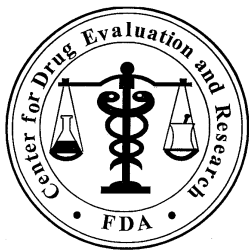


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-311

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



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

Date: November 24, 2008
To: Robert Justice, M.D., Director
Division of Drug Oncology Products (DDOP)
Through: Claudia Karwoski, Pharm.D., Director (Acting)
Division of Risk Management (DRISK)
From: OSE Mozobil Risk Management Team

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Subject: Review of Proposed Risk Management Plan
Drug Name(s): Mozobil® (Plerixafor)
Application
Type/Number: NDA 22-311
Applicant/sponsor: Genzyme Corporation
OSE RCM #: 2008-1284

1 INTRODUCTION

This review follows the August 12, 2008 request from the Division of Drug Oncology Products (DDOP) for the Office of Surveillance and Epidemiology (OSE) to review the Genzyme Corporation's submission dated June 16, 2008 (NDA 22-311) containing a proposed risk management plan for Mozobil®.

Mozobil® (plerixafor) is a new molecular entity small molecule reversible chemokine (C-X-C motif) receptor 4 (CXCR4) inhibitor with the proposed indication to enhance the mobilization of hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma (MM). It is supplied as a single-use vial containing a 20 mg/mL solution. The proposed dosing regimen is 240 mcg/kg body weight by subcutaneous injection administered 1 to 11 hours prior to initiation of apheresis. Mozobil® is commonly used for 2 to 4 consecutive days, but has been used for up to 7 consecutive days in a clinical setting. According to the proposed labeling, patients with severe renal insufficiency (creatinine clearance ≤ 30 mL/min) should have their dose of Mozobil® reduced to 160 mcg/kg. The label also states that there is insufficient information to make dosage recommendations in patients receiving hemodialysis.

Orphan Drug Designation (03-1679) was granted on July 10, 2003. Genzyme Corporation received a Priority Review Designation on June 16, 2008. (b) (4)

2 MATERIALS REVIEWED

The following materials were reviewed:

- Proposed Risk Management Plan submitted for Mozobil® (plerixafor), NDA 22-311, submitted June 16, 2008, by Genzyme Corporation.
- Proposed Mozobil® package insert submitted June 16, 2008.
- Neupogen® (Filgrastim) approved product labeling, Amgen, Inc., Thousand Oaks, CA. Revised May 2002.
- Neulasta® (Pegfilgrastim) approved product labeling, Amgen, Inc., Thousand Oaks, CA. Approved July 2007.
- FDA Priority Review Designation Letter to Genzyme Corporation, signed August 12, 2008.
- Bi-weekly risk management meeting presentation notes authored by LCDR Tim Lape, Pharm.D., Safety Evaluator, Division of Pharmacovigilance II (DPV).
- Clinical review slides from Mid-Cycle Meeting authored by Michael Brave, M.D., Ramzi Dagher, M.D., and Ann Farrell, M.D., Medical Officers, Division of Drug Oncology Products (DDOP).
- Clinical review, Michael Brave, M.D., Medical Officer, Division of Drug Oncology Products (DDOP), dated November 21, 2008.

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

Two pivotal, placebo-controlled, phase 3 studies were conducted supporting the use of Mozobil, in conjunction with G-CSF, to achieve an increase in number and more rapid mobilization of stem cells than patients treated with G-CSF alone.¹ Patients were randomized to receive either Mozobil 240 mcg/kg or placebo on each evening prior to apheresis. All patients received daily morning doses of G-CSF 10 mcg/kg for 4 days prior to the first dose of Mozobil or placebo and on each morning prior to apheresis.²

The safety risks were analyzed according to specific periods of autologous Hematopoietic Stem Cell Transplantation (HSCT) procedure.

- Period 1: Administration of granulocyte colony-stimulating factor (G-CSF), resulting in mobilization of HSCs followed by apheresis.
- Period 2: Ablative chemotherapy to provide immunosuppression to prevent transplant rejection and eradicate the disease for which the transplant is being performed, followed by stem cell transplantation.
- Period 3: Post-engraftment period
- Periods 4 and 5: Similar to periods 2 and 3 for patients undergoing tandem transplants.

Plerixafor was generally well tolerated in clinical studies, with overall incidences of adverse events similar between treatment arms in the two randomized trials during each period of study. The majority of serious adverse events occurred during and following administration of ablative chemotherapy when patients were no longer receiving study drug (Period 2).³ In the clinical trials, adverse events associated with Mozobil[®] were more likely to occur during Period 1 (as opposed to other periods) due to proximity to dosing.⁴ Adverse events reported during Period 1 that occurred in $\geq 5\%$ of lymphoma and MM patients receiving Mozobil[®] and more frequent than placebo included diarrhea, nausea, vomiting, flatulence, fatigue, injection site erythema, injection site pruritis, arthralgia, headache, dizziness, and anxiety.⁵ No deaths were attributed to plerixafor.

The sponsor outlined the following “identified” and “potential” risks:

- **Systemic reactions with injection:** In Phase 2 and 3 oncology clinical studies, six of 659 (0.9%) patients experienced mild or moderate systematic reactions within approximately 30 minutes after Mozobil[®] administration. Events included hypotension (n=1), urticaria (n=2), eye swelling (n=2), dyspnea (n=1) or hypoxemia (n=1). Associated events included flushing, hyperhidrosis, dizziness, oral paraesthesia, and chest discomfort. Symptoms responded to treatment or responded spontaneously. Patients should be monitored for systemic reactions following Mozobil[®] injection.⁶
- **Hematologic effects:** The sponsor states that concomitant administration of Mozobil[®] and G-CSF increases circulating leukocytes, and leukocyte count should be monitored during Mozobil[®] use. Although rare instances of hyperleukocytosis resulting in

¹ Bi-weekly risk management meeting presentation notes authored by LCDR Tim Lape, Pharm.D., Safety Evaluator, Division of Pharmacovigilance II (DPV).

² Proposed Mozobil[®] package insert submitted June 16, 2008.

³ Clinical review, Michael Brave, M.D., Medical Officer, Division of Drug Oncology Products (DDOP), dated November 21, 2008.

⁴ Clinical review slides from Mid-Cycle Meeting authored by Michael Brave, M.D., Ramzi Dagher, M.D., and Ann Farrell, M.D., Medical Officers, Division of Drug Oncology Products (DDOP).

⁵ Proposed Mozobil[®] package insert submitted June 16, 2008.

⁶ Proposed Risk Management Plan submitted for Mozobil[®] (plerixafor), NDA 22-311, submitted June 16, 2008, by Genzyme Corporation.

leukostasis have been reported rarely in non-leukemic conditions, there were no reports among patients in clinical trials. Labels of other G-CSF products suggest monitoring CBC counts twice weekly to avoid potential complications of excessive leukocytosis.⁷

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.”⁸

The second patient has increased plasma cells (15%) in the apheresis product.”¹² The sponsor has included language in the proposed labeling that states that Mozobil® is not intended for HSC mobilization and harvest in patients with leukemia.

- **Drug exposure during pregnancy:** Mozobil® is classified as pregnancy category (b) (4) [REDACTED] (b) (4) [REDACTED] ring pregnancy unless the potential benefit [REDACTED]
- **Decreased clearance:** Decreased clearance applies to patients with severe renal insufficiency (creatinine clearance ≤ 30 mL/min). The proposed labeling suggests a dose reduction to 160 mcg/kg.
- **Parasthesia:** Parasthesias are commonly observed in oncology patients undergoing autologous transplantation (Period 2). The incidence in the Mozobil® and placebo groups was 20.5% and 21.7%, respectively in placebo-controlled Phase 3 studies.

The Warnings and Precautions section of the sponsor’s proposed labeling includes tumor cell mobilization in leukemia patients, hematologic events including leukocytosis (potentially leading to leukostasis) and thrombocytopenia, potential for tumor cell mobilization in lymphoma and multiple myeloma patients, systemic reactions following injection, increased spleen size, and laboratory monitoring (WBCs, platelets).

The sponsor is conducting an on-going randomized, double-blind, placebo- and positive-control crossover study to evaluate the effect of Mozobil (in therapeutic and supra-therapeutic doses) on QT/QTc interval. The study is anticipated to be completed by first quarter 2009.

3.2 SPONSOR’S RISK MANAGEMENT PROPOSAL

The sponsor proposes routine pharmacovigilance for all identified and potential risks in compliance with the applicable post-marketing requirements. The sponsor plans to conduct periodic evaluations of cumulative data to evaluate safety signals and communicate new safety information to regulatory authorities worldwide. Labeling will be updated on a regular basis to incorporate new post-marketing safety data. Informational letters to treating physicians may also be used to disseminate new safety information.

4 DISCUSSION AND CONCLUSION

Mozobil is the first product in the class of CXCR4 Inhibitors, hence there are not direct comparators based on mechanism of action. Chemotherapeutic agents such as cyclophosphamide were the first clinically useful means of hematopoietic progenitor cell mobilization. G-CSF and granulocyte-macrophage colony stimulating factor (GM-CSF) are the only drugs currently approved for autologous stem cell mobilization. Frequent adverse effects of G-CSF and GM-CSF are bone pain, fatigue, and headache. G-CSF causes transient spleen enlargement, and spontaneous splenic rupture has been reported. Rare complications include thrombosis, flare of autoimmune disease, and precipitation of sickle-cell crisis. Transient neutropenia and thrombocytopenia usually follow apheresis.¹³

¹² Proposed Risk Management Plan submitted for Mozobil® (plerixafor), NDA 22-311, submitted June 16, 2008, by Genzyme Corporation.

¹³ Clinical review, Michael Brave, M.D., Medical Officer, Division of Drug Oncology Products (DDOP), dated November 21, 2008.

According to the medical officer's review, the adverse event profile of Mozobil is relatively similar to that of the granulocyte colony-stimulating products and the risk-benefit profile of Mozobil does not appear to pose an increased risk compared to that of other granulocyte colony-stimulating products used in hematopoietic stem cell mobilization.

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. Additional strategies such as a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use do not appear to be warranted to minimize any of the risks described. Should DDOP raise further concerns with the risks outlined above or identify additional risks associated with plerixafor warranting more extensive risk mitigation or a formal risk evaluation and mitigation strategy (REMS), please send a consult to OSE Division of Risk Management.

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/s/

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11/25/2008 07:09:07 AM
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Mary Willy Acting for Claudia Karwoski Acting DRISK Director

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