Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Addendum to sBLA 103948\5139 Package

Date:	**October 21, 2013**
To:	**Members of the Peripheral and Central Nervous System Drugs Advisory Committee**
From:	**Division of Risk Management** **Office of Medication Error Prevention and Risk Management** **Office of Surveillance and Epidemiology (OSE)**
Subject:	**Risk Management Options**
Product:	**Alemtuzumab (sBLA 103948)**

1 Introduction

This memorandum summarizes Genzyme Corporation's proposed risk evaluation and mitigation strategy (REMS) and provides an analysis of the minimally required risk mitigation tools necessary to address the risk of autoimmune conditions (immune thrombocytopenic purpura [ITP], thyroid disorders, and nephropathies), malignancies, infusion reactions and serious infections associated with alemtuzumab for the proposed treatment of relapsing forms of multiple sclerosis (MS).

2 Background

2.1 Product Information

Proposed Indication

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody. Genzyme is seeking approval to market alemtuzumab (sBLA 103948) for the treatment of patients with relapsing forms of multiple sclerosis (MS).

Alemtuzumab, under the proprietary name Campath®, was approved on May 7, 2001 under BLA 103948 for the treatment of B-cell chronic lymphocytic leukemia (B-CLL). While no longer available commercially (effective September 4, 2012), Campath® is available at no cost to qualified patients in the U.S. through the *US Campath Distribution Program*.

Product Dosage and Administration

Alemtuzumab for the proposed MS indication will be available as a 12mg/1.2 mL single use vial (10 mg/mL). The proposed initial dosage is 12mg/day for 5 consecutive days administered as an IV infusion, followed by a second treatment course of 12mg/day for 3 consecutive days. The second treatment course is administered 12 months after initial treatment. Premedication with corticosteroids immediately prior to alemtuzumab administration for the first 3 days of any treatment course is recommended.

2.2 Intended Population: Patients with relapsing forms of MS

Multiple Sclerosis (MS) is a chronic disorder of the central nervous system that can cause disability ranging from relatively benign, to severe, including complete paralysis. Often referred to as an autoimmune disease, the disorder occurs when the body (through its immune system) launches an attack on its own nerve-insulating myelin. Patients with MS often present with initial symptoms that include motor weakness, blurred or double vision, paresthesia (numbness or tingling sensation of the skin), or even bladder dysfunction. A latency period of 1 to 10 years or longer can occur between the presentation of initial symptoms and the subsequent development of more characteristic signs of the disease such as the radiologic appearance of lesions primarily affecting the white matter of the brain and spinal cord.

While there are several recognized forms of MS including "primary progressive disease" and "secondary progressive disease", "relapsing–remitting disease" is most common.[1] In patients with relapsing-remitting MS, there is an interval of months to years between the presentation of initial symptoms and a recurrence of those symptoms or development of new clinical findings. Eventually the relapses in patients with this form of MS tend to occur more frequently along with incomplete remissions, leading to increased disability.

2.3 Risk Evaluation and Mitigation Strategies[2]

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

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[1] Aminoff MJ, Kerchner GA. Chapter 24. Nervous System Disorders. In: Papadakis MA, McPhee SJ, Rabow MW, Berger TG, eds. *CURRENT Medical Diagnosis & Treatment 2014*. New York: McGraw-Hill; 2013.

[2] FDA Draft Guidance for Industry – *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, dated September 2009. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

3 Risks of Concern

Alemtuzumab is associated with serious risks that may exceed the benefits, including the risk of autoimmune diseases, malignancies, serious infections, and infusion reactions.

Autoimmune Diseases

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody that depletes cells carrying CD52; its use can increase a patient's risk for autoimmune conditions including thyroid disorders, cytopenias and nephropathies. Altered immune reconstitution is a likely underlying mechanism of the autoimmunity with alemtuzumab.

- Thyroid disorders- Patient thyroid function was monitored quarterly during clinical trials. Thyroid disorders (defined as a thyroid adverse event and/or thyroid laboratory abnormality) occurred in 38.6% of alemtuzumab 12mg/day treated patients compared to 28.2% in the IFNB-1a group, based on analysis of data in all active-controlled studies. Thyroid disorders observed included hypothyroidism, hyperthyroidism and Basedow's disease (also known as Graves' disease). The risk of experiencing a "first thyroid AE" was most increased between 6 and 42

months post-infusion. Serious thyroid AEs were reported in 30 of 1485 alemtuzumab-treated patients, 19 of which required thyroidectomy.

- Immune Cytopenias seen after alemtuzumab treatment include immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA), and autoimmune pancytopenia. ITP was confirmed in 26 of 1485 (1.8%) of alemtuzumab-treated patients as of November 26, 2012, including one death in a 39-year old male who died from ITP and cerebral hemorrhage 7 months after receiving his second cycle of treatment with alemtuzumab. Confirmed ITP was typically diagnosed 4-51 months post-initial alemtuzumab dose and 1-39 months after the last dose.
- Autoimmune kidney diseases, including anti-Glomerular Basement Membrane (anti-GBM) disease (also known as Goodpasture's disease) and membranous glomerulonephritis, have occurred after alemtuzumab treatment. Two published cases and two Medwatch cases describe alemtuzumab-treated patients who developed anti-GBM disease and subsequent end-stage renal disease or chronic dialysis dependence, despite anti-GBM disease treatment.

Sponsor-proposed labeling recommends periodic monitoring of complete blood counts, serum creatinine levels and urinalysis (with urine cell counts) during treatment and until 48 months after the last infusion for patients receiving alemtuzumab. This proposed monitoring is less frequent than what was performed in clinical trials. The proposal does not include the monthly ITP symptom monitoring survey (offset by 2 weeks from blood testing), which was performed in Phase 3 trials. Quarterly urinalyses are proposed, compared to the monthly urinalyses done in Phase 3 trials.

Malignancies

A total of 22 of 1485 alemtuzumab-treated subjects had a treatment-emergent malignancy, including cases of thyroid cancer, melanoma, breast cancer, and HPV related cancers. All but one of these cases occurred in female patients. The incidence of thyroid cancer was of particular concern, with 6 cases (5 in females) reported in alemtuzumab treated subjects. The SEER[3] reference rate for thyroid cancer for U.S. females (all races) was 18.2 cases per 100,000 person-years, while the rate for female alemtuzumab patients as observed in clinical trials, was 129.6 cases per 100,000 person-years.

Infusion Reactions

Infusion of alemtuzumab is associated with a cytokine release syndrome. Serious infusion reactions were reported in 37 of 1485 (2.5%) alemtuzumab treated subjects.

Infusion-related SAEs reported include:

- Chest pain
- Sinus bradycardia
- Headache
- Atrial fibrillation
- Hypotension

[3] National Cancer Institute, Surveillance Epidemiology and End Results-SEER Stat Fact Sheets: Thyroid. Available at: http://seer.cancer.gov/statfacts/html/thyro.html.

- Anaphylactic shock
- Hypertension
- Sinus tachycardia
- Increased liver transaminases
- Rash
- Brain stem syndrome
- Angioedema
- Pleuritis
- Pyrexia
- Edema
- Cellulitis

Vital signs were not systemically measured during and after infusion in Phase 2 and 3 trials.

Serious Infections

There is appreciable evidence linking MS to chronic infections, with several studies suggesting the presence of persistent viral infections in the etiology of chronic neurological diseases such as multiple sclerosis.[4] While infections were frequently reported in both alemtuzumab and IFNB-1a treated patients, the incidence of infection–related AEs was greater with alemtuzumab 12 mg/day (70.9%) compared to IFNB-1a (53.2%).

4 Risk Management Options

A variety of strategies are used to minimize risks associated with drugs and therapeutic biologics. These strategies minimize risks in a number of ways. They can communicate specific risk information, as well as information regarding optimal product use. In addition, they can provide guidance and/or assure adherence to certain prescribing, dispensing, or monitoring requirements, and/or limit use of a product to only the most appropriate situations or patient populations.

4.1 Sponsor Proposed REMS

Genzyme's proposed REMS for alemtuzumab for the MS indication includes the following elements: a Medication Guide, communication plan, elements to assure safe use (ETASU), Implementation System and a Timetable for Submission of Assessments of the REMS.

The proposed REMS includes the following goals and elements:

Goals

The sponsor's proposed REMS goals for Lemtrada are:

[4] Gilden DH. Infectious causes of multiple sclerosis. Lancet Neurol. 2005;4:195–202.

- To inform patients and healthcare providers (HCPs) about the serious risks associated with the use of Lemtrada, including autoimmune conditions (immune thrombocytopenic purpura [ITP], thyroid disorders, and nephropathies including anti-glomerular basement membrane disease [anti-GBM disease]) and serious infections.
- To mitigate the severity and sequelae of incident autoimmune events (ITP, thyroid disorders, and nephropathies [including anti-GBM disease]) and serious infections by educating patients and HCPs on the appropriate monitoring for, as well as the prompt identification of, signs and symptoms of these events.

REMS Elements

A. Medication Guide

A Medication Guide will be dispensed with each Lemtrada prescription in accordance with 21 CFR§208.24.

B. Communication Plan

The sponsor has proposed a communication plan targeting HCPs (primarily neurologists) who diagnose, treat, and manage patients with MS. Dear Healthcare Provider (DHCP) letters will be sent to prescribers who have written at least one prescription within the last 2 years for a drug to treat MS. Letters will be sent prior to first availability of Lemtrada to HCPs, and at 12- and 24-months post-approval. Prescribing Information, Medication Guide and a "Guide to Important Safety Information Brochure" will also be sent with these mailings.

C. Element to Assure Safe Use

The Sponsor proposed the following elements to assure safe use:

- Prescriber certification: Alemtuzumab would only be prescribed by healthcare providers who are specially certified by enrolling in the REMS Program (also referred to by the Sponsor as the Lemtrada Alliance Program).Training and education will target neurologists as the likely prescribers of LEMTRADA.

  The proposed Lemtrada Alliance Program consists of the following materials to support the training and educational process:
  - Full Prescribing Information
  - Medication Guide
  - Starting Lemtrada (alemtuzumab): An Overview of the Lemtrada Alliance Program (prescriber educational slide deck)
  - Lemtrada Alliance Program Overview
  - Guide to Important Safety Information Brochure
  - Lemtrada Alliance Patient Card

- Healthcare facility certification: Alemtuzumab would only be dispensed by pharmacies, practitioners, or health care settings that are specially certified.

Dispensing facilities (e.g., infusion centers and physician practices) would be required to enroll in the Lemtrada Alliance Program and have a system to verify prescriber and patient enrollment, as well as to maintain records and other documentation of compliance with program requirements. Staff involved in Lemtrada dispensing and administration will be educated on the program requirements.

Certified healthcare facilities place orders with the Lemtrada Alliance Program who will then transmit orders to authorized specialty pharmacies or a distribution center.

- Patient enrollment: Certified prescribers would enroll patients in the Lemtrada Alliance Program. Patients would be counseled and attest to understanding the risks and benefits of Lemtrada and the monitoring requirements in order to receive Lemtrada. Certified healthcare facilities would be required to verify patient enrollment as documentation of safe-use conditions before dispensing or administering Lemtrada.

Genzyme states that they are considering an annual reauthorization process whereby enrolled prescribers would be required to document their continued requirement to counsel patients on any identified risks, to perform lab monitoring and to review these labs on an ongoing basis. In addition, a Lemtrada Alliance Program Call Center and website will be established to support enrolled HCPs, patients and dispensing facilities.

D. Implementation System

A restricted distribution system will be established to ensure that alemtuzumab is distributed only through certified healthcare facilities.

Under the proposed implementation system for alemtuzumab, the sponsor will:

- Maintain a validated and secure database of all HCPs, healthcare facilities and patients enrolled in the Lemtrada Alliance Program to monitor and evaluate implementation of the REMS ETASU.
- Monitor distribution and prescription data to ensure that only enrolled HCPs are prescribing alemtuzumab, enrolled healthcare facilities dispensing and administering alemtuzumab, and enrolled patients are receiving alemtuzumab.
- Update the status of enrolled patients to include any change in prescriber, discontinuation of treatment or lost to follow-up.
- Maintain a Lemtrada Alliance Program Call Center to provide support for enrolled HCPs, patients and healthcare facilities. A toll-free number and Lemtrada website will also be established.
- Update materials and notify HCPs and healthcare facilities (as applicable) if there are substantial changes to the Lemtrada Alliance Program.

Genzyme has also proposed to utilize a centralized laboratory service that will be offered to all enrolled prescribers and patients. This service will provide the following:

- Labs conducted at no cost at a facility local to the patient; the services of a traveling phlebotomist will also be provided.

- Tracking of compliance with laboratory monitoring through data collected once patients have completed each lab visit.
- Test reminders (through phone calls, emails, text messages and/or postal mail) sent to patients reminding them of their testing commitment and the importance of compliance with the laboratory monitoring requirements.
- Notification to prescribers if any of their participating patients have missed lab tests. Prescribers enrolled in the service will also be provided with a monthly status report on compliance among their participating patients.

Genzyme anticipates that most prescribers enrolled in the LEMTRADA Alliance Program will choose to utilize this centralized laboratory service.

E. Timetable for Submission of Assessment

The sponsor proposes to submit REMS Assessments to the Agency at 12 months from the date of initial approval of the Lemtrada REMS, and then annually for up to 7 years. 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. The sponsor will submit each assessment so that it will be received by the FDA on or before the due date.

REMS Assessment Plan

The sponsor-proposed REMS assessment plan will include the following to assess whether the REMS is meeting its intended goals:

1. Survey study to evaluate patient and prescriber understanding of the serious risks associated with Lemtrada, identification of signs and symptoms, and laboratory monitoring requirements. Survey protocol and data collection instruments will be submitted to the Agency for review at least 90 days before the evaluation is conducted.
2. Assessment of the Medication Guide dispensing and distribution in accordance with 21 CFR§208.24 during the reporting period and cumulatively. The assessment will include information on any failures to adhere to dispensing and distribution requirements.
3. Assessment of patient, HCP and healthcare facility enrollment in the Lemtrada Alliance Program. Reported information will include the following:
    a. Number of enrolled HCPs trained and certified during the reporting period and cumulatively
    b. Number and status of enrolled patients during the reporting period and cumulatively
    c. Number of enrolled healthcare facilities during the reporting period and cumulatively
    d. Number of HCPs and healthcare facilities de-enrolled during the reporting period and cumulatively; reported by reason for deactivation (including noncompliance)
4. Metrics regarding the number of Lemtrada orders received and shipped for the reporting period and cumulatively; reporting to include a subset by compliance with program requirements.

5. Corrective and preventive measures implemented to address issues of noncompliance with distribution and dispensing requirements.
6. Descriptive analyses of post-marketing adverse events reports of autoimmune conditions (immune thrombocytopenic purpura [ITP], thyroid disorders, and nephropathies including anti-glomerular basement membrane disease [anti-GBM disease]) and serious infection with LEMTRADA use during the reporting period and cumulatively.
7. Assessment of whether the REMS is meeting its goals and if modifications to the REMS are needed based on the information collected.
8. Information on the status of any post-approval study required under section 505(o) or otherwise undertaken to investigate a safety issue.

4.2 Summary of Agency Recommendations

While the sponsor-proposed REMS provides strategies to educate prescribers and patients on the serious risks and the need for appropriate monitoring with the use of alemtuzumab for MS, they do not propose strategies to ensure that safe use conditions are followed and patients are monitored appropriately. As such, it is critical that data on compliance with laboratory monitoring requirements and the occurrence of drug-related adverse events of interests is documented and reported through the REMS. In addition, due to the serious infusion related adverse events observed during clinical trials, the monitoring of patient's vital signs during and post-infusion is also necessary.

In addition to the sponsor-proposed REMS enrollment and certification requirements for healthcare providers who wish to prescribe and for healthcare facilities who wish to dispense and infuse alemtuzumab for the MS indication, these entities would undertake the following requirements:

1) Certified prescribers will complete and submit periodic patient status reports to document the following:
   a) Compliance with the laboratory monitoring requirements during the reporting period (to be specified)
   b) The occurrence of any adverse events of special interests (to be further defined in the patient status report) during the reporting period

2) Certified healthcare facilities will complete and submit an infusion checklist to screen patients prior to infusion, and monitor patients during- and post-infusion. This checklist will document at a minimum the following:
   a) That a patient status report has been submitted that includes the name and date for all required laboratory monitoring conducted during the specified timeframe
   b) The setting in which the infusion is being administered (e.g., hospital)
   c) The monitoring of patient's vital signs during and for a specified timeframe (yet to be determined) post-infusion

Patients would be subject to the laboratory monitoring requirements described in the sponsor's educational materials and compliance with these requirements would be linked to distribution. Certified healthcare facilities would be required to confirm that patient status reports have been submitted documenting compliance with the required laboratory monitoring before receiving authorization to administer the infusion.

5 Discussion

If alemtuzumab is approved for the proposed MS indication, a risk mitigation strategy (beyond labeling) will be necessary to ensure the benefits outweigh the serious risks including autoimmune disorders, malignancies, serious infection, and infusion reactions. This strategy, at a minimum, should include controls to ensure patients are monitored during and post infusion and that there are strategies in place to ensure that patients are being monitored during the 12 month timeframe between each treatment course, including compliance with laboratory monitoring.

The FDA's minimum requirements strive to balance the mitigation of the serious risks with the burden on the healthcare system. Similar REMS requirements have been implemented for a currently marketed MS product. The advantages of ensuring that the requirements outlined in the minimum strategy are met are that it encourages patient and prescriber compliance with the laboratory monitoring requirements. These minimum requirements also help to ensure that healthcare facilities confirm a patient's level of compliance with laboratory monitoring requirements before infusion. In addition, the requirement for monitoring of patient vital signs supports the prompt identification and treatment of infusion reactions. This program however adds burden to the certified prescribers and certified healthcare facilities.

While the FDA proposed REMS with ETASU contains the minimally necessary requirements to provide some assurance that the patients will be monitored appropriately, the REMS will not prevent all serious adverse events associated with the administration of alemtuzumab. The frequency of laboratory monitoring is less than what was done during clinical testing, so it is possible that event rates will be even higher than those observed in clinical trials. Additionally, laboratory monitoring and outcomes in patients who choose not continue a second course of therapy may not be captured as there will be no incentive to report this through the REMS program once the product is discontinued.

6 Conclusion

This document presents and evaluates the possible risk mitigation options for alemtuzumab for the MS indication, in the context of the serious risks discussed above, as observed in Phase 2 and 3 clinical trials. In considering the REMS for alemtuzumab to treat MS, we ask Advisory Committee members to address the following:

If the available data support approval, does the Agency's proposed risk mitigation strategy adequately address the safety risks without being unduly burdensome?

1. What additional strategies could be used to improve the proposed REMS?
2. How should compliance with the laboratory monitoring requirements be documented and reported through the REMS?
3. Discuss the appropriate infusion setting and duration of post-infusion monitoring.

The details of the committee's discussion will be considered in the final design of the risk mitigation strategy, should alemtuzumab for the MS indication be approved.