One of those patients had evidence of locally advanced disease.

Lymphoproliferative disorders and lymphoma

Cases of lymphoproliferative disorders and lymphoma have occurred in LEMTRADA-treated patients with MS, including a MALT lymphoma, Castleman’s Disease, and a fatality following treatment of non-Epstein Barr Virus-associated Burkitt’s lymphoma. There are postmarketing reports of Epstein Barr Virus-associated lymphoproliferative disorders in non-MS patients.

Overview of LEMTRADA monitoring

CONDITION	ACTIVITY	TIMING	
Immune Thrombocytopenia (ITP)	Complete blood count with differential	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
Glomerular Nephropathies, including anti-GBM disease	Urine protein to creatinine ratio	Prior to initiating LEMTRADA treatment	
	Serum creatinine	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
	Urinalysis with microscopy	Prior to initiating LEMTRADA treatment	Monthly until 48 months after last infusion
Thyroid Disorders	Thyroid function tests (such as TSH)	Prior to initiating LEMTRADA treatment	Every 3 months until 48 months after last infusion
Autoimmune Hepatitis	Serum transaminases (ALT and AST) and total bilirubin levels	Prior to initiating LEMTRADA treatment	Periodically until 48 months after last infusion
Melanoma	Skin examinations	Prior to initiating LEMTRADA treatment	Yearly

Monitoring for malignancies

Patients and healthcare providers 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.

Perform baseline and yearly skin examinations to monitor for melanoma in patients receiving LEMTRADA.

Patient counseling and management

As part of patient counseling and management, you must:

- Inform your patient about the risks associated with LEMTRADA, including the risks of autoimmune conditions, infusion reactions, stroke and malignancies, and the need for baseline and periodic monitoring. A patient-directed educational guide has been developed for you to use in informing your patients on the risks associated with LEMTRADA (*LEMTRADA Treatment and Infusion Reactions Patient Guide*). You should review this guide with your patient on an ongoing basis. You must provide each patient with a copy of this guide and a LEMTRADA Patient Safety Information Card.
- Perform the baseline and periodic monitoring described above and in the Prescribing Information for LEMTRADA.
- Complete the LEMTRADA REMS Patient Status Form 6 months after the patient's first infusion with LEMTRADA, and every 6 months thereafter, until 48 months after the completion of the patient's last infusion of LEMTRADA, and submit the completed form to the LEMTRADA REMS.
- Notify Sanofi if an enrolled patient who has received LEMTRADA within the last 48 months is no longer under your care.

