CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-311

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10/30/08
From	Ann T. Farrell, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22311
Applicant	Genzyme
Date of Submission	6/16/08
PDUFA Goal Date	12/16/08
Proprietary Name / Established (USAN) names	Mozobil/plerixafor/AMD3100
Dosage forms / Strength	Single-use vial containing 24 mg of plerixafor for subcutaneous injection
Proposed Indication(s)	1. Mozobil is indicated to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.
Recommended:	Approval

1. Introduction

On June 16, 2008, Genzyme submitted an NDA for Mozobil (plerixafor) for the following indication, "to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma".

Plerixafor is a small molecule bicyclam derivative. According to Genzyme, plerixafor "selectively and reversibly antagonizes the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor 1α (SDF-1α, also known as CXCL12). The interruption of the CXCR4/SDF-1α interaction provides a novel mechanism for mobilization of CD34+ haematopoietic stem cells (HSC) from the bone marrow to the peripheral blood where they can be collected for peripheral blood haematopoietic stem cell (PBHSC) transplantation. In contrast to granulocyte colony stimulating factor (G-CSF), plerixafor does not affect cell proliferation and is presumed to exert a direct mobilizing effect by releasing CD34+ HSC into the peripheral blood."

Genzyme proposes that "A significant proportion of patients may not be able to mobilize a sufficient or target number of cells for transplantation(s) with current HSC mobilization regimens, including cytokines with or without chemotherapy. These

patients require multiple mobilizations, thus increasing associated costs and the potential of disease progression between the first and subsequent mobilization attempts. Furthermore, while potentially effective for HSC mobilization and treatment of the underlying malignancy, chemotherapy is associated with multiple risks such as febrile neutropenia, infection, and bleeding which require treatment and may require hospitalization and could be avoided if another effective mobilization regimen were used."

The NDA is a complete submission for all disciplines and includes a 120-day safety update.

Issues for this review include: potential for tumor cell mobilization and splenomegaly noted in rats

2. Background

Genzyme is seeking an indication for plerixafor for the mobilization of hematopoietic stem cells (HSC) from peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma. Plerixafor will be given in conjunction with Neupogen® (G-CSF (granulocyte colony-stimulating factor)) to mobilize these cells. Neupogen® has approval as a single agent to mobilize hematopoietic stem cells.

Patients with malignancies who plan to undergo an autologous transplant receive chemotherapy and G-CSF to mobilize HSC which are then collected and stored. In order to undergo a transplant, patients need to have collected and stored an adequate amount of HSC (defined as CD34+). Patients, who have difficulty mobilizing a sufficient number of HSC, are known as poor mobilizers. At transplant, patients receive high dose chemotherapy, which can eradicate their hematopoietic system. To replenish this system, patients are given the previously collected and stored HSC.

For some diseases an autologous transplant may prolong survival or progression-free survival. Therefore the mobilization procedure can be very beneficial.

3. CMC/Device

From the chemistry review:
"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 when stored at room temperature.

No microbiology deficiencies were identified that would preclude approval. See Dr. Pawar's review for details.

There are no outstanding CMC issues. There are no proposed post marketing agreements or requests.

4. Nonclinical Pharmacology/Toxicology

Plerixafor is not mutagenic. Carcinogenicity studies were not performed.

From the preclinical studies, the target organs are bone, liver, spleen, cardiovascular, and central nervous system. Reproductive toxicity studies (rat and rabbit) demonstrated fetal toxicity with malformations. The product labeling carries a Pregnancy D category which describes the teratogenicity findings. Preclinical testing in rats demonstrated an increase in spleen size with plerixafor administration. A statement in warnings section about this potential for splenomegaly exists. This statement is important because Mozobil will be given in combination with G-CSF which is known to cause splenomegaly and rupture.

There are no outstanding non-clinical pharmacology/toxicology issues. For details please see Dr. Lee's and Dr. Saber's reviews.

5. Clinical Pharmacology/Biopharmaceutics

Since plerixafor has limited oral bioavailability, plerixafor was developed for subcutaneous injection. Peak plasma concentrations are observed 30 to 60 minutes after dosing. The percentage of plerixafor bound to protein is estimated to range from 37-58%. The mean terminal elimination half-life ranged from 3 to 6 hours.

The sponsor did not perform a human mass balance study; however, the major route of elimination is the kidney. From the clinical pharmacology review "Preclinical studies and *in vitro* screening assays using human liver microsomes and hepatocytes indicate that plerixafor does not undergo metabolism."

The review did uncover concerns about dosing in patients with NHL who weigh less than 85 kg based on a population PK analysis. A similar concern was not observed with those patients with MM who weigh less than 85 kg. See Issue #1 below.

(b) (4) .

The sponsor has not studied drug-drug interactions.

A thorough TQT trial is completed and the sponsor plans to submit the completed trial report and data in January 2009.

The clinical pharmacology review did not uncover any issues that would preclude approval of plerixafor. However, the review team did identify issues that they recommended the sponsor study or incorporate in the labeling.

Issues #1- From the clinical pharmacology review:
"A population pharmacokinetic (PK) analysis conducted by OCP indicated a decreased response rate in NHL patients weighing < 85 kg. The population PK analysis also indicated that the proposed mcg/kg-based dose calculation leads to an increased plerixafor exposure in patients weighing > 160 kg and a decreased plerixafor exposure in patients weighing < 85 kg, when compared to patients in the weight range of 85 kg to 160 kg. "

Therefore a request was sent to the sponsor to design, conduct and submit a clinical trial to optimize dosing in NHL patients with low drug exposure and low baseline CD34+ cell counts. The review team recommended that Genzyme compare the results to the currently proposed dose and dosing schedule.

Issues #2- From the review:
"Results from the dedicated renal impairment study showed an increase in plerixafor exposure with increasing severity of renal impairment. The population PK analysis also indicated an increased exposure in patients with moderate and severe renal impairment compared to patients with mild and normal renal function. OCP recommends a dose reduction of one-third (160 mcg/kg) across all body weights for patients with moderate to severe renal impairment…"

This recommendation is incorporated into the labeling.

Issue #3- From the review:
"Plerixafor was not screened *in vitro* to assess whether it is a substrate or inhibitor of Pglycoprotein."

The review team has recommended that the sponsor conduct an *in vitro* screen to assess this.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

The efficacy and safety data from 2 major phase 3 controlled trials are listed in the table below. The phase 3 trials were supported by trials in both healthy volunteers

and in patients which determined optimal dose, dosing and sequence of G-CSF and plerixafor. Two of the phase 2 trials (2102 and 2109) were conducted in patients deemed “poor mobilizers” whose prior attempt at mobilization was unsuccessful or in those patients who were predicted to have difficulty with stem cell mobilization using current methods.

Please see Dr. Brave’s review for details not provided in the table below.

Major Plerixafor Mobilization Trials

Trial number	Design	Primary Endpoint	Supportive Secondary endpoints
3101	Randomized, double-blind, placebo-control comparing G-CSF + plerixafor with G-CSF + placebo trial with 311 patients with NHL planning to undergo an autologous transplant*	Percentage of patients undergoing mobilization and achieving ≥ 5 X 10^6 CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions: 59% of NHL patients who were mobilized with plerixafor and G-CSF compared with 20% of patients who were mobilized with placebo and G-CSF ($p < 0.001$).	Percentage of patients undergoing mobilization and achieving ≥ 2 X 10^6 CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions: 87% patients randomized to G-CSF/plerixafor compared to 47% patients randomized to G-CSF/placebo ($p < 0.001$).
3102	Randomized, double-blind, placebo-control comparing G-CSF + plerixafor with G-CSF + placebo trial with 303 patients with NHL planning to undergo an autologous transplant	Percentage of patients undergoing mobilization and achieving ≥ 6 X 10^6 CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions: 72% of NHL patients who were mobilized with plerixafor and G-CSF compared with 34% of patients who were mobilized with placebo and G-CSF ($p < 0.001$).	Percentage of patients undergoing mobilization and achieving ≥ 6 X 10^6 CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions: 76% patients randomized to G-CSF/plerixafor compared to 51% patients randomized to G-CSF/placebo ($p < 0.001$). Percentage of patients undergoing mobilization and achieving ≥ 2 X 10^6 CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions: 95% patients randomized to G-CSF/plerixafor compared to 88% patients randomized to G-CSF/placebo ($p < 0.028$).

* Although 311 patients enrolled, 298 patients were used for the final analysis by prior agreement with the Agency as a few patients received Rituxan.

Reviewer’s Comment: The two randomized trials support the sponsor’s proposal that plerixafor in combination with G-CSF is useful to mobilize hematopoietic stem cells that may be later used for transplantation.

The following 2 tables from Dr. Brave's review show the engraftment results from Study 3101.

Table 1. Study 3101 neutrophil and platelet engraftment (non-rescue transplanted pop.)

	G-CSF/plerixafor (n = 135)	G-CSF/placebo (n = 82)
Neutrophil engraftment		
Achieved (y/n)[a]	135 (100%)	82 (100%)
Median time to achieve (days)[b]	10	10
Platelet engraftment		
Achieved (y/n)[c]	132 (98%)	81 (99%)
Median time to achieve[d]	20	20

Source: [a] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PMNGFTYN)
[b] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PMNGFTTT)

[c] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PLTGFTYN)
[d] (ENGRAFT1.xpt where RITUX = missing and ITT2 = 1) by (TRTGRPC and PLTGFTTT)

Table 2. Study 3101 graft durability (transplanted pop.)

	G-CSF/plerixafor (n = 135)	G-CSF/placebo (n = 82)
Graft durability at 100 days		
N	135	82
Yes	128 (95%)	78 (95%)
Graft durability at 6 months		
N	123	78
Yes	120 (98%)	77 (99%)
Graft durability at 1 year		
N	112	65
Yes	110 (98%)	65 (100%)

Source: (GRFTDR01.xpt and COMMONV.xpt) and Sponsor's program 14.2.6.1.1.2

Reviewer's Comment: Similar results were seen for Study 3102. Dr. Brave's review provides additional details on the number of patients who underwent transplantation for 3102 with the further details regarding durability of graft, time to neutrophil and platelet engraftment.

Although the trials are ongoing, these results do not suggest that the use of plerixafor is associated with particular efficacy or safety issues regarding engraftment.

Dr. Brave recommends approval of this application.

Statistical consult

The statistical team's review of the application concluded:

"Based on the data submitted, the study results support the claims in the primary endpoints and key secondary endpoints."

The statistical reviewer noted that there were a number of protocol violations in both major trials. Dr. Brave and I reviewed these protocol violations and noted that the violations were evenly distributed across arms in both trials. We also noted that the majority could be considered relatively minor and did not affect the ability of the study to demonstrate the effectiveness of plerixafor when added to G-CSF.

Reviewer Comment: I concur with Dr. Brave and the statistical review team regarding the effectiveness of plerixafor.

8. Safety

The safety database submitted for this application included data from 21 trials and contained an adequate number of patients with adequate exposure for assessment of short-term risk. The drug is not marketed anywhere at this time.

The evaluation of safety is difficult in this application due to the many concomitant medications. The sponsor organized the safety reporting in terms of periods. Period 1 is the period of mobilization where study drug was administered. Periods 2-5 involved the transplantation procedure and post-transplant time periods. Please see Dr. Brave's review for further details regarding these time periods.

From Dr. Brave's review

"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%). "

No grade 4 adverse reactions were attributed to plerixafor use. Less than 6% of enrolled patients experienced a grade 3 reaction in Period 1. More patients treated with G-CSF alone experienced a grade 3 reaction. Grade 3 reactions associated with plerixafor included atrial fibrillation (1 case), catheter site hemorrhage (2 cases), pyrexia (2 cases), disease progression (1 case), and catheter bacteremia (1 case).

Although Dr. Brave has slightly different numbers for the safety denominator in his safety section compared with the sponsor, the differences were slight (one or two patients) and did not alter the conclusions from the trials.

In summary, the application has information on Mozobil's short-term and long-term safety issues. The short term safety issues are systemic reactions including urticaria, swelling, dyspnea, and hypotension, and gastrointestinal reactions (vomiting, diarrhea, flatulence). Long term safety issues for this product are addressed by the information on graft durability at 100 days, 6 months, and 12 months, and time to neutrophil and platelet engraftment.

An outstanding regulatory safety requirement is the need for a TQT trial to evaluate the potential for QT prolongation. Genzyme has completed a trial to evaluate the potential of plerixafor to prolong the QT interval. The sponsor anticipates that the completed trial report will be submitted in the first quarter of 2009.

Other Issues for Mozobil

Tumor Mobilization

During the course of drug development the sponsor has been asked to address whether Mozobil mobilizes tumor cells. Mozobil is intended to be marketed for use in combination with G-CSF. G-CSF is known to mobilize tumor cells and this information is in the G-CSF label.

During the drug development, the sponsor assayed apheresis collections for tumor cells in some trials. The data are provided in a table below.

Tumor Cell Mobilization in Trials

Study Number	Number of enrolled patients	Number studied	Results	Comment
2102	35 patients (10 with MM and 25 with NHL) receiving plerixafor subcutaneously	10 patients with MM who failed prior attempts at mobilization	No aneuploid cells detected; 1 patient had 2% kappa cells; 8 patients received a first transplant and 6 received a second transplant	Dr. **(b) (4)** stated that the study strongly suggests that AMD3100 did not mobilize myeloma cells; however the study does not completely eliminate the possibility that a minor fraction of < 1% myeloma cells was mobilized.
EU21	35 patients treated with both G-CSF and plerixafor	7 patients with MM	6/6 after plerixafor mobilization did have tumor cells mobilized (note G-CSF was also given)	Dr. **(b) (4)** conclusion is "In summary, G-CSF significantly mobilized clonotypical cells in multiple myeloma while addition of AMD to G-CSF did not lead to significant myeloma cell mobilization."
Compassionate	368 patients in CUP who	2 patients with MM; 4	2/2 patients with MM may have	All patients received G-CSF plus plerixafor.

Use program (CUP)/2112	received G-CSF and plerixafor	patients with AML; still ongoing	been developing plasma cell leukemia on or about the time of apheresis; 3/4 patients with AML had leukemic cells detected	
3101	311 patients with NHL	3 patients with follicular NHL treated with plerixafor/G-CSF; 5 patients with follicular NHL treated with G-CSF alone	0/3 plerixafor plus G-CSF treated patients had the BCL-2 translocation detected; 1/5 GSF-alone treated patients had the BCL-2 translocation detected	FDA comment- too few to make definitive comment.
2101	25 patients with NHL receiving G-CSF and AMD3100	3 patients with follicular NHL treated with plerixafor/G-CSF	0/3 had the BCL-2 translocation detected	FDA comment- too few to make definitive comment.
2103	13 patients with NHL receiving G-CSF and AMD3100	10 patients patient's products tested	0/10 had the BCL-2 translocation detected	Dr. (b) (4), author of report, stated that none of the apheresis collections was contaminated with tumor cells; however he noted too few patients studied to make conclusion about AMD3100's ability to mobilize tumor cells.

Reviewer Comment: The sponsor's data suggests the combination may mobilize leukemia cells. The sponsor has proposed a warning in the labeling about this potential.

The sponsor's data above does not suggest that plerixafor alone mobilizes tumor cells.

Relapse Data
If the addition of plerixafor mobilized more tumor cells than G-CSF alone, then the relapse rates may be higher in the plerixafor plus G-CSF arm than in the G-CSF arm.

In the Integrated Summary of Safety, the reported adverse events due to malignancy in the phase 3 trials are: plerixafor plus G-CSF 0 (0%) and G-CSF alone 1 (< 1%).

The death due to disease progression/relapse rates for the two trials are 12 (3%) for the plerixafor plus G-CSF arm and 15 (5%) for the G-CSF alone arm.

Reviewer's Comment: Currently there is neither data nor a signal to suggest that Mozobil mobilizes tumor cells. The theoretical possibility exists.

The sponsor was asked to agree to commit to perform an additional study to determine whether Mozobil mobilized tumor cells. In response, the company submitted a white paper which was reviewed by Dr. Brave.

From his review:

"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."

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.

Splenomegaly and Potential for Splenic Rupture

Although splenomegaly was reported in non-clinical studies with rats, few cases of splenomegaly were reported in the clinical safety database. All clinical cases were related to disease progression. Routine pharmacovigilance should assess for this AE; however, since plerixafor will be given with G-CSF, attribution may be difficult. The label for G-CSF already contains information regarding the potential for splenic rupture. A statement in warnings section about this potential for splenomegaly is in the Mozobil labeling because rats given Mozobil developed splenomegaly and Mozobil will be given in combination with G-CSF, which is known to cause splenomegaly and rupture.

9. Advisory Committee Meeting

This application was not taken to an Advisory Committee for several reasons. The protocols for the two major trials were part of the Special Protocol Assessment program. Both protocols were reviewed by an external expert 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

Mozobil has Orphan Status.

11. Other Relevant Regulatory Issues

In summary, there are no Application Integrity Policy (AIP) issues, exclusivity or patent issues of concern, financial disclosures, other GCP issues, DSI audits, other discipline consults and any other outstanding regulatory issues.

Although some physicians who enrolled patients in the pivotal study received compensation or had a proprietary interest, the design of the pivotal trials prevented undue influence by enrolling physicians. Dr. Brave stated that

"The following features of the phase 3 studies minimized the potential for the financial arrangements disclosed to have biased the plerixafor development program:

- The studies were double-blinded and placebo-controlled.
- Patients were randomized centrally.
- The studies were conducted at multiple centers.
- Efficacy endpoints were assessed by a central laboratory.

- The statistical analyses were prospectively defined, and analyses of the primary endpoints were based on the ITT populations."

Reviewer Comments: I agree with Dr. Brave's analysis of why the design of the key phase 3 trials minimized the potential for the financial arrangements to have biased the results. There were a few physicians who did not return financial disclosure forms. An exploratory efficacy analysis performed removing those sites' data from the analyses did not change the conclusion that Mozobil is a highly effective therapy when used in combination with G-CSF.

Please see Dr. Brave's Medical Officer review for details of financial disclosure.

12. Labeling

All disciplines made recommendations for labeling which were incorporate. DMEPA approved the name Mozobil and made recommendations regarding carton and container labeling. Nearly all of DMEPA, SEALD, and DDMAC's recommendations were incorporated into the physician labeling.

Given the relative safety of this drug no black box warning was necessary. In the warnings section of the label, the following issues were noted: Potential for Tumor Cell Mobilization, Hematologic Effects, Potential for Splenic Rupture, and Pregnancy category D.

13. Recommendations/Risk Benefit Assessment

- 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

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/s/

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MEDICAL OFFICER