APPLICATION NUMBER: 22-311

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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

Scientific Lead:
LCDR Kendra Worthy, Pharm.D., Senior Drug Risk Management Analyst (DRISK)

Team Members:
Suzanne Berkman, Pharm.D., Senior Drug Risk Management Analyst (Acting) Team Leader (DRISK)
Mary Dempsey, Risk Management Program Coordinator (DRISK)
LCDR Sandra Griffith, BSN, RN, Regulatory Project Manager (OSE)
Timothy Lape, Pharm.D., Safety Evaluator (DPV II)
Susan Lu, R.Ph., Safety Evaluator Team Leader, Division of Pharmacovigilance (DPV II)

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 11 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.


2 MATERIALS REVIEWED

The following materials were reviewed:

- 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.\textsuperscript{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 Mozovil or placebo and on each morning prior to apheresis.\textsuperscript{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).\textsuperscript{3} In the clinical trials, adverse events associated with Mozobil\textsuperscript{®} were more likely to occur during Period 1 (as opposed to other periods) due to proximity to dosing.\textsuperscript{4} Adverse events reported during Period 1 that occurred in ≥ 5% of lymphoma and MM patients receiving Mozobil\textsuperscript{®} and more frequent than placebo included diarrhea, nausea, vomiting, flatulence, fatigue, injection site erythema, injection site pruritis, arthralgia, headache, dizziness, and anxiety.\textsuperscript{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\textsuperscript{®} 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\textsuperscript{®} injection.\textsuperscript{6}

- **Hematologic effects:** The sponsor states that concomitant administration of Mozobil\textsuperscript{®} and G-CSF increases circulating leukocytes, and leukocyte count should be monitored during Mozobil\textsuperscript{®} use. Although rare instances of hyperleukocytosis resulting in

---

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

\textsuperscript{2} Proposed Mozobil\textsuperscript{®} package insert submitted June 16, 2008.

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

\textsuperscript{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).

\textsuperscript{5} Proposed Mozobil\textsuperscript{®} package insert submitted June 16, 2008.

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.\(^7\)

The proposed labeling also states that Mozobil\(^b\) is not intended for HSC mobilization and harvest in patients with leukemia.\(^8\)

- **Splenomegaly**: Higher doses (4-fold the dose recommended for human use) and prolonged Mozobil\(^b\) therapy (2-4 weeks) produced increased spleen weights in rats. Splenic size was not evaluated in the Mozobil\(^b\) clinical trials. Labels of other G-CSF products include bolded warnings regarding rare instances of splenic rupture, including some fatal cases. The sponsor states that with the concomitant administration of Mozobil\(^b\) and G-CSF, splenic enlargement cannot be ruled out, and patients who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity. This information is including in the labels of other G-CSF products.

- **Thrombocytopenia**: In phase 3 studies, 0.7% of Mozobil-treated patients versus 1.0% of patients treated with G-CSF/placebo had severe thrombocytopenia. It is a known complication of apheresis, has been observed in clinical trials, and should also be monitored while on Mozobil\(^b\) therapy.\(^10\)

- **Myocardial infarction**: Seven of 599 oncology patients experienced myocardial infarctions after HSC mobilization with Mozobil\(^b\) and G-CSF. All events occurred at least 14 days after the last Mozobil\(^b\) dose. Two additional patients in the compassionate use program experienced MI; one occurring 4 days after last Mozobil\(^b\) dose. The sponsor states that the lack of temporal relationship suggests that myocardial infarction is a not direct risk of Mozobil\(^b\) administration but should be monitored.\(^11\)

- **Interstitial lung disease**: One case of interstitial pneumonitis was reported in the compassionate use program as was assessed as possibly related to G-CSF or Mozobil\(^b\). Interstitial lung disease has been reported in patients receiving G-CSF.

- **Plasmacytosis**: Mozobil\(^b\) administration during the compassionate use program is thought to have exacerbated the conditions of two MM patients thought to have previously unidentified plasma cell leukemia by causing plasmacytosis. Plasma cell leukemia is a variant of MM that can occur as a late manifestation of MM. “One patient had documented increased blast cells present in peripheral blood prior to Mozobil\(^b\) administration. Following Mozobil\(^b\) administration, the number of blast cells increased.

---


\(^8\) Proposed Mozobil\(^b\) package insert submitted June 16, 2008.


\(^11\) Proposed Mozobil\(^b\) package insert submitted June 16, 2008.
The second patient has increased plasma cells (15%) in the apheresis product.\textsuperscript{12} The sponsor has included language in the proposed labeling that states that Mozobil\textsuperscript{®} is not intended for HSC mobilization and harvest in patients with leukemia.

- **Drug exposure during pregnancy:** Mozobil\textsuperscript{®} is classified as pregnancy category \textsuperscript{(b) (4)} during pregnancy unless the potential benefit outweighs the risk. The proposed labeling suggests a dose reduction to 160 mcg/kg.

- **Decreased clearance:** Decreased clearance applies to patients with severe renal insufficiency (creatinine clearance \( \leq 30 \) 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\textsuperscript{®} 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 ongoing 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.\textsuperscript{13}


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

/s/
Mary Dempsey
11/25/2008 07:09:07 AM
DRUG SAFETY OFFICE REVIEWER
Mary Willy Acting for Claudia Karwoski Acting DRISK Director

Mary Willy
11/25/2008 07:57:32 AM
DRUG SAFETY OFFICE REVIEWER
Acting Director DRISK signing for Claudia Karwoski