DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103948/S-5160/S-5165

SUPPLEMENT APPROVAL
REMS MODIFICATION NOTIFICATION

Sanofi Genzyme
Attention: Priti C. Lad, Pharm.D.
Director, Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Lad:

Please refer to your Supplemental Biologics License Applications (sBLAs), dated and received October 19, 2017, and September 14, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lemtrada (alemtuzumab).

We also refer to our letter dated August 16, 2018, notifying you, under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA), of new safety information that we believe should be included in the labeling for alemtuzumab. This information pertains to the risk of stroke (including ischemic and hemorrhagic stroke) and cervicocephalic arterial dissection.

Supplemental Biologics License Application 5165 provides for revisions to the labeling for Lemtrada, consistent with our August 16, 2018, Safety Labeling Change Notification letter.

Supplemental Biologics License Application 5160 provides for the following revisions:

- Revisions to Section 2 (Dosage and Administration) to allow for additional as-needed treatment courses
- Updated information about exposure and adverse drug reactions
- Conversion to labeling consistent with the Pregnancy and Lactation Labeling Rules (PLLR).

Supplemental Biologics License Application 5160 also provides for proposed modifications to the approved Lemtrada risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are 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 prescribing information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (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 Effected" (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 these supplemental applications, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt 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 April 5, 2016. 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.

Approval of Supplement 5160 REMS Modification

Your proposed modifications to the REMS consist of updating the REMS document to the new format, changes to the REMS document and REMS materials to conform to labeling changes being approved with supplement 5160, as well as editorial changes to the REMS document and materials.

Your proposed modified REMS, submitted on October 19, 2017, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on November 14, 2014.

There are no changes to the REMS assessment plan described in our April 13, 2016, letter.

REMS Modification Notification to align REMS with safety labeling changes being approved under supplement 5165

We refer to our letter dated August 16, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for alemtuzumab (Lemtrada), and the approval of the safety labeling changes being approved under supplement 5165. The labeling changes pertain to the risks of stroke (including ischemic and hemorrhagic stroke) and cervicocephalic arterial dissection.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for Lemtrada must be modified to ensure that the benefits of the drug outweigh its risks.

This determination is based on the need to align the approved REMS to the safety labeling changes being approved under supplement 5165.

Your approved REMS must be modified as follows:

- Modifications must be made to the REMS document and REMS forms and materials to incorporate information about reports of stroke and cervicocephalic arterial dissection in Lemtrada-treated patients, consistent with the labeling changes being approved under supplement 5165.

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on November 14, 2014.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a modified REMS as described above is necessary to ensure the benefits of Lemtrada outweigh the risks, you must submit a proposed REMS modification within 60 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your BLA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR BLA 103948/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT 5165

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

BLA 103948/S-XXXX
PROPOSED REMS MODIFICATION-AMENDMENT

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

Other REMS-related information

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 the 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

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 LABEL 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, include the SPL file with your proposed REMS modification submission.

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

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 prescribing information to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, 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.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance of cases of stroke and/or cervicocephalic dissection in patients treated with Lemtrada. We request expedited reporting of all cases directly to the Division of Neurology Products and we request annual reporting as follows:

1. Provide a summary and analysis of cases of stroke and/or cervicocephalic dissection in patients treated with Lemtrada. Use the same search methods (including the same Preferred Terms) used in the July 16, 2018, response to the FDA request for information.

2. Provide a dataset listing (sas transport file) of all cases of stroke (ischemic or hemorrhagic) or arterial dissection. Provide a description of your search criteria. Each row should represent an individual patient. In the dataset, provide columns with the following data:
    a. Manufacturer case ID in the format used in FAERS (starting with 2-letter country code, e.g., FR-SA-2015SA061351, US-SA-2015SA071958, US-SA-2015SA074374)
    b. Adverse event Preferred Term(s)
    c. Patient sex
    d. Patient age (years)
    e. Patient country of origin
    f. Start date for first adverse event (adverse event applicable to this search)
    g. Date of first Lemtrada infusion
    h. Date of last Lemtrada infusion (prior to adverse event start date)
    i. Number of days from date of last Lemtrada infusion (prior to adverse event start date) to first adverse event start date
    j. Serious adverse event (Yes/No)

2. Provide a listing of which case IDs are duplicate cases (applicable to Item 2).

3. For each of the cases listed in the response to Item 2, provide the adverse event reports submitted to FAERS. Provide a table of contents listing each case ID (as listed in the response to Item 1) with a hyperlink to the corresponding case report.

4. Using the cut-off date applied to the case search, provide the total number of patients exposed to Lemtrada: a) worldwide; and b) in the United States.

5. Using the cut-of date applied to the case search, provide the total number of person-years of patient exposure to Lemtrada: a) worldwide; and b) in the United States.

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 LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
11/28/2018