

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-311

SUMMARY REVIEW

Summary Review for Regulatory Action

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|---|---|
| Date | December 15, 2008 |
| From | Richard Pazdur, MD |
| Subject | Office Director Summary Review |
| NDA/BLA # | 22-311 |
| Supplement # | |
| Applicant Name | Genzyme |
| Date of Submission | June 16, 2008 |
| PDUFA Goal Date | December 16, 2008 |
| Proprietary Name / Established (USAN) Name | Mozobil/ plerixafor injection |
| Dosage Forms / Strength | single-use vial is filled to deliver 1.2 mL of 20 mg/mL solution containing 24 mg of plerixafor |
| Proposed Indication(s) | Mozobil™ (plerixafor injection) is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). |
| Action/Recommended Action for NME: | <i>Approval</i> |

| | |
|------------------------------------|-----|
| Material Reviewed/Consulted | |
| OND Action Package, including: | |
| Medical Officer Review | X |
| Statistical Review | X |
| Pharmacology Toxicology Review | X |
| CMC Review/OBP Review | X |
| Microbiology Review | X |
| Clinical Pharmacology Review | X |
| DDMAC | X |
| DSI | X |
| CDTL Review | X |
| OSE/DMEPA | X |
| OSE/DRISK | X |
| OSE/DSRCS | N/A |
| Other | |

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Errors and Prevention Analysis

DSI=Division of Scientific Investigations

DRISK= Division of Risk Management

DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

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OFFICE DIRECTOR MEMO

The efficacy and safety of plerixafor in combination with G-CSF in NHL and MM were evaluated in two placebo-controlled studies (Studies 1 and 2). Patients were randomized to receive either plerixafor, 0.24 mg/kg, or placebo on each evening prior to apheresis. All patients received G-CSF, 10 micrograms/kg daily for 4 days, prior to the first dose of plerixafor or placebo and prior to apheresis. Results from 298 patients with NHL from study 1 and 302 patients with MM from study 2 were analyzed.

In Study 1, 59% of patients with NHL mobilized with plerixafor and G-CSF collected $\geq 5 \times 10^6$ CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions, compared with 20% who were mobilized with placebo with G-CSF ($p < 0.001$). The median number of days to reach $\geq 5 \times 10^6$ CD34+ cells/kg was 3 days for the plerixafor group and not evaluable for the placebo group.

In Study 2, 72% of MM patients who were mobilized with plerixafor and G-CSF collected $\geq 6 \times 10^6$ CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions, compared with 34% who were mobilized with placebo and G-CSF ($p < 0.001$). The median number of days to reach $\geq 6 \times 10^6$ CD34+ cells/kg was 1 day for the plerixafor group and 4 days for the placebo group.

Safety data for plerixafor in combination with G-CSF were obtained from two placebo-controlled studies and 10 uncontrolled studies in 540 patients. Patients were primarily treated with plerixafor at daily doses of 0.24 mg/kg SC. Median exposure to plerixafor was 2 days (range 1 to 7 days). The most common adverse reactions ($\geq 10\%$) reported in patients who received plerixafor in conjunction with G-CSF and were more frequent than placebo were diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness and vomiting. Prescribing physicians and patients should be aware of the potential for tumor cell mobilization in leukemia patients, increased circulating leukocytes and decreased platelet counts, splenic enlargement and fetal harm when administered to pregnant women.

Please refer to the primary reviews and Dr. Justice's summary of the chemistry and manufacturing review, clinical pharmacology review, nonclinical pharmacology and toxicology reviews, medical reviews and statistical reviews. All reviews recommended approval.

A concern in the reviews was the theoretical potential for tumor cell mobilization (noted in 5.3 of the Warnings and Precautions section). This was addressed by the applicant in a "white paper" and was discussed by both the clinical reviewer and CDTL. The clinical reviewer made the following conclusion and recommendation. "Tumor cell mobilization by plerixafor has not been well studied. The available information is limited by imperfect methods of detecting circulating tumor cells and by short clinical follow-up. The possibility that plerixafor could mobilize tumor cells and that subsequent reinfusion of those tumor cells could contribute in some cases to disease relapse cannot be ruled out." Dr. Justice review comments that the potential risk of disease relapse due to re-infused plerixafor-mobilized tumor cells is relatively

low. Three lines of evidence provide some reassurance of the safety of plerixafor-mobilized stem cells. First, patients in the G-CSF/plerixafor treatment arms of Studies 3101 and 3102 followed for up to 12 months following autologous HSCT showed no evidence of an increased risk of disease relapse compared to the G-CSF/placebo treatment arms. Second, the correlative data summarized above from Studies 2101, 2103, 3101, and EU21 show no evidence that plerixafor mobilizes MM or NHL cells. Third, published literature is unclear whether detectable tumor cells in the apheresis product directly contribute to relapse or are merely a marker of increased risk of relapse. The CDTL review noted that since neither data nor a signal exists regarding tumor mobilization, the issue of tumor mobilization is only a theoretical possibility. In 2006, the company submitted two protocols to obtain long term follow up data from Trials 3101 and 3102 and is collecting this data now. The company has agreed to provide five years of annual reports on this issue.

The CDTL Review of 12/12/08 made the following recommendations. The recommended regulatory action is approval. Mozobil has a relatively favorable risk-benefit ratio with few grade 3 adverse reactions associated with treatment. Genzyme does not plan any additional risk minimization measures beyond routine pharmacovigilance activities including labeling, packaging, and comprehensive post-marketing surveillance. Recommendation for other post marketing requirements/commitments include the following: **1.** The sponsor should provide longer follow-up on disease status particularly relapse from trials 3101 and 3102. This information could be helpful in answering the question whether Mozobil mobilizes tumor cells. **2.** The sponsor should complete and submit the results from their ongoing TQT trial. **3.** The sponsor is asked to screen plerixafor *in vitro* assess whether it is a substrate and inhibitor of P-glycoprotein. Depending on the results of this study, an *in vivo* drug-drug interaction study may be needed. **4.** The sponsor is asked to study the question of whether an alternative dose is more appropriate for patients with NHL who weigh less than 85 kg.

Office recommended regulatory action: APPROVAL

Recommendation for other Postmarketing Study Commitments/Requirements

The following is a post-marketing study requirement recommended by Clinical Pharmacology.

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.

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

The following are post-marketing trial requirements. Requirements 2 and 3 are intended to address the theoretical risk of tumor cell mobilization into the leukapheresis product. Requirement 4 is required by ICH E14.

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

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 Study 3102-LTF for 5 years which will include death and disease status (relapse or disease-free). Updated status reports to be submitted annually.

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.

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

The following is a post-marketing commitment recommended by Clinical Pharmacology to optimize dosing in lower weight non-Hodgkin's lymphoma patients.

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.

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

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

/s/

Richard Pazdur
12/15/2008 09:58:30 AM
MEDICAL OFFICER

Summary Review for Regulatory Action

| | |
|---|---|
| Date | December 13, 2008 |
| From | Robert L. Justice, M.D., M.S. |
| Subject | Division Director Summary Review |
| NDA/BLA # | 22-311 |
| Supplement # | |
| Applicant Name | Genzyme |
| Date of Submission | June 16, 2008 |
| PDUFA Goal Date | December 16, 2008 |
| Proprietary Name / Established (USAN) Name | Mozobil/ plerixafor injection |
| Dosage Forms / Strength | single-use vial is filled to deliver 1.2 mL of 20 mg/mL solution containing 24 mg of plerixafor |
| Proposed Indication(s) | Mozobil™ (plerixafor injection) is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). |
| Action/Recommended Action for NME: | <i>Approval</i> |

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| Material Reviewed/Consulted | |
| OND Action Package, including: | |
| Medical Officer Review | X |
| Statistical Review | X |
| Pharmacology Toxicology Review | X |
| CMC Review/OBP Review | X |
| Microbiology Review | X |
| Clinical Pharmacology Review | X |
| DDMAC | X |
| DSI | X |
| CDTL Review | X |
| OSE/DMEPA | X |
| OSE/DRISK | X |
| OSE/DSRCS | N/A |
| Other | |

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Division Director Summary Review

1. Introduction

This new drug application was submitted on June 16, 2008 and seeks approval of Mozobil™ (plerixafor injection) for use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). This review will summarize the efficacy and safety data submitted in support of the application and the recommendations of each review discipline.

2. Background

The following description of plerixafor and its mechanism of action are summarized in this excerpt from the agreed-upon package insert.

Plerixafor is an inhibitor of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1 α (SDF-1 α). SDF-1 α and CXCR4 are recognized to play a role in the trafficking and homing of human hematopoietic stem cells (HSCs) to the marrow compartment. Once in the marrow, stem cell CXCR4 can act to help anchor these cells to the marrow matrix, either directly via SDF-1 α or through the induction of other adhesion molecules. Treatment with plerixafor resulted in leukocytosis and elevations in circulating hematopoietic progenitor cells in mice, dogs and humans. CD34+ cells mobilized by plerixafor were capable of engraftment with long-term repopulating capacity up to one year in canine transplantation models.

Two randomized studies of stem cell mobilization with plerixafor plus G-CSF vs. G-CSF prior to autologous transplantation were submitted in support of the application. One was conducted in patients with non-Hodgkin's lymphoma and the other was conducted in patients with multiple myeloma. Both were conducted under Special Protocol Assessment agreements. The designs and results are described below.

3. CMC/Device

CMC Review

The CMC Review made the following recommendation and conclusion on approvability.

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending an “acceptable” overall recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product.

The proposed 36-month expiration dating period is acceptable for the drug product stored at the proposed controlled room temperature.

There were no recommendations for post-marketing commitments, agreements, and/or risk management steps.

The final CMC Memo of 12/12/08 concluded the following.

This memo serves to update the overall CMC recommendation for NDA 22-311. The Office of Compliance issued an overall acceptable recommendation for this application on 10-DEC-2008. All major CMC labeling issues are resolved, and acceptable container/carton labels were submitted on 12-DEC-2008. There is one outstanding labeling recommendation (see above), which is not a CMC approvability issue.

Accordingly, from a CMC perspective, approval of NDA 22-311 is recommended.

Comment: I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of 36 months. There are no other outstanding issues.

Product Quality Microbiology Review

The Product Quality Microbiology Review stated that the application is recommended for approval. No phase 4 commitments were recommended.

Comment: I concur with the recommendation of the microbiology reviewer.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation made the following recommendations.

Recommendation on approvability

There are no pharmacology/toxicology issues which preclude approval of plerixafor (Mozobil®) for the requested indication.

Recommendation for nonclinical studies

No additional non-clinical studies are required for the proposed indication and duration of administration.

Recommendations on labeling

Recommendations on labeling have been provided within team meetings and communicated to the sponsor.

The Acting Pharmacology/Toxicology Team Leader's Memo made the following recommendation.

I concur with Dr. Lee's conclusion that pharmacology and toxicology data support the approval of NDA 22,311 for Mozobil. There are no outstanding non-clinical issues related to the approval of Mozobil for the proposed indication.

Comment: I concur with the conclusions reached by the pharmacology/toxicology reviewer and acting team leader that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review made the following recommendation.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-311. This NDA is considered acceptable from a clinical pharmacology perspective.

Three Phase 4 commitments were recommended.

1. You should screen plerixafor in vitro assess whether it is a substrate and inhibitor of P-glycoprotein. Depending on the results of this study, an in vivo drug-drug interaction study may be needed.
2. You should submit the study report and data from your thorough QT/QTc study report upon its completion.
3. The currently proposed body weight adjusted dosing of plerixafor (240 mcg/kg) results in a lower exposure to plerixafor in patients with low body weight compared to patients with higher body weights. This decreased exposure was associated with significantly decreased efficacy in patients with low body weight. Based on the logistic regression analysis, both low body weight (i.e. low exposure) and low CD34+ baseline cell counts, were predictors of poor response to CD34+ mobilization therapy with plerixafor + G-CSF. The applicant agrees to design, conduct and submit a clinical study to optimize dosing in NHL patients by matching exposure in lower weights to that in patients over 85 kg. The applicant should also compare this result to the currently proposed dose and dosing schedule. Consideration should be given baseline CD34+ count, and flat dosing regimens. The applicant should conduct sparse PK sampling and measure CD34+ cell counts at baseline and time points prior to G-CSF administration and prior to apheresis as was done in protocol AMD3100-3101. This protocol should be submitted to the division for review by February 1, 2009. The protocol should be initiated by July

2009, and the study should be completed by July 2010 and submitted to the Agency by October 2010.

Comment: I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval and with the recommended PMC's.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The clinical program and the efficacy results are summarized in the following excerpt from the agreed-upon package insert.

The efficacy and safety of Mozobil in conjunction with G-CSF in non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) were evaluated in two placebo-controlled studies (Studies 1 and 2). Patients were randomized to receive either Mozobil 0.24 mg/kg or placebo on each evening prior to apheresis. Patients received daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first dose of Mozobil or placebo and on each morning prior to apheresis. Two hundred and ninety-eight (298) NHL patients were included in the primary efficacy analyses for Study 1. The mean age was 55.1 years (range 29-75) and 57.5 years (range 22-75) in the Mozobil and placebo groups, respectively, and 93% of subjects were Caucasian. Three hundred and two (302) MM patients were included in the primary efficacy analyses for Study 2. The mean age was 58.2 years (range 28-75) and 58.5 years (range 28-75) in the Mozobil and placebo groups, respectively, and 81% of subjects were Caucasian.

In Study 1, 59% of NHL patients who were mobilized with Mozobil and G-CSF collected $\geq 5 \times 10^6$ CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions, compared with 20% of patients who were mobilized with placebo and G-CSF ($p < 0.001$). Other CD34+ cell mobilization outcomes showed similar findings (Table 4).

Table 4: Study 1 Efficacy Results – CD34+ Cell Mobilization in NHL Patients

| Efficacy Endpoint | Mozobil and G-CSF (n = 150) | Placebo and G-CSF (n = 148) | p-value ^a |
|---|-----------------------------|-----------------------------|----------------------|
| Patients achieving $\geq 5 \times 10^6$ cells/kg in ≤ 4 apheresis days | 89 (59%) | 29 (20%) | < 0.001 |
| Patients achieving $\geq 2 \times 10^6$ cells/kg in ≤ 4 apheresis days | 130 (87%) | 70 (47%) | < 0.001 |

^ap-value calculated using Pearson's Chi-Squared test

The median number of days to reach $\geq 5 \times 10^6$ CD34+ cells/kg was 3 days for the Mozobil group and not evaluable for the placebo group. Table 5 presents the proportion of patients who achieved $\geq 5 \times 10^6$ CD34+ cells/kg by apheresis day.

Table 5: Study 1 Efficacy Results – Proportion of Patients Who Achieved $\geq 5 \times 10^6$ CD34+ cells/kg by Apheresis Day in NHL Patients

| Days | Proportion ^a in Mozobil and G-CSF (n=147 ^b) | Proportion ^a in Placebo and G-CSF (n=142 ^b) |
|------|--|--|
| 1 | 27.9% | 4.2% |
| 2 | 49.1% | 14.2% |
| 3 | 57.7% | 21.6% |
| 4 | 65.6% | 24.2% |

^aPercents determined by Kaplan Meier method

^bn includes all patients who received at least one day of apheresis

In Study 2, 72% of MM patients who were mobilized with Mozobil and G-CSF collected $\geq 6 \times 10^6$ CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions, compared with 34% of patients who were mobilized with placebo and G-CSF ($p < 0.001$). Other CD34+ cell mobilization outcomes showed similar findings (Table 6).

Table 6: Study 2 Efficacy Results – CD34+ Cell Mobilization in Multiple Myeloma Patients

| Efficacy Endpoint | Mozobil and G-CSF (n = 148) | Placebo and G-CSF (n = 154) | p-value ^a |
|---|--------------------------------|--------------------------------|----------------------|
| Patients achieving $\geq 6 \times 10^6$ cells/kg in ≤ 2 apheresis days | 106 (72%) | 53 (34%) | < 0.001 |
| Patients achieving $\geq 6 \times 10^6$ cells/kg in ≤ 4 apheresis days | 112 (76%) | 79 (51%) | < 0.001 |
| Patients achieving $\geq 2 \times 10^6$ cells/kg in ≤ 4 apheresis days | 141 (95%) | 136 (88%) | 0.028 |

^ap-value calculated using Pearson's Chi-Squared test

The median number of days to reach $\geq 6 \times 10^6$ CD34+ cells/kg was 1 day for the Mozobil group and 4 days for the placebo group. Table 7 presents the proportion of patients who achieved $\geq 6 \times 10^6$ CD34+ cells/kg by apheresis day.

Table 7: Study 2 – Proportion of Patients Who Achieved $\geq 6 \times 10^6$ CD34+ cells/kg by Apheresis Day in MM Patients

| Days | Proportion ^a in Mozobil and G-CSF (n=144 ^b) | Proportion ^a in Placebo and G-CSF (n=150 ^b) |
|------|--|--|
| 1 | 54.2% | 17.3% |
| 2 | 77.9% | 35.3% |
| 3 | 86.8% | 48.9% |
| 4 | 86.8% | 55.9% |

^aPercents determined by Kaplan Meier method

^bn includes all patients who received at least one day of apheresis

Multiple factors can influence time to engraftment and graft durability following stem cell transplantation. For transplanted patients in the Phase 3 studies, time to neutrophil and platelet engraftment and graft durability were similar across the treatment groups.

Clinical Review

The Clinical Review provided the following recommendations and risk benefit assessment.

1.1 Recommendation on Regulatory Action

The clinical review team recommends regular approval of plerixafor in combination with granulocyte-colony stimulating factor (G-CSF/plerixafor) to mobilize hematopoietic stem cells (HSC) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

1.2 Risk Benefit Assessment

The efficacy database for this application consisted of primary data from two randomized, placebo-controlled trials in patients with NHL (Study 3101) and MM (Study 3102) plus corroborative support from phase 2 studies in patients with NHL and MM (Study 2101) and Hodgkin's disease (HD; Study 2106). The safety database was composed of patients from those four studies plus eight single-arm, open-label studies of multiple doses of plerixafor with or without G-CSF in patients with NHL, HD, and/or MM (2101, 2102, 2103, 2105, 2106, 2108, 2109, C201, and EU21), one single-arm open-label study of G-CSF/plerixafor in poor mobilizers with malignancies (2112), two studies of patients with malignancies undergoing mobilization with G-CSF/plerixafor plus chemotherapy (2104) or rituximab (2113), one study in renally impaired patients (1101), and one study in patients with the human immunodeficiency virus (HIV; 2001).

Study 2101 enrolled 25 patients age 18 to 75 years with NHL or MM in first or second complete or partial remission who were eligible for autologous HSCT. It had a crossover design with the primary objective to evaluate the difference in the number of CD34+ cells/kg collected with G-CSF/plerixafor compared to G-CSF alone. Patients with NHL had a mean average daily CD34+ collection of 2.9×10^6 cells/kg with G-CSF/plerixafor, compared to 1.0×10^6 cells/kg with G-CSF alone ($p < 0.001$, paired t-test). Patients with MM collected a daily average of 6.6×10^6 CD34+ cells/kg with G-CSF/plerixafor, compared to 2.5×10^6 cells/kg with G-CSF alone ($p = 0.025$, paired t-test).

Study 2106 was designed to determine the proportion of patients with HD who collected $\geq 5 \times 10^6$ CD34+ cells/kg with G-CSF/plerixafor. The median number of CD34+ cells collected was 6.9×10^6 /kg. Fifteen of 22 patients (68%) succeeded in

meeting the primary efficacy endpoint of collecting a total of $= 5 \times 10^6$ CD34+ cells/kg.

Study 3101 randomized 298 patients with NHL who were planning to undergo autologous hematopoietic stem cell transplantation (HSCT) to G-CSF/plerixafor versus G-CSF plus placebo (G-CSF/placebo). The primary endpoint was the collection of $= 5 \times 10^6$ CD34+ cells/kg within 4 apheresis days. Secondary endpoints were the percentage of patients collecting $= 2 \times 10^6$ CD34+ cells/kg within four apheresis days, the number of apheresis days required to reach $= 5 \times 10^6$ CD34+ cells/kg, time to neutrophil and platelet engraftment, and the percentage of patients with durable engraftment at post-transplant Day 100, 6 months, and 12 months.

The combination arm showed statistically significant improvement in the primary endpoint and all secondary endpoints. Eighty nine (59%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of $= 5 \times 10^6$ CD34+ cells/kg within 4 apheresis days, compared to 29 (20%) patients randomized to G-CSF/placebo ($P < 0.001$).

Study 3102 randomized 302 patients with MM who were planning to undergo autologous HSCT to G-CSF/plerixafor versus G-CSF/placebo. The primary efficacy endpoint was the collection of a total of $= 6 \times 10^6$ CD34+ cells/kg within two apheresis days. Secondary endpoints were the percentages of patients collecting $= 6 \times 10^6$ CD34+ cells/kg within four apheresis days and $= 2 \times 10^6$ CD34+ cells/kg within four apheresis days, the number of apheresis days required to reach $= 6 \times 10^6$ CD34+ cells/kg, time to neutrophil and to platelet engraftment, and the percentage of patients with graft durability at 100 days, 6 months, and 12 months.

The combination arm showed statistically significant improvement in the primary endpoint and all secondary endpoints. One hundred and six (72%) patients randomized to G-CSF/plerixafor met the primary efficacy endpoint of mobilization of $= 6 \times 10^6$ CD34+ cells/kg within two apheresis days, compared to 53 (34%) patients randomized to G-CSF/placebo ($P < 0.001$).

The results of Studies 3101 and 3102 show that G-CSF/plerixafor provides an improvement over G-CSF alone in the mobilization of CD34+ cells for autologous HSCT, a potentially life-saving procedure for patients with NHL and MM. The addition of plerixafor increased the proportion of patients who were able to collect a minimum transplantable cell dose (defined prospectively as $= 2 \times 10^6$ CD34+ cells/kg) and an optimal cell dose for transplantation (defined prospectively as $= 5 \times 10^6$ CD34+ cells/kg in < 4 apheresis days for NHL patients and $= 6 \times 10^6$ CD34+ cells/kg in < 2 apheresis days of for MM patients). As a result, more patients treated with G-CSF/plerixafor underwent transplantation.

The addition of plerixafor reduced the median number of apheresis sessions required to collect an optimum transplantable cell dose compared to G-CSF/placebo. This

reduction should theoretically allow more optimal use of apheresis machines and related resources, as well as reduce the morbidity associated with apheresis.

Approximately 99% of all transplanted patients achieved neutrophil and platelet engraftment. The number of days to neutrophil and platelet engraftment and graft durability rates through 12 months post-transplant were similar between the G-CSF/plerixafor and G-CSF/placebo groups. Among transplanted patients, the addition of plerixafor did not appear to affect the likelihood of graft durability at 100 days, at 6 months, or at one year.

The most common toxicities with G-CSF/plerixafor were gastrointestinal symptoms such as nausea, vomiting, and diarrhea. These symptoms were usually mild and rarely led to dose modification or study discontinuation.

The overall incidences and timing of AE and Grade 3 or 4 AEs were similar between treatment arms in the two randomized trials. The majority of SAEs occurred during and following the period when patients received ablative chemotherapy and were no longer receiving study drug. No deaths were attributed to plerixafor.

The most frequently reported (>10% in either treatment group) AEs during the administration of study drug were diarrhea, nausea, bone pain, fatigue, injection site erythema, headache, paresthesia, back pain, hypokalemia, arthralgia, catheter site pain and dizziness. Common AEs with an incidence = 2% higher in the G-CSF/plerixafor group compared to G-CSF/placebo during Period 1 were diarrhea (38 vs. 17%), nausea (34 vs. 22%), vomiting (10 vs. 6%), flatulence (7 vs. 4%), injection site erythema (26 vs. 5%), injection-site pruritus (6 vs. 1%), and dizziness (10 vs. 6%). Common AEs with an incidence = 2% higher in the G-CSF/placebo group compared to G-CSF/plerixafor during Period 1 were catheter site pain (14 vs. 11%), bone pain (36 vs. 32%), back pain (22 vs. 18%), extremity pain (7 vs. 5%).

There was no evidence that the risk of any toxicity was significantly higher in patients of any particular age group, gender, or race. Although no racial or ethnic groups were excluded from the randomized studies, most patients (87%) were Caucasian. The safety and efficacy of plerixafor in persons under age 18 and in pregnant or breast feeding women has not been established. Because of preclinical teratogenicity findings, plerixafor will be characterized pregnancy Category D.

1.3 Recommendations for Postmarketing Risk Management Activities

None

1.4 Recommendations for Postmarketing Studies or Trials

1. In accordance with ICH E14, a thorough QT study is ongoing (Protocol MOZ00707) to evaluate the effect of single therapeutic and suprathreshold doses of plerixafor (0.24 and 0.4 µg/kg, respectively) on cardiac repolarization

in healthy volunteers. The final study report should be submitted upon its completion.

2. Plerixafor has not been screened in vitro to assess whether it is a substrate or inhibitor of P-glycoprotein. The Applicant should perform such in vitro screen. Depending on the results, an in vivo drug-drug interaction study may be needed.
3. The currently proposed body weight adjusted dosing of plerixafor resulted in lower exposure to plerixafor in patients with low body weight compared to patients with higher body weights. This decreased exposure was associated with decreased efficacy in patients with low body weight. In a logistic regression analysis, both low body weight and low CD34+ baseline cell counts were predictors of poor CD34+ cell mobilization with G-CSF/plerixafor. The applicant should design, conduct and submit a clinical study to optimize dosing in NHL patients with low exposure and low baseline CD34+ count. The applicant should compare the results to the currently proposed dose and dosing schedule. Consideration should be given baseline CD34+ count, and flat dosing regimens. The applicant should conduct sparse PK sampling and measure CD34+ counts at time points similar to those in Study 3101. This protocol should be submitted to the division for review by February 1, 2009. The protocol should be initiated by July 2009, and the study should be completed by July 2010 and submitted to the Agency by October 2010.

Statistical Review and Evaluation

The Statistical Review and Evaluation made the following conclusions and recommendations.

The results from the two studies submitted showed statistically significant results that plerixafor reduced the number of aphereses sessions required to collect transplantable cell dose and increased the percentage of patients able to undergo autologous HSC transplantations. There were significant amount of protocol violations in both studies. However, the violations are evenly distributed among the two study arms, and the results from both studies are robust after removing the patients with major protocol violations.

Based on the data submitted, the study results support the claims in the primary endpoints and key secondary endpoints. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

8. Safety

The following summary of safety is excerpted from the agreed-upon package insert.

The most common adverse reactions ($\geq 10\%$) reported in patients who received Mozobil in conjunction with G-CSF regardless of causality and more frequent with Mozobil than placebo during HSC mobilization and apheresis were diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting.

Safety data for Mozobil in combination with G-CSF were obtained from two placebo-controlled studies and 10 uncontrolled studies in 543 patients. Patients were primarily treated with Mozobil at daily doses of 0.24 mg/kg SC. Median exposure to Mozobil in these studies was 2 days (range 1 to 7 days).

In the two randomized studies in patients with NHL and MM, a total of 301 patients were treated in the Mozobil and G-CSF group and 292 patients were treated in the placebo and G-CSF group. Patients received daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first dose of Mozobil 0.24 mg/kg SC or placebo and on each morning prior to apheresis. The adverse reactions that occurred in $\geq 5\%$ of the patients who received Mozobil regardless of causality and were more frequent with Mozobil than placebo during HSC mobilization and apheresis are shown in Table 2...

Table 2: Adverse Reactions in $\geq 5\%$ of Non-Hodgkin's Lymphoma and Multiple Myeloma Patients Receiving Mozobil and More Frequent than Placebo During HSC Mobilization and Apheresis

| | Percent of Patients (%) | | | | | |
|---|--------------------------------|---------|---------|--------------------------------|---------|---------|
| | Mozobil and G-CSF (n = 301) | | | Placebo and G-CSF (n = 292) | | |
| | All Grades ^a | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Gastrointestinal disorders | | | | | | |
| Diarrhea | 37 | < 1 | 0 | 17 | 0 | 0 |
| Nausea | 34 | 1 | 0 | 22 | 0 | 0 |
| Vomiting | 10 | < 1 | 0 | 6 | 0 | 0 |
| Flatulence | 7 | 0 | 0 | 3 | 0 | 0 |
| General disorders and administration site conditions | | | | | | |
| Injection site reactions | 34 | 0 | 0 | 10 | 0 | 0 |
| Fatigue | 27 | 0 | 0 | 25 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Arthralgia | 13 | 0 | 0 | 12 | 0 | 0 |
| Nervous system disorders | | | | | | |
| Headache | 22 | < 1 | 0 | 21 | 1 | 0 |
| Dizziness | 11 | 0 | 0 | 6 | 0 | 0 |
| Psychiatric disorders | | | | | | |
| Insomnia | 7 | 0 | 0 | 5 | 0 | 0 |

^aGrades based on criteria from the World Health Organization (WHO)

In the randomized studies, 34% of patients with NHL or MM had mild to moderate injection site reactions at the site of subcutaneous administration of Mozobil. These included erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, swelling, and urticaria.

Mild to moderate systemic reactions were observed in less than 1% of patients approximately 30 min after Mozobil administration. Events included one or more of the following: urticaria (n = 2), periorbital swelling (n = 2), dyspnea (n = 1) or hypoxia (n = 1). Symptoms generally responded to treatments (e.g., antihistamines, corticosteroids, hydration or supplemental oxygen) or resolved spontaneously.

Vasovagal reactions, orthostatic hypotension, and/or syncope can occur following subcutaneous injections. In Mozobil oncology and healthy volunteer clinical studies, less than 1% of subjects experienced vasovagal reactions following subcutaneous administration of Mozobil doses ≤ 0.24 mg/kg. The majority of these events occurred within 1 hour of Mozobil administration. Because of the potential for these reactions, appropriate precautions should be taken.

Other adverse reactions that occurred in $< 5\%$ of patients but were reported as related to Mozobil during HSC mobilization and apheresis included abdominal pain, hyperhidrosis, abdominal distention, dry mouth, erythema, stomach discomfort, malaise, hypoesthesia oral, constipation, dyspepsia, and musculoskeletal pain.

The following warnings and precautions are also included in the package insert.

5.1 Tumor Cell Mobilization in Leukemia Patients

For the purpose of HSC mobilization, Mozobil may cause mobilization of leukemic cells and subsequent contamination of the apheresis product. Therefore, Mozobil is not intended for HSC mobilization and harvest in patients with leukemia.

5.2 Hematologic Effects

Leukocytosis

Administration of Mozobil in conjunction with G-CSF increases circulating leukocytes as well as HSC populations. Monitor white blood cell counts during Mozobil use. Exercise clinical judgment when administering Mozobil to patients with peripheral blood neutrophil counts above 50,000/mcL.

Thrombocytopenia

Thrombocytopenia has been observed in patients receiving Mozobil. Monitor platelet counts in all patients who receive Mozobil and then undergo apheresis.

5.3 Potential for Tumor Cell Mobilization

When Mozobil is used in combination with G-CSF for HSC mobilization, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of potential reinfusion of tumor cells has not been well-studied.

5.4 Splenic Enlargement and Potential for Rupture

Higher absolute and relative spleen weights associated with extramedullary hematopoiesis were observed following prolonged (2 to 4 weeks) daily plerixafor SC administration in rats at doses approximately 4-fold higher than the recommended

human dose based on body surface area. The effect of Mozobil on spleen size in patients was not specifically evaluated in clinical studies. Evaluate individuals receiving Mozobil in combination with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain for splenic integrity.

5.5 Pregnancy

Pregnancy Category D

Mozobil may cause fetal harm when administered to a pregnant woman. Plerixafor was teratogenic in animals. There are no adequate and well-controlled studies in pregnant women using Mozobil. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Mozobil. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The theoretical potential for tumor cell mobilization noted in 5.3 of the Warnings and Precautions section was addressed by the applicant in a “white paper” and was discussed by both the clinical reviewer and CDTL in reviews dated December 12, 2008. The clinical reviewer made the following conclusion and recommendation.

Tumor cell mobilization by plerixafor has not been well studied. The available information is limited by imperfect methods of detecting circulating tumor cells and by short clinical follow-up. The possibility that plerixafor could mobilize tumor cells and that subsequent reinfusion of those tumor cells could contribute in some cases to disease relapse can not be ruled out. Because this represents a serious safety concern, the Applicant should study this area further.

My recommendation includes a review of the Sponsor’s white paper which included a discussion of the fact that the risk of disease relapse due to re-infused plerixafor-mobilized tumor cells is relatively low. Three lines of evidence provide some reassurance of the safety of plerixafor-mobilized stem cells. First, patients in the G-CSF/plerixafor treatment arms of Studies 3101 and 3102 followed for up to 12 months following autologous HSCT showed no evidence of an increased risk of disease relapse compared to the G-CSF/placebo treatment arms. Second, the correlative data summarized above from Studies 2101, 2103, 3101, and EU21 show no evidence that plerixafor mobilizes MM or NHL cells. Third, published literature is unclear whether detectable tumor cells in the apheresis product directly contribute to relapse or are merely a marker of increased risk of relapse. The Applicant has fully agreed to comply with this Post- Marketing Requirement.

This reviewer recommends that the following language be incorporated into the approval letter:

- 1. To continue to follow patients in the randomized Studies 3101 and 3102 and submit a full Clinical Study Report when a median follow-up time of five years has been attained.*

The CDTL Review stated the following regarding the potential for tumor cell mobilization.

I agree with Dr. Brave's assessment.

In addition, the white paper was reviewed and discussed with two internal consultants who were previously professors of medicine and have performed many bone marrow transplants. Both consultants agreed with the company's position that an additional study would be difficult to do. One of the consultants recommended that the best evidence of whether Mozobil causes tumor mobilization could be ascertained by obtaining follow up information on disease status from Trials 3101 and 3102. The other consultant agreed with that recommendation.

Subsequently in a teleconference, the division and sponsor agreed that providing longer follow-up on disease status, particularly relapse from trials 3101 and 3102 could be helpful in answering the question whether Mozobil causes tumor cell mobilization. The labeling will carry a warning about the potential for tumor mobilization which is important considering Mozobil is given with G-CSF.

Conclusion: Since neither data nor a signal exists regarding tumor mobilization, the issue of tumor mobilization is only a theoretical possibility. In 2006, the company submitted two protocols to obtain long term follow up data from Trials 3101 and 3102 and is collecting this data now. The company has agreed to provide five years of annual reports on this issue.

Comment: I concur with the recommendations of the clinical reviewer and cross-discipline team leader. The available evidence does not suggest that Mozobil mobilizes tumor cells in patients with non-Hodgkin's lymphoma or multiple myeloma. However, long-term follow-up for tumor recurrence in trials 3101 and 3102 should be a post-marketing requirement.

9. Advisory Committee Meeting

This application was not taken to an Advisory Committee for several reasons. The protocols for the two major clinical trials were conducted under Special Protocol Assessment (SPA) agreements. As part of the SPA, both protocols were reviewed by a Special Government Employee (SGE) with expertise in bone marrow transplantation. The improvements in CD34+ cell mobilization with G-CSF plus plerixafor compared with G-CSF plus placebo were clinically and statistically robust. The safety profile was acceptable for use in patients with NHL or MM who are candidates for autologous hematopoietic stem cell transplantation.

10. Pediatrics

Not applicable. The applicant has orphan drug exclusivity for these indications.

11. Other Relevant Regulatory Issues

Clinical Inspection Summary

The Division of Scientific Investigations concluded that “Three clinical sites, and the applicant were inspected as part of the data audit for this application. Data appears to be valid and may be used in evaluating this NDA.”

Financial Disclosure

See section 3.3 of the Clinical Review and the CDTL review. Financial conflicts of interest are unlikely to have affected the study results.

DDMAC Consult

DDMAC recommendations were discussed and incorporated as appropriate during labeling meetings.

DMEPA Consult

DMEPA found the proprietary name to be acceptable. Most of the recommendations regarding the package insert and container and carton labels were incorporated into the labeling.

DRISK Consult

DRISK noted that “The Sponsor has proposed routine labeling and routine pharmacovigilance to address the risks associated with Mozobil. DRISK believes that this approach is reasonable at this time and is consistent with the management of other granulocyte colony-stimulating products.”

CDTL Review

The CDTL Review of 12/12/08 made the following recommendations.

- Recommended regulatory action
Approval
- Risk Benefit Assessment
Mozobil has a relatively favorable risk-benefit ratio with few grade 3 adverse reactions associated with treatment.
- Recommendation for Post marketing Risk Management Activities
Genzyme does not plan any additional risk minimization measures beyond routine pharmacovigilance activities including labeling, packaging, and comprehensive post-marketing surveillance.

- Recommendation for other Post marketing Study Requirements/Commitments

1. The sponsor should provide longer follow-up on disease status particularly relapse from trials 3101 and 3102. This information could be helpful in answering the question whether Mozobil mobilizes tumor cells.

2. The sponsor should complete and submit the results from their ongoing TQT trial.

3. The sponsor is asked to screen plerixafor in vitro assess whether it is a substrate and inhibitor of P-glycoprotein. Depending on the results of this study, an in vivo drug-drug interaction study may be needed.

4. The sponsor is asked to study the question of whether an alternative dose is more appropriate for patients with NHL who weigh less than 85 kg.

- Recommended Comments to Applicant None

Comment: There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: DMEPA concurs with the proprietary name.
- Physician labeling: Except for two minor pending edits which do not affect approvability, agreement has been reached on the physician labeling.
- Carton and immediate container labels: Agreement has been reached on the carton and container labels.
- Patient labeling/Medication guide: not applicable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk:Benefit Assessment

As noted above, the improvements in CD34+ cell mobilization with G-CSF plus plerixafor compared with G-CSF plus placebo were clinically and statistically robust. The most common adverse reactions ($\geq 10\%$) reported in patients who received Mozobil in conjunction with G-CSF regardless of causality and more frequent with Mozobil than placebo during HSC mobilization and apheresis were diarrhea, nausea, fatigue, injection site

reactions, headache, arthralgia, dizziness, and vomiting. Grade 3 or 4 adverse reactions were uncommon. The risk:benefit assessment is acceptable for use in patients with NHL or MM who are candidates for autologous hematopoietic stem cell transplantation.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments/Requirements

The following is a post-marketing study requirement recommended by Clinical Pharmacology.

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.

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

The following are post-marketing trial requirements. Requirements 2 and 3 are intended to address the theoretical risk of tumor cell mobilization into the leukapheresis product. Requirement 4 is required by ICH E14.

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

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 Study 3102-LTF for 5 years which will include death and disease status (relapse or disease-free). Updated status reports to be submitted annually.

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.

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

The following is a post-marketing commitment recommended by Clinical Pharmacology to optimize dosing in lower weight non-Hodgkin's lymphoma patients.

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.

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

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

/s/

Robert Justice
12/13/2008 09:29:14 PM
MEDICAL OFFICER