

BLA 103948/S-5180

SUPPLEMENT APPROVAL

Genzyme Corporation
Attention: Ying Zheng, PhD
Global Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Zheng:

Please refer to your supplemental biologics license application (sBLA), dated and received April 10, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lemtrada (alemtuzumab) injection.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Lemtrada risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Lemtrada was originally approved on November 14, 2014, and the most recent REMS modification was approved on October 29, 2019. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to minimize the burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Assessment Acknowledgment/REMS Modification Notification letter dated August 5, 2020.

In addition, your proposed modifications to the REMS include the following:

- Changes to the REMS materials to align with the labeling changes in supplements 5177 and 5179, which were approved on September 25, 2020
- Changes to enable online enrollment of patients (and to enable an online digital signature for LEMTRADA REMS patient enrollment forms)
- Changes to allow pharmacies to obtain authorization to ship product online via www.lemtradarems.com
- Incorporation of formatting, layout, and wording changes to the Infusion Checklist to provide clarity and consistency with LEMTRADA REMS materials
- Consolidation of selected REMS materials in order to eliminate redundancy
- Change in the timeframe to return unused Lemtrada vials from 50 business days to 75 business days

- Addition of a Patient Transfer of Care Form as a new REMS material

Communication Plan: We have determined that the communication plan is no longer necessary as an element of the REMS to ensure the benefits of Lemtrada (alemtuzumab) outweigh its risks because the communication plan has been completed and the most recent assessment demonstrates that the communication plan has met its goals. No further assessments are necessary to assess the current communication plan.

Your proposed modified REMS, submitted on April 10, 2020, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS must be revised to submit a REMS assessments on November 14, 2021, and every 2 years thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Program Operation and Performance Data (per reporting period and cumulatively):
 - a. REMS Website
 - i. Number of unique visits to the LEMTRADA REMS Website
 - ii. Number of REMS materials downloaded or printed for each material
 - b. REMS Call Center
 - i. Summary of call center data frequently asked questions
 - ii. Unintended system interruptions and resolution
 - iii. Summary report of REMS-related problems identified and resulting corrective actions
2. REMS Certification and Enrollment Statistics (per reporting period and cumulatively)
 - a. Prescriber certification:
 - i. Number of newly certified prescribers reported by region
 1. Number of attempts at knowledge assessment prior to successful completion
 2. Most frequently missed knowledge assessment questions
 - ii. Number of active certified prescribers (i.e., have prescribed the drug during the reporting period for at least one patient)
 - iii. Number of prescribers deactivated and reasons for deactivation
 - iv. Number of these that subsequently become re-certified
 - b. Patient enrollment:

- i. Number of newly enrolled patients
 - ii. Number of active patients (i.e., those who received at least one dose or who are in follow-up during the reporting period)
 - a. Number of unique patients who received at least one dose during the reporting period
 - b. Number of unique patients who are in follow-up during the reporting period
 - c. Certified infusion sites:
 - i. Number and kind of facility (free-standing infusion center, hospital-based infusion center, other) for newly certified healthcare facilities; geographic region
 - ii. Number of active certified healthcare facilities (i.e., have administered LEMTRADA at least once during the reporting period reported in total and aggregate by kind of facility)
 - d. Certified pharmacies:
 - i. Number and geographical region of newly certified pharmacies
 - ii. Total number of active certified pharmacies (i.e., have dispensed LEMTRADA at least once during the reporting period)
- 3. LEMTRADA Utilization Data
 - a. Dispensing activity:
 - i. Number of orders received and number of orders shipped
 - ii. Total number of infusions administered
 - iii. Number of vials distributed
 - 1. Number distributed by distributors
 - 2. Number distributed by certified pharmacies
 - iv. Number of vials returned outside of 75-business day window
 - v. Disposition of vials once returned (retained or destroyed)
- 4. REMS Compliance (per reporting period and cumulatively)
 - a. Stakeholder Program Compliance (for each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
 - i. Prescribers:
 - a. Number of non-certified prescribers who have written one or more prescriptions
 - ii. Pharmacies:
 - a. Number of orders shipped to non-certified infusion centers
 - b. Number of certified pharmacies deactivated and reason for deactivation
 - iii. Distributors:
 - 1. Number of orders shipped to non-certified healthcare facilities
 - 2. Number of orders shipped to non-certified pharmacies
 - iv. Infusion centers
 - 1. Number of administrations occurring in non-certified infusion centers

2. Number of administrations occurring in non-verified patients
 3. Number of infusion checklists submitted
 4. Number of infusion checklists expected
 5. Number of days between last infusion and receipt of infusion checklist (median, mean, range)
 6. Number of infusion checklists that are submitted beyond the targeted time frame of five days during each reporting period
 7. Number of infusion centers that did not have the necessary equipment (i.e., to manage serious infusion reactions including anaphylaxis, cardiac and respiratory emergencies). Include the number of patients involved.
 8. Number of certified healthcare facilities deactivated and reason for deactivation
- b. Audit findings (per reporting period and cumulatively)
- i. A summary of audit activities to ensure all processes and procedures are in place and functioning to support the requirements of the LEMTRADA REMS Program
 - Provide a copy of the audit plan for each stakeholder.
 - Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event led to de-certification from the REMS.
 - ii. Reports of observations identified and the associated corrective and preventive action (CAPA) plans, and whether the CAPA plans were satisfactorily completed; include the following:
 - The number of audits expected, and the number of audits performed. Provide detailed analysis for any audits not conducted as required.
 - Specific criteria for observation classifications as they relate to REMS requirements
 - The number and type of deficiencies noted for each group of audited stakeholders.
 - For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
 - For any that did not complete the CAPA within one month of the audit, describe actions taken.
 - Include a unique identifier for each stakeholder that had deviations to track deviations by stakeholder over time
 - Verification for each audited stakeholder's site that the designated authorized representative remains the same. If different, include the number of new authorized representative and verification of the site's recertification.

Safe Use Behaviors

5. REMS Patient Authorization and Baseline Lab Form (per reporting period and cumulatively)
 - a. Time between receipt of initial *Patient Authorization and Baseline Lab Form* and LEMTRADA administration (in days: mean, median, range), the total number of patient authorization forms submitted, the number of patient authorizations submitted beyond 30 days during each reporting period, and reason for delays beyond 30 days after receipt of the initial authorization
6. Patient Status Form (per reporting period and cumulatively)
 - a. The total number of Patient Status Forms expected, and the number and percentage received
 - i. The number of Patient Status Forms received reporting “no” for the patient had completed the periodic monitoring within the last 6 months
 - ii. The number of Patient Status Forms received reporting the patient is no longer under the care of the current healthcare provider
 1. The number of Patient Forms received reporting the patient’s current healthcare provider is unknown
 - b. The total number of unique patients who are not being followed for the required 48 months of lab monitoring
 - i. Reason no longer in follow-up (e.g. death, patient refused, graduated, lost to follow-up)
 - ii. Duration of follow-up that was completed
 - c. The number of unique patients who did not have labs completed as reported on the Patient Status Form

Knowledge

7. Evaluation of knowledge (every two years with each assessment report)
 - a. An evaluation of patient understanding of the serious risks of autoimmune conditions, infusion reactions, stroke, and malignancies associated with treatment with LEMTRADA, and the need for baseline and periodic monitoring
 - b. An evaluation of healthcare providers’ understanding of the serious risks of autoimmune conditions, infusion reactions, stroke, and malignancies associated with LEMTRADA, the need to counsel patients regarding these risks and the need for baseline and periodic monitoring
 - c. An evaluation of healthcare facility staff understanding of the risks of infusion reactions associated with LEMTRADA administration and the management and documentation of these reactions, as well as the requirements of the LEMTRADA REMS including pre-infusion counseling prior to each infusion
8. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the

strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted

assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 103948 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES,
AUDIT PLAN, DRUG USE STUDY)**

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 103948 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR BLA 103948/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 103948/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 103948/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103948/ S-000
REMS ASSESSMENT**

PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 103948

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Candido Alicea, Regulatory Project Manager, at (240) 402-8310.

Sincerely,

{See appended electronic signature page}

Alice T.D. Hughes, MD
Deputy Director for Safety
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE:

- REMS

U.S. Food and Drug Administration
Silver Spring, MD 20993
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/s/

ALICE HUGHES
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