DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-311 **NDA APPROVAL**

Genzyme Corporation
Attention: Laura Mondano
Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Mondano:

Please refer to your new drug application (NDA) dated June 16, 2008, received June 16, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Mozobil™ (plerixafor injection) 20 mg/mL.

We acknowledge receipt of your submissions dated August 13, 26, September 4, 15, October 15, 21, 27, November 7, 12, 14, 21, 26, December 3, 8, 12, and 15, 2008.

This new drug application provides for the use of Mozobil™ (plerixafor injection) 20 mg/mL to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.

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

This application was not taken to an Advisory Committee for review because the efficacy results, as demonstrated by the improvements in CD34+ cell mobilization with G-CSF plus plerixafor compared with G-CSF plus placebo, were clinically and statistically robust. In addition, the safety profile was acceptable for use in patients with NHL or MM who are candidates for autologous hematopoietic stem cell transplantation.

## 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize 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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

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 a signal of a serious risk of altered drug levels resulting from metabolic inhibition.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a study.

1. Screen plerixafor *in vitro* to assess whether it is a substrate and inhibitor of P-glycoprotein. Depending on the results of this study, an *in vivo* drug-drug interaction trial may be needed.

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   | Protocol Submission Date: | by January 31, 2009 |
   | Study Start: | by March 31, 2009 |
   | Final Report Submission: | by June 30, 2009 |

In addition, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess unexpected serious risks of mobilization of malignant cells in the bone marrow and of Q-T prolongation.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following trials.

2. To provide follow up safety and efficacy information for trial 3101-LTF for 5 years which will include death and disease status (relapse or disease-free). Updated status reports to be submitted annually.

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   | Protocol Submission Date: | April 3, 2006 |
   | Trial Start Date: | December 15, 2006 |
   | First Annual Report: | February 2010 |
   | Second Annual Report: | February 2011 |
   | Third Annual Report: | February 2012 |
   | Fourth Annual Report: | February 2013 |
   | Fifth Annual Report: | February 2014 |

3. To provide follow up safety and efficacy information for trial 3102-LTF for 5 years which will include death and disease status (relapse or disease-free). Updated status reports to be submitted annually.

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   | Protocol Submission Date: | April 20, 2006 |
   | Trial Start Date: | January 11, 2007 |
   | First Annual Report: | February 2010 |
   | Second Annual Report: | February 2011 |
   | Third Annual Report: | February 2012 |
   | Fourth Annual Report: | February 2013 |
   | Fifth Annual Report: | February 2014 |

4. Complete and submit the data and final report from the thorough QT/QTc trial.

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   | Protocol Submission: | October 24, 2007 |
   | Trial Start: | March 31, 2008 |
   | Final Report Submission: | by January 31, 2009 |

Submit the protocol to your IND 55,851 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study and clinical trial requirements:

- **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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii) 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 314.81(b)(2(vii). 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.

## POSTMARKETING COMMITMENTS

We remind you of your postmarketing commitment in your submission dated December 11, 2008. The commitment is listed below.

5. Design, conduct and submit a clinical trial to evaluate weight based and flat dosing schedules in lower weight NHL patients. The applicant should conduct sparse PK sampling and measure CD34+ cell counts at time points similar to those in protocol AMD3100-3101.

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| Protocol Submission: | by September 30, 2009 |
| Trial Start: | by March 31, 2010 |
| Trial Completion: | by September 30, 2012 |
| Final Report Submission: | by April 30, 2013 |

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved NDA 22-311."

## CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 12, 2008, submission containing final printed carton and container labels.

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

## 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
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), 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. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

**LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

**MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Susan Jenney, Regulatory Project Manager, at (301) 796-0062.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.
Office Director
Office of Drug Oncology Products
Center of Drug Evaluation and Research

Enclosure (Package Insert)

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

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/s/

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Richard Pazdur

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