



BLA 103948/5139

SUPPLEMENT APPROVAL

Genzyme Corporation
Attention: Jennifer Panagoulas, RAC
Global Therapeutic Head, Regulatory Affairs Neurology
500 Kendall Square
Cambridge, MA 02142

Dear Ms. Panagoulas:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received November 27, 2012, submitted under section 351 of the Public Health Service Act for Lemtrada (alemtuzumab) injection.

We acknowledge receipt of your amendments dated April 15, 2014, May 15, 2014, May 20, 2014, June 13, 2014, July 1, 2014, July 2, 2014, July 10, 2014 (2), July 15, 2014, July 18, 2014, July 21, 2014, July 22, 2014, July 23, 2014, July 29, 2014, July 30, 2014, August 4, 2014, August 6, 2014, August 7, 2014, August 8, 2014, August 27, 2014, September 5, 2014, September 8, 2014, September 12, 2014, October 15, 2014, October 21, 2014, October 27, 2014, November 7, 2014, November 12, 2014, November 13, 2014, and November 14, 2014 (3).

The April 15, 2014, and May 15, 2014, submissions constituted a complete response to our December 27, 2013, action letter.

This Prior Approval supplemental biologics application provides a new indication, the use of Lemtrada for the treatment of patients with relapsing forms of multiple sclerosis, and an associated risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effectuated” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 15, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “Product Correspondence – Final Printed Carton and Container Labels for approved BLA 103948/5139.” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups. The evidence includes the known risks of serious autoimmune conditions, malignancies, and infections for which patients may be at risk for several years after the last infusion, as well as the risk of potentially fatal infusion reactions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of embryoletality or to identify the unexpected serious risk of adverse maternal, fetal, and infant outcomes in women exposed to Lemtrada (alemtuzumab) during pregnancy, and of adverse effects on postnatal growth and development in exposed fetuses. In addition, analysis of spontaneous postmarketing adverse events will not be sufficient to assess the known serious risks of autoimmune conditions, malignancies, serious infections including opportunistic infections, and pneumonitis that may occur after a currently undefined period of time following completion of therapy with Lemtrada (alemtuzumab), or the known serious risk of infusion reactions (including anaphylaxis and cardiac and respiratory emergencies) that occur during or after Lemtrada (alemtuzumab) infusion.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2832-1 A prospective, registry-based observational exposure cohort study conducted in the United States, that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Lemtrada (alemtuzumab) during pregnancy to unexposed control populations (one with women with multiple sclerosis who have not been exposed to Lemtrada (alemtuzumab) in pregnancy and the other in women without multiple sclerosis). The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/15
Study Completion: 06/20
1st Annual Interim Report: 11/15
2nd Annual Interim Report: 11/16
3rd Annual Interim Report: 11/17
4th Annual Interim Report: 11/18
5th Annual Interim Report: 11/19
Final Report Submission: 04/21

2832-2 A pre- and postnatal development (including maternal function) study of Lemtrada (alemtuzumab) in rHu CD52 mouse.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/15
Study Completion: 03/16
Final Report Submission: 09/16

2832-3 A prospective observational registry study in adult patients with relapsing multiple sclerosis, with the primary objective of determining the necessary duration of monitoring following treatment with Lemtrada (alemtuzumab) for multiple sclerosis and to further inform appropriate monitoring conditions. Events of interest include autoimmune-mediated conditions, malignancies, serious infections including opportunistic infections, and pneumonitis. A minimum of 5000 multiple sclerosis patients treated with Lemtrada (alemtuzumab) should be enrolled and followed for a minimum of 10 years following the first exposure to Lemtrada (alemtuzumab). The protocol should specify an appropriate comparator population(s) to which observed incidence rates will be compared.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/15
Study Completion:	08/28
1 st Annual Interim Report:	11/15
2 nd Annual Interim Report:	11/16
3 rd Annual Interim Report:	11/17
4 th Annual Interim Report:	11/18
5 th Annual Interim Report:	11/19
6 th Annual Interim Report:	11/20
7 th Annual Interim Report:	11/21
8 th Annual Interim Report:	11/22
9 th Annual Interim Report:	11/23
10 ^h Annual Interim Report:	11/24
11 th Annual Interim Report:	11/25
12 th Annual Interim Report:	11/26
13 th Annual Interim Report:	11/27
Final Report Submission:	03/29

2832-4 A prospective study in adult patients with relapsing multiple sclerosis to assess patient safety during and after Lemtrada (alemtuzumab) infusion in multiple sclerosis patients. Measurements of interest include: 1) Duration of infusion; 2) Vital signs at baseline, during infusion, and during post-infusion observation for each infusion in the infusion cycle; 3) Serious adverse events that occur during and start within 24 hours of infusion; and 4) Serious adverse events that start within 7 days of infusion. A minimum of 300 multiple sclerosis patients treated with Lemtrada (alemtuzumab) should be enrolled.

The timetable you submitted on November 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/15
Study Completion:	01/17
Final Report Submission:	07/17

The final protocols for these PMRs should reflect Agency agreement and be submitted prior to starting the studies.

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 010717, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required**

Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Lemtrada (alemtuzumab) to ensure the benefits of the drug outweigh the risks of autoimmune conditions, infusion reactions, and malignancies.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Pursuant to 505-1(f)(1), we have also determined that Lemtrada (alemtuzumab) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of autoimmune conditions, infusion reactions, and malignancies that are listed in the labeling. The elements to assure safe use will ensure that only certified prescribers prescribe Lemtrada (alemtuzumab), ensure that Lemtrada (alemtuzumab) is dispensed only in certain healthcare settings, specifically, certified pharmacies, and certified infusion sites that have on-site access to equipment and personnel trained to manage infusion reactions; that certified infusion sites monitor patients for infusion reactions during and after each Lemtrada (alemtuzumab) infusion; that only enrolled and authorized patients receive Lemtrada (alemtuzumab); and that certified prescribers submit documentation of periodic monitoring of patients who receive Lemtrada (alemtuzumab) to identify autoimmune conditions and malignancies.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval

of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on November 14, 2014, and appended to this letter, is approved. 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.

Your REMS must be fully operational before you introduce Lemtrada into interstate commerce.

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

1. REMS Program Outreach/Communication Plan activities: Genzyme will provide the following:
 - a. Numbers of REMS letters sent to prescribers. Include information on initial and follow up mailings via regular mail or email, and the number of mailings that were returned (regular mail) or unopened (email) as well as those that were sent hard copy letters following failure to open second email.
 - b. Number of unique visits to the Lemtrada REMS website
2. REMS Program Utilization Statistics
 - a. Prescriber certification: for the current reporting period and cumulatively
 - i. Number, specialty, and geographic location of newly certified prescribers
 1. Breakdown of number of attempts at knowledge assessment prior to successful completion
 2. Most frequently missed knowledge assessment questions
 - ii. Total number of active certified prescribers (i.e., have prescribed the drug during the reporting period for at least 1 patient)
 - iii. Number of prescribers deactivated and reasons for deactivation
 1. Number of these that subsequently become re-certified
 - b. Patient enrollment: for the current reporting period and cumulatively
 - i. Number of newly enrolled patients
 - ii. Total number of patients
 - c. Certified Infusion sites: for the current reporting period and cumulatively:
 - i. Number, geographical location, and site affiliation (academic or community medical center, or other) of newly certified healthcare facilities
 - ii. Total number of active certified healthcare facilities (i.e., have administered Lemtrada at least once during the reporting period)
 - iii. Number of certified healthcare facilities deactivated and reason for deactivation

- d. Certified pharmacies: for the current reporting period and cumulatively:
 - i. Number and geographical location of newly certified pharmacies
 - ii. Total number of active certified pharmacies (i.e., have dispensed Lemtrada at least once during the reporting period)
 - iii. Number of certified pharmacies deactivated and reason for deactivation
 - e. Dispensing activity: for the current reporting period and cumulatively
 - i. Number of orders received and number of orders shipped
 - ii. Total number of vials distributed
 - 1. Number distributed by distributors
 - 2. Number distributed by certified pharmacies
 - iii. Number of vials returned outside of 50 day window
 - iv. Disposition of vials once returned (retained or destroyed)
3. REMS Program Infrastructure and Performance
- a. Time between receipt of initial Prescription Ordering and Authorization Form and Lemtrada administration (mean, median, range) and an analysis summarizing any reasons for delays
 - b. Summary of call center data frequently asked questions
 - c. Unintended system interruptions and resolution
 - d. Program compliance
 - i. Prescribers
 - 1. Number of non-certified prescribers who have written one or more prescriptions
 - ii. Pharmacies
 - 1. Number of orders shipped to non-certified healthcare facilities
 - iii. Distributors
 - 1. Number of orders shipped to non-certified healthcare facilities
 - 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)
 - v. Patient status forms - see proposed table for provision of data*
 - e. Audit findings
 - 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

- ii. Reports of critical observations identified and the associated corrective and preventive action (CAPA) plans, and whether the CAPA plans were satisfactorily completed
4. Evaluation of knowledge – first submission with the 12 month assessment and each annual assessment thereafter
 - a. An evaluation of patient understanding of the serious risks of autoimmune conditions, infusion reactions, 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, 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.
 5. 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.

*Compliance with patient status forms

Number received reporting period		Number received program-to-date	Number Expected reporting period	Number Expected program-to-date	% compliance reporting period	% compliance cumulative
stating "no" labs completed						
# no longer under MD care						
without new MD identified						

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, 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.

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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

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

**BLA 103948 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 103948
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103948
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING SURVEILLANCE

We request that you provide expedited reporting of the following postmarketing adverse events when they are serious: immune thrombocytopenia, other cytopenias or bleeding events, glomerular nephropathies, herpes viral infections, and opportunistic infections. Annual reporting should include a cumulative analysis of these events.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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 Hamet Touré, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
11/14/2014