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BLA 103948 LEMTRADA[®] (alemtuzumab)

CD52-directed cytolytic antibody

Genzyme Corporation

500 Kendall Street, Cambridge, MA 02142

Phone: 1-800-745-4447

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the LEMTRADA REMS is to mitigate the risks of autoimmune conditions, infusion reactions, and malignancies associated with LEMTRADA by:

Helping to ensure informed decisions about the safe use of LEMTRADA by:

- Informing patients about the serious risks of autoimmune conditions, infusion reactions, and malignancies with LEMTRADA and the need for baseline and periodic monitoring; and
- Informing healthcare providers about the serious risks of autoimmune conditions, infusion reactions, and malignancies with LEMTRADA, the need to counsel patients, and the need for baseline and periodic monitoring.

Helping to ensure the safe use of LEMTRADA by:

- Ensuring that only certified prescribers prescribe LEMTRADA;
- Ensuring that LEMTRADA is dispensed only in certain healthcare settings, by certified pharmacies, and certified infusion sites, which have on-site access to equipment and personnel trained to manage infusion reactions; and
- Ensuring that only enrolled and authorized patients receive LEMTRADA;
- Ensuring that certified prescribers submit documentation of periodic monitoring of patients who receive LEMTRADA to identify autoimmune conditions and malignancies

II. REMS ELEMENTS

A. Communication Plan

Genzyme will implement the following communication plan to healthcare providers likely to diagnose, treat, and manage patients with multiple sclerosis. The communication plan will include:

1. REMS Letter for Healthcare Providers

Genzyme will send a *REMS Letter for Healthcare Providers* within 60 days of approval of the LEMTRADA REMS and again at 12 months, 24 months, and 36 months from the date of the REMS approval. The REMS Letters will address the risk of autoimmune conditions, infusion reactions, and malignancies associated with LEMTRADA as well as support the implementation of the LEMTRADA REMS program. A copy of or a link to the Prescribing Information will accompany each *REMS Letter for Healthcare Providers*.

Genzyme will use email as the primary method to disseminate the REMS Letter. If an email is marked as unopened, Genzyme will send a second email within 30 calendar days. If the second email is marked as unopened, Genzyme will mail the REMS Letter within 30 calendar days. If an email address is not available or if the email is undeliverable, Genzyme will mail the REMS Letter within 30 calendar days.

Genzyme will send the *REMS Letter for Healthcare Providers* to prescribers who have written at least one prescription within the previous 2 years for a prescription drug indicated for the treatment of multiple sclerosis.

2. REMS Website

Genzyme will ensure that the website (www.LemtradaREMS.com) will be available for the duration of the REMS. Genzyme will ensure that the website will:

- Contain information on the LEMTRADA REMS
- Provide access to all approved REMS materials and the Prescribing Information
- Provide the option to complete and submit all approved REMS materials online (except the LEMTRADA REMS Patient Enrollment Form and the LEMTRADA REMS Prescription Ordering Form)
- Provide the ability to search for a REMS certified prescriber or infusion site within the U.S. and its territories
- Allow for the review of patient authorization and enrollment status, and prescriber and infusion site certification status

The following are part of the REMS and are appended:

- [The *REMS Letter for Healthcare Providers* \(print and email versions\)](#)
- [The LEMTRADA REMS Website](#)

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe LEMTRADA are specially certified.

- a. To become specially certified to prescribe LEMTRADA in the LEMTRADA REMS Program, healthcare providers must:
 - i. Review the Prescribing Information for LEMTRADA.
 - ii. Review the *LEMTRADA REMS Program Overview* and *LEMTRADA REMS Education Program for Prescribers* and successfully complete the *LEMTRADA REMS Knowledge Assessment*.
 - iii. Enroll in the LEMTRADA REMS Program by completing and signing the *LEMTRADA REMS Prescriber Enrollment Form* and submitting it to the LEMTRADA REMS Program.
- b. As a condition of certification, prescribers must agree to:
 - i. Enroll each patient in the LEMTRADA REMS Program by:
 - 1) Informing the patient about the risks associated with LEMTRADA, including the risks of autoimmune conditions, infusion reactions, and malignancies, and the need for baseline and periodic monitoring, by counselling on and providing each patient with *What You Need to Know About LEMTRADA Treatment: A Patient Guide* and a *LEMTRADA Patient Safety Information Card*.
 - 2) Completing the *LEMTRADA REMS Patient Enrollment Form* for each patient and providing a completed copy to the patient. The completed form must be submitted to the LEMTRADA REMS Program and a copy should be stored in the patient's records.
 - ii. Submit a *LEMTRADA REMS Prescription Ordering Form* for each LEMTRADA prescription to the LEMTRADA REMS Program.
 - iii. Perform the baseline and periodic monitoring described in the Prescribing Information.
 - iv. Submit a *LEMTRADA REMS Patient Authorization and Baseline Lab Form* to the LEMTRADA REMS Program indicating completion of each patient's baseline laboratory testing within 30 days prior to the patient's infusion date.
 - v. 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 Program.
 - vi. Report any adverse events suggestive of autoimmune conditions, infusion reactions, and malignancies to Genzyme.
 - vii. Notify Genzyme if an enrolled patient who has received LEMTRADA within the last 48 months is no longer under your care.
- c. Genzyme will:
 - i. Ensure that healthcare providers who prescribe LEMTRADA are specially certified, in accordance with the requirements described above.

- ii. Ensure that prescriber enrollment and documentation of training can be submitted by fax to (1-855-557-2478) to the LEMTRADA REMS Program or online via the LEMTRADA REMS website (www.LemtradaREMS.com).
- iii. Ensure that healthcare providers are notified when they have been certified by the LEMTRADA REMS Program.
- iv. Maintain a validated, secure database of healthcare providers who are certified to prescribe LEMTRADA in the LEMTRADA REMS Program. Genzyme will ensure that the healthcare provider's certification requirements are met and may de-certify non-compliant healthcare providers if the requirements do not continue to be met.
- v. Send a *LEMTRADA REMS Patient Status Reminder Letter* electronically or by mail 6 months after each patient's first LEMTRADA infusion, and every 6 months thereafter for 48 months, to certified prescribers enrolled in the LEMTRADA REMS Program, who must submit a completed *LEMTRADA REMS Patient Status Form* for an enrolled patient who has received LEMTRADA within the last 48 months.
- vi. Provide the *LEMTRADA REMS Prescriber Enrollment Form*, *LEMTRADA REMS Patient Enrollment Form*, *LEMTRADA REMS Program Overview*, *LEMTRADA REMS Education Program for Prescribers*, *LEMTRADA REMS Patient Status Form*, *LEMTRADA REMS Prescription Ordering Form*, *LEMTRADA REMS Patient Authorization and Baseline Lab Form*, *What You Need to Know About LEMTRADA Treatment: A Patient Guide* and the Prescribing Information to healthcare providers who (1) attempt to prescribe LEMTRADA and are not yet certified, or (2) inquire about how to become certified.
- vii. Ensure that the REMS materials listed below are available on the LEMTRADA REMS Program Website (www.LemtradaREMS.com) and can be accessed or by calling the REMS call center (1-855-676-6326).

The following materials are part of the REMS and are appended:

- [*LEMTRADA REMS Program Overview*](#)
- [*LEMTRADA REMS Education Program for Prescribers*](#)
- [*LEMTRADA REMS Knowledge Assessment*](#)
- [*LEMTRADA REMS Prescriber Enrollment Form*](#)
- [*LEMTRADA REMS Patient Enrollment Form*](#)
- [*LEMTRADA REMS Patient Status Form*](#)
- [*What You Need to Know About LEMTRADA Treatment: A Patient Guide*](#)
- [*LEMTRADA REMS Prescription Ordering Form*](#)
- [*LEMTRADA REMS Patient Authorization and Baseline Lab Form*](#)

- [The LEMTRADA REMS Website](#)
- [LEMTRADA REMS Patient Status Reminder Letter](#)

2. LEMTRADA is dispensed only in certain healthcare settings, by pharmacies and infusion sites that are specially certified.

- a. To become specially certified to dispense LEMTRADA in the LEMTRADA REMS Program,
 - i. Each pharmacy must:
 - 1) Designate an authorized representative to complete enrollment by submitting the completed *LEMTRADA REMS Pharmacy Enrollment Form* on behalf of the pharmacy.
 - 2) Ensure the authorized representative will oversee implementation and compliance with the LEMTRADA REMS Program requirements by:
 - a. Reviewing the *LEMTRADA REMS Program Overview*.
 - b. Ensuring that all relevant staff involved in the dispensing of LEMTRADA are educated and trained using the *LEMTRADA REMS Program Overview*.
 - c. Putting processes and procedures in place, and following such processes and procedures, to ensure the following verifications and safe use conditions are met prior to dispensing LEMTRADA:
 - i. The *LEMTRADA REMS Prescription Ordering Form* is received for each prescription.
 - ii. LEMTRADA is dispensed to certified infusion sites only.
 - iii. The prescriber is certified, the infusion site is certified, and the patient is enrolled and authorized to receive LEMTRADA by calling the LEMTRADA REMS Program prior to dispensing LEMTRADA.
 - d. Complying with request to be audited to ensure all training, processes and procedures are in place and being followed for the LEMTRADA REMS Program and appropriate documentation is available upon request.
 - e. Agreeing to renew enrollment in the LEMTRADA REMS Program every 2 years from initial enrollment.
 - ii. Each infusion site must:
 - 1) Designate an authorized representative to complete enrollment by submitting the completed *LEMTRADA REMS Healthcare Facility Enrollment Form* on behalf of the infusion site.

- 2) Ensure the authorized representative will oversee implementation and compliance with the LEMTRADA REMS Program requirements by:
 - a. Reviewing the *LEMTRADA REMS Program Overview* and *LEMTRADA REMS Education Program for Healthcare Facilities*.
 - b. Ensuring that all relevant staff involved in the dispensing and administration of LEMTRADA are educated and trained using the *LEMTRADA REMS Program Overview* and the *LEMTRADA REMS Education Program for Healthcare Facilities*.
 - c. Putting processes and procedures in place, and following such processes and procedures, to ensure the following verifications and safe use conditions are met prior to, during, and following dispensing LEMTRADA:
 - i. The *LEMTRADA REMS Prescription Ordering Form* is received for each prescription.
 - ii. The prescriber is certified and the patient is enrolled and authorized to receive LEMTRADA by either calling the LEMTRADA REMS Program or verifying this information via the LEMTRADA REMS website (www.LemtradaREMS.com) prior to dispensing LEMTRADA.
 - iii. Patients are counseled about the risk for infusion reactions and provided with *What You Need to Know about LEMTRADA Treatment and Infusion Reactions: A Patient Guide* prior to dispensing LEMTRADA.
 - iv. The infusion site is equipped with the necessary equipment and personnel to manage infusion reactions.
 - v. LEMTRADA is not dispensed outside of the authorized representative's certified infusion site.
 - vi. Monitoring patients for infusion reactions during and for at least 2 hours after each LEMTRADA infusion.
 - vii. Completing a *LEMTRADA REMS Infusion Checklist* for each patient at the conclusion of each treatment course and submitting the form within 5 business days either by fax (1-855-557-2478) or via the LEMTRADA REMS website (www.LemtradaREMS.com) to the LEMTRADA REMS Program.
 - viii. Renewing enrollment in the LEMTRADA REMS Program every 2 years from initial enrollment.

- 3) Ensuring that unused vials of LEMTRADA are returned to a distributor within 50 business days from the date of submission of the *LEMTRADA Patient Authorization and Baseline Lab Form*.
- 4) Complying with request to be audited to ensure that all training, processes and procedures are in place and are being followed for the LEMTRADA REMS Program and appropriate documentation is available upon request.

b. Genzyme will:

- i. Ensure that LEMTRADA is dispensed only by pharmacies and infusion sites that are specially certified in accordance with the requirements described above.
- ii. Ensure that pharmacy and infusion site enrollment and certification can be submitted by fax (1-855-557-2478) or via the LEMTRADA REMS website (www.LemtradaREMS.com) to the LEMTRADA REMS Program.
- iii. Ensure that pharmacies and infusion sites are notified when they have been certified by the LEMTRADA REMS Program.
- iv. Ensure that certified pharmacies and certified infusion sites are provided access to the database of certified health care providers and enrolled and authorized patients by contacting the LEMTRADA REMS Program (1-855-676-6326); infusion sites also have the option to view this information via the LEMTRADA REMS website (www.LemtradaREMS.com).
- v. Contact certified infusion sites if a completed *LEMTRADA REMS Infusion Checklist* has not been received by the LEMTRADA REMS Program within 40 days from the date of submission of the *LEMTRADA Patient Authorization and Baseline Lab Form*.
- vi. Verify annually that the authorized representative is the current designated authorized representative for the certified pharmacy and certified infusion site.

The following materials are part of the REMS and are appended:

- [*LEMTRADA REMS Healthcare Facility Enrollment Form*](#)
- [*LEMTRADA REMS Pharmacy Enrollment Form*](#)
- [*LEMTRADA REMS Education Program for Healthcare Facilities*](#)
- [*LEMTRADA REMS Program Overview*](#)
- [*LEMTRADA REMS Infusion Checklist*](#)
- [*What You Need to Know about LEMTRADA Treatment and Infusion Reactions: A Patient Guide*](#)

3. LEMTRADA will be dispensed¹ to patients only in certain health care settings, specifically, certified infusion sites that have the necessary on-site equipment and personnel to manage infusion reactions.

Genzyme will ensure that LEMTRADA will only be available to be dispensed to patients in an infusion site that has the necessary on-site equipment and personnel to appropriately manage serious infusion reactions (including anaphylaxis, cardiac and respiratory emergencies) and is certified in the LEMTRADA REMS Program.

The following materials are part of the REMS and are appended:

- [*LEMTRADA REMS Healthcare Facility Enrollment Form*](#)
- [*LEMTRADA REMS Infusion Checklist*](#)
- [*What You Need to Know about LEMTRADA Treatment and Infusion Reactions: A Patient Guide*](#)
- [*LEMTRADA REMS Program Overview*](#)
- [*LEMTRADA REMS Education Program for Healthcare Facilities*](#)

4. LEMTRADA will be dispensed to patients with evidence or other documentation of safe-use conditions.

- a. To become enrolled in the LEMTRADA REMS Program, each patient must sign a *LEMTRADA REMS Patient Enrollment Form* indicating that he/she has:
 - i. Been counselled with and provided *What You Need to Know About LEMTRADA Treatment: A Patient Guide*;
 - ii. Been counselled by the prescriber regarding the risks associated with LEMTRADA, including the risks of autoimmune conditions, infusion reactions and malignancies;
 - iii. Been counselled by the prescriber regarding the need for baseline and periodic monitoring recommendations contained in the LEMTRADA Prescribing Information;
 - iv. Been counselled with and provided a *LEMTRADA Patient Safety Information Card*.
- b. Genzyme will:

¹ For the purposes of this REMS, dispensed to patients only in certain health care settings includes dispensing and administration in health care settings, specifically infusion sites.

- i. Ensure that the certified prescriber is able to submit the completed *LEMTRADA REMS Patient Enrollment Form* to the LEMTRADA REMS Program by fax (1-855-557-2478).
- ii. Ensure that each patient treated with LEMTRADA is enrolled in the LEMTRADA REMS Program before LEMTRADA is dispensed to the patient, by verification prior to dispensing and administration (see Section B.2.).
- iii. Ensure that LEMTRADA is dispensed to patients only if there is evidence or other documentation that they have met the following safe use conditions:
 - 1) Patients have been counselled with and provided a *LEMTRADA Patient Safety Information Card*, *What You Need to Know about LEMTRADA Treatment: A Patient Guide*, and *What You Need to Know about LEMTRADA Treatment and Infusion Reactions: A Patient Guide*, on the risks associated with LEMTRADA, including the risks of autoimmune conditions, infusion reactions, and malignancies.
 - 2) Patients have completed the *LEMTRADA REMS Patient Enrollment Form*.
- iv. Send a *LEMTRADA REMS Patient Reminder Letter* to patients enrolled in the LEMTRADA REMS Program. These monthly communications will be sent to patients who have received LEMTRADA within the last 48 months, reminding the patient to obtain the needed periodic monitoring as described in the Prescribing Information, and will include a request for the patient's preferred method of contact for receiving future monthly reminders.

The following materials are part of the REMS and are appended:

- [*What You Need to Know about LEMTRADA Treatment: A Patient Guide*](#)
- [*LEMTRADA Patient Safety Information Card*](#)
- [*What You Need to Know about LEMTRADA Treatment and Infusion Reactions: A Patient Guide*](#)
- [*LEMTRADA REMS Patient Reminder Letter*](#)

C. Implementation System

An implementation system will be established for the LEMTRADA REMS Program to monitor and evaluate whether the elements to assure safe use are meeting the program's goals.

1. Genzyme will ensure that LEMTRADA is only distributed to certified pharmacies and certified infusion sites by:
 - a. Ensuring that distributors who distribute LEMTRADA to certified pharmacies and certified infusion sites comply with the program requirements for distributors. In order for a distributor to distribute LEMTRADA, the distributor must:

- i. Put processes and procedures in place to verify, prior to distributing LEMTRADA, that the pharmacies and infusion sites are certified by calling the LEMTRADA REMS Program (1-855-676-6326).
 - ii. Train all relevant staff on the LEMTRADA REMS Program requirements.
 - iii. Agree to be audited to ensure that all processes and procedures are in place and are being followed for the LEMTRADA REMS Program.
 - iv. Agree to provide distribution data to the LEMTRADA REMS Program.
 - b. Ensuring that distributors maintain patient level distribution records of all shipments of LEMTRADA to certified pharmacies and certified infusion sites and agree to provide the data to the LEMTRADA REMS Program.
 - c. Genzyme will monitor and audit the distributors within 180 days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the LEMTRADA REMS Program. Corrective action will be instituted by Genzyme if noncompliance is identified.
2. Genzyme will maintain a list of pharmacies and infusion sites which are certified to dispense and/or administer LEMTRADA in the LEMTRADA REMS Program. Genzyme will ensure that the pharmacies' and infusion sites' certification requirements are met and may de-certify non-compliant pharmacies and infusion sites if the requirements do not continue to be met. This list is available by telephone (1-855-676-6326) for certified prescribers of LEMTRADA. A list of certified prescribers and infusion sites is also available via the LEMTRADA REMS website (www.LemtradaREMS.com).
3. Genzyme will maintain a LEMTRADA REMS Program Call Center to support healthcare providers, pharmacies, infusion sites, and patients interfacing with the LEMTRADA REMS Program.
4. Genzyme will send monthly reminders to patients enrolled and authorized in the LEMTRADA REMS Program and who have received at least one LEMTRADA treatment, reminding them of the requirement for ongoing monitoring.
5. Genzyme will ensure that all materials listed in or appended to the LEMTRADA REMS document are available through the LEMTRADA REMS Program Website (www.LemtradaREMS.com) or can be accessed by calling the REMS call center (1-855-676-6326).
6. Genzyme will monitor and audit the certified pharmacies and infusion sites within 180 days after certification and after it has dispensed at least one LEMTRADA prescription, to ensure that all processes and procedures are in place and functioning to support the requirements of the LEMTRADA REMS Program. Corrective action will be instituted by Genzyme if noncompliance is identified.

7. Genzyme will maintain a validated, secure database of patients who are enrolled in the LEMTRADA REMS Program.
8. Genzyme will take reasonable steps to improve implementation of and compliance with the requirements in the LEMTRADA REMS Program based on monitoring and evaluation of the LEMTRADA REMS Program.

D. Timetable for Submission of Assessments

Genzyme will submit REMS Assessments to FDA at 6 and 12 months from the date of the approval of the LEMTRADA REMS, and then annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Genzyme will submit each assessment so that it will be received by FDA on or before the due date.