

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-311

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MOZOBIL safely and effectively. See full prescribing information for MOZOBIL.

MOZOBIL (plerixafor injection), Solution for Subcutaneous use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

Mozobil, a hematopoietic stem cell mobilizer, 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 and multiple myeloma. (1)

DOSAGE AND ADMINISTRATION

- Initiate Mozobil treatment after the patient has received G-CSF once daily for 4 days. (2.1)
- Repeat Mozobil dose up to 4 consecutive days. (2.1)
- Select dose based on 0.24 mg/kg actual body weight. (2.1)
- Administer by subcutaneous injection approximately 11 hours prior to initiation of apheresis. (2.1)
- Renal impairment: If creatinine clearance is \leq 50 mL/min, decrease dose by one-third to 0.16 mg/kg. (2.3)

DOSAGE FORMS AND STRENGTHS

- Single-use vial containing 1.2 mL of a 20 mg/mL solution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Tumor Cell Mobilization in Leukemia Patients: Mozobil may mobilize leukemic cells and should not be used in leukemia patients. (5.1)
- Hematologic Effects: Increased circulating leukocytes and decreased platelet counts have been observed. Monitor blood cell counts and platelet counts during Mozobil use. (5.2)
- Potential for Tumor Cell Mobilization: Tumor cells may be released from marrow during HSC mobilization with Mozobil and G-CSF. Effect of reinfusion of tumor cells is unknown. (5.3)
- Potential for Splenic Rupture: Evaluate patients who report left upper abdominal and/or scapular or shoulder pain. (5.4)
- Pregnancy: May cause fetal harm. Advise women not to become pregnant when taking Mozobil. (5.5, 8.1)

ADVERSE REACTIONS

Most common adverse reactions (\geq 10%): diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-877-4MOZOBIL or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

2.2 Recommended Concomitant Medications

2.3 Dosing in Renal Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Tumor Cell Mobilization in Leukemia Patients

5.2 Hematologic Effects

5.3 Potential for Tumor Cell Mobilization

5.4 Splenic Enlargement and Potential for Rupture

5.5 Pregnancy

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

Vials should be inspected visually for particulate matter and discoloration prior to administration and should not be used if there is particulate matter or if the solution is discolored.

Begin treatment with Mozobil after the patient has received G-CSF once daily for four days. [see *Dosage and Administration (2.2)*] Administer Mozobil approximately 11 hours prior to initiation of apheresis for up to 4 consecutive days.

The recommended dose of Mozobil is 0.24 mg/kg body weight by subcutaneous (SC) injection. Use the patient's actual body weight to calculate the volume of Mozobil to be administered. Each vial delivers 1.2 mL of 20 mg/mL solution, and the volume to be administered to patients should be calculated from the following equation:

$$0.012 \times \text{patient's actual body weight (in kg)} = \text{volume to be administered (in mL)}$$

In clinical studies, Mozobil dose has been calculated based on actual body weight in patients up to 175% of ideal body weight. Mozobil dose and treatment of patients weighing more than 175% of ideal body weight have not been investigated.

Based on increasing exposure with increasing body weight, the plerixafor dose should not exceed 40 mg/day. [see *Clinical Pharmacology (12.3)*]

2.2 Recommended Concomitant Medications

Administer daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first evening dose of Mozobil and on each day prior to apheresis. [see *Clinical Studies (14)*]

2.3 Dosing in Renal Impairment

In patients with moderate and severe renal impairment (estimated creatinine clearance (CL_{CR}) \leq 50 mL/min), reduce the dose of Mozobil by one-third to 0.16 mg/kg as shown in Table 1. If CL_{CR} is \leq 50 mL/min the dose should not exceed 27 mg/day, as the mg/kg-based dosage results in increased plerixafor exposure with increasing body weight. [see *Clinical Pharmacology (12.3)*] Similar systemic exposure is predicted if the dose is reduced by one-third in patients with moderate and severe renal impairment compared with subjects with normal renal function. [see *Clinical Pharmacology (12.3)*]

Table 1: Recommended Dosage of Plerixafor in Patients with Renal Impairment

Estimated Creatinine Clearance (mL/min)	Dose
> 50	0.24 mg/kg once daily (not to exceed 40 mg/day)
≤ 50	0.16 mg/kg once daily (not to exceed 27 mg/day)

The following (Cockcroft-Gault) formula may be used to estimate CL_{CR} :

Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine clearance (mL/min)} = 0.85 \times \text{value calculated for males}$$

There is insufficient information to make dosage recommendations in patients on hemodialysis.

3 DOSAGE FORMS AND STRENGTHS

Single-use vial containing 1.2 mL of a 20 mg/mL solution.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

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. *[see Use In Specific Populations (8.1)]*

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The following serious adverse reactions are discussed elsewhere in the labeling:

- Potential for tumor cell mobilization in leukemia patients *[see Warnings and Precautions (5.1)]*
- Increased circulating leukocytes and decreased platelet counts *[see Warnings and Precautions (5.2)]*
- Potential for splenic enlargement *[see Warnings and Precautions (5.4)]*

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.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

7 DRUG INTERACTIONS

Based on *in vitro* data, plerixafor is not a substrate, inhibitor or inducer of human cytochrome P450 isozymes. Plerixafor is not likely to be implicated in *in vivo* drug-drug interactions involving cytochrome P450s. [see *Clinical Pharmacology (12.3)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Plerixafor was teratogenic in animals. Plerixafor administered to pregnant rats induced embryo-fetal toxicities including fetal death, increased resorptions and post-implantation loss, decreased fetal weights, anophthalmia, shortened digits, cardiac interventricular septal defect, ringed aorta, globular heart, hydrocephaly, dilatation of olfactory ventricles, and retarded skeletal development. Embryo-fetal toxicities occurred mainly at a dose of 90 mg/m^2 (approximately 10 times the recommended human dose of 0.24 mg/kg when compared on a mg/m^2 basis or 10 times the AUC in subjects with normal renal function who received a single dose of 0.24 mg/kg).

8.3 Nursing Mothers

It is not known whether plerixafor is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Mozobil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Mozobil in pediatric patients have not been established in controlled clinical studies.

8.5 Geriatric Use

Of the total number of subjects in controlled clinical studies of Mozobil, 24% were 65 and over, while 0.8% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Since plerixafor is mainly excreted by the kidney, no dose modifications are necessary in elderly individuals with normal renal function. In general, care should be taken in dose selection for elderly patients due to the greater frequency of decreased renal function with advanced age. Dosage adjustment in elderly patients with $CL_{CR} \leq 50$ mL/min is recommended. [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]

8.6 Renal Impairment

In patients with moderate and severe renal impairment ($CL_{CR} \leq 50$ mL/min), reduce the dose of plerixafor by one-third to 0.16 mg/kg. [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]

10 OVERDOSAGE

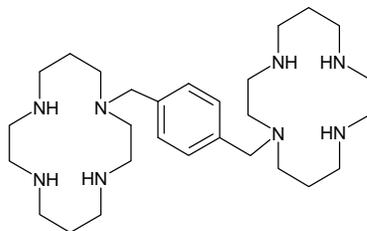
Based on limited data at doses above the recommended dose of 0.24 mg/kg SC, the frequency of gastrointestinal disorders, vasovagal reactions, orthostatic hypotension, and/or syncope may be higher.

11 DESCRIPTION

Mozobil (plerixafor injection) is a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution for subcutaneous injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 1.2 mL of the sterile solution that contains 24 mg of plerixafor and 5.9 mg of sodium chloride in Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required.

Plerixafor is a hematopoietic stem cell mobilizer with a chemical name 1, 1'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane. It has the molecular formula $C_{28}H_{54}N_8$. The molecular weight of plerixafor is 502.79 g/mol. The structural formula is provided in Figure 1.

Figure 1: Structural Formula



Plerixafor is a white to off-white crystalline solid. It is hygroscopic. Plerixafor has a typical melting point of 131.5 °C. The partition coefficient of plerixafor between 1-octanol and pH 7 aqueous buffer is < 0.1 .

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

Data on the fold increase in peripheral blood CD34+ cell count (cells/mL) by apheresis day were evaluated in two placebo-controlled clinical studies in patients with NHL and MM (Study 1 and Study 2, respectively). The fold increase in CD34+ cell count (cells/mL) over the 24-hour period starting from the day prior to the first apheresis and ending the next morning just before the first apheresis is summarized in Table 3. During this 24-hour period, a single dose of Mozobil or placebo was administered 10 to 11 hours prior to apheresis.

Table 3: Fold Increase in Peripheral Blood CD34+ Cell Count Following Pretreatment with G-CSF and Administration of Plerixafor

Study	Mozobil and G-CSF		Placebo and G-CSF	
	Median	Mean (SD)	Median	Mean (SD)
Study 1	5.0	6.2 (5.4)	1.4	1.9 (1.5)
Study 2	4.8	6.4 (6.8)	1.7	2.4 (7.3)

In pharmacodynamic studies of Mozobil in healthy volunteers, peak mobilization of CD34+ cells was observed between 6 and 9 hours after administration. In pharmacodynamic studies of Mozobil in conjunction with G-CSF in healthy volunteers, a sustained elevation in the peripheral blood CD34+ count was observed from 4 to 18 hours after plerixafor administration with a peak CD34+ count between 10 and 14 hours.

12.3 Pharmacokinetics

The single-dose pharmacokinetics of plerixafor 0.24 mg/kg were evaluated in patients with NHL and MM following pre-treatment with G-CSF (10 micrograms/kg once daily for 4 consecutive days). Plerixafor exhibits linear kinetics between the 0.04 mg/kg to 0.24 mg/kg dose range. The pharmacokinetics of plerixafor were similar across clinical studies in healthy subjects who received plerixafor alone and NHL and MM patients who received plerixafor in combination with G-CSF.

A population pharmacokinetic analysis incorporated plerixafor data from 63 subjects (NHL patients, MM patients, subjects with varying degrees of renal impairment, and healthy subjects) who received a single SC dose (0.04 mg/kg to 0.24 mg/kg) of

plerixafor. A two-compartment disposition model with first order absorption and elimination was found to adequately describe the plerixafor concentration-time profile. Significant relationships between clearance and creatinine clearance (CL_{CR}), as well as between central volume of distribution and body weight were observed. The distribution half-life ($t_{1/2\alpha}$) was estimated to be 0.3 hours and the terminal population half-life ($t_{1/2\beta}$) was 5.3 hours in patients with normal renal function.

The population pharmacokinetic analysis showed that the mg/kg-based dosage results in an increased plerixafor exposure (AUC_{0-24h}) with increasing body weight. There is limited experience with the 0.24 mg/kg dose of plerixafor in patients weighing above 160 kg. Therefore the dose should not exceed that of a 160 kg patient (i.e., 40 mg/day if CL_{CR} is > 50 mL/min and 27 mg/day if CL_{CR} is ≤ 50 mL/min). [see *Dosage and Administration* (2.1, 2.3)]

Absorption

Peak plasma concentrations occurred at approximately 30 - 60 minutes after a SC dose.

Distribution

Plerixafor is bound to human plasma proteins up to 58%. The apparent volume of distribution of plerixafor in humans is 0.3 L/kg demonstrating that plerixafor is largely confined to, but not limited to, the extravascular fluid space.

Metabolism

The metabolism of plerixafor was evaluated with *in vitro* assays. Plerixafor is not metabolized as shown in assays using human liver microsomes or human primary hepatocytes and does not exhibit inhibitory activity *in vitro* towards the major drug metabolizing cytochrome P450 enzymes (1A2, 2C9, 2C19, 2D6, and 3A4/5). In *in vitro* studies with human hepatocytes, plerixafor does not induce CYP1A2, CYP2B6, or CYP3A4 enzymes. These findings suggest that plerixafor has a low potential for involvement in cytochrome P450-dependent drug-drug interactions.

Elimination

The major route of elimination of plerixafor is urinary. Following a 0.24 mg/kg dose in healthy volunteers with normal renal function, approximately 70% of the dose was excreted in the urine as the parent drug during the first 24 hours following administration. In studies with healthy subjects and patients, the terminal half-life in plasma ranges between 3 and 5 hours. The ability of plerixafor to act as a substrate or as an inhibitor of P-glycoprotein has not been investigated.

Renal Impairment

Following a single 0.24 mg/kg SC dose, plerixafor clearance was reduced in subjects with varying degrees of renal impairment and was positively correlated with CL_{CR} . The mean AUC_{0-24h} of plerixafor in subjects with mild (CL_{CR} 51-80 mL/min), moderate (CL_{CR} 31-50 mL/min), and severe ($CL_{CR} < 31$ mL/min) renal impairment was 7%, 32%, and 39% higher than healthy subjects with normal renal function, respectively. Renal

impairment had no effect on C_{max} . A population pharmacokinetic analysis indicated an increased exposure (AUC_{0-24h}) in patients with moderate and severe renal impairment compared to patients with $CL_{CR} > 50$ mL/min. These results support a dose reduction of one-third in patients with moderate to severe renal impairment ($CL_{CR} \leq 50$ mL/min) in order to match the exposure in patients with normal renal function. The population pharmacokinetic analysis showed that the mg/kg-based dosage results in an increased plerixafor exposure (AUC_{0-24h}) with increasing body weight; therefore if CL_{CR} is ≤ 50 mL/min the dose should not exceed 27 mg/day. [see *Dosage and Administration (2.3)*]

Since plerixafor is primarily eliminated by the kidneys, coadministration of plerixafor with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of plerixafor or the coadministered drug. The effects of coadministration of plerixafor with other drugs that are renally eliminated or are known to affect renal function have not been evaluated.

Race

Clinical data show similar plerixafor pharmacokinetics for Caucasians and African-Americans, and the effect of other racial/ethnic groups has not been studied.

Gender

Clinical data show no effect of gender on plerixafor pharmacokinetics.

Age

Clinical data show no effect of age on plerixafor pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with plerixafor have not been conducted.

Plerixafor was not genotoxic in an *in vitro* bacterial mutation assay (Ames test in *Salmonella*), an *in vitro* chromosomal aberration test using V79 Chinese hamster cells, or an *in vivo* bone marrow micronucleus test in rats after subcutaneous doses up to 25 mg/kg (150 mg/m^2).

The effect of plerixafor on human fertility is unknown. The effect of plerixafor on male or female fertility was not studied in designated reproductive toxicology studies. The staging of spermatogenesis measured in a 28-day repeated dose toxicity study in rats revealed no abnormalities considered to be related to plerixafor. No histopathological evidence of toxicity to male or female reproductive organs was observed in 28-day repeated dose toxicity studies.

14 CLINICAL STUDIES

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each single-use vial is filled to deliver 1.2 mL of 20 mg/mL solution containing 24 mg of plerixafor.

NDC Number: 58468-0140-1

- Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [see USP Controlled Room temperature]
- Each vial of Mozobil is intended for single use only. Any unused drug remaining after injection must be discarded.

17 PATIENT COUNSELING INFORMATION

Advise patients of the signs and symptoms of potential systemic reactions such as urticaria, periorbital swelling, dyspnea, or hypoxia during and following Mozobil injection. *[see Adverse Reactions (6.1)]*

Patients should inform a health care professional immediately if symptoms of vasovagal reactions such as orthostatic hypotension or syncope occur during or shortly after their Mozobil injection. *[see Adverse Reactions (6.1)]*

If patients experience itching, rash, or reaction at the site of injection, they should notify a health care professional as these symptoms have been treated with over-the-counter medications during clinical trials. *[see Adverse Reactions (6.1)]*

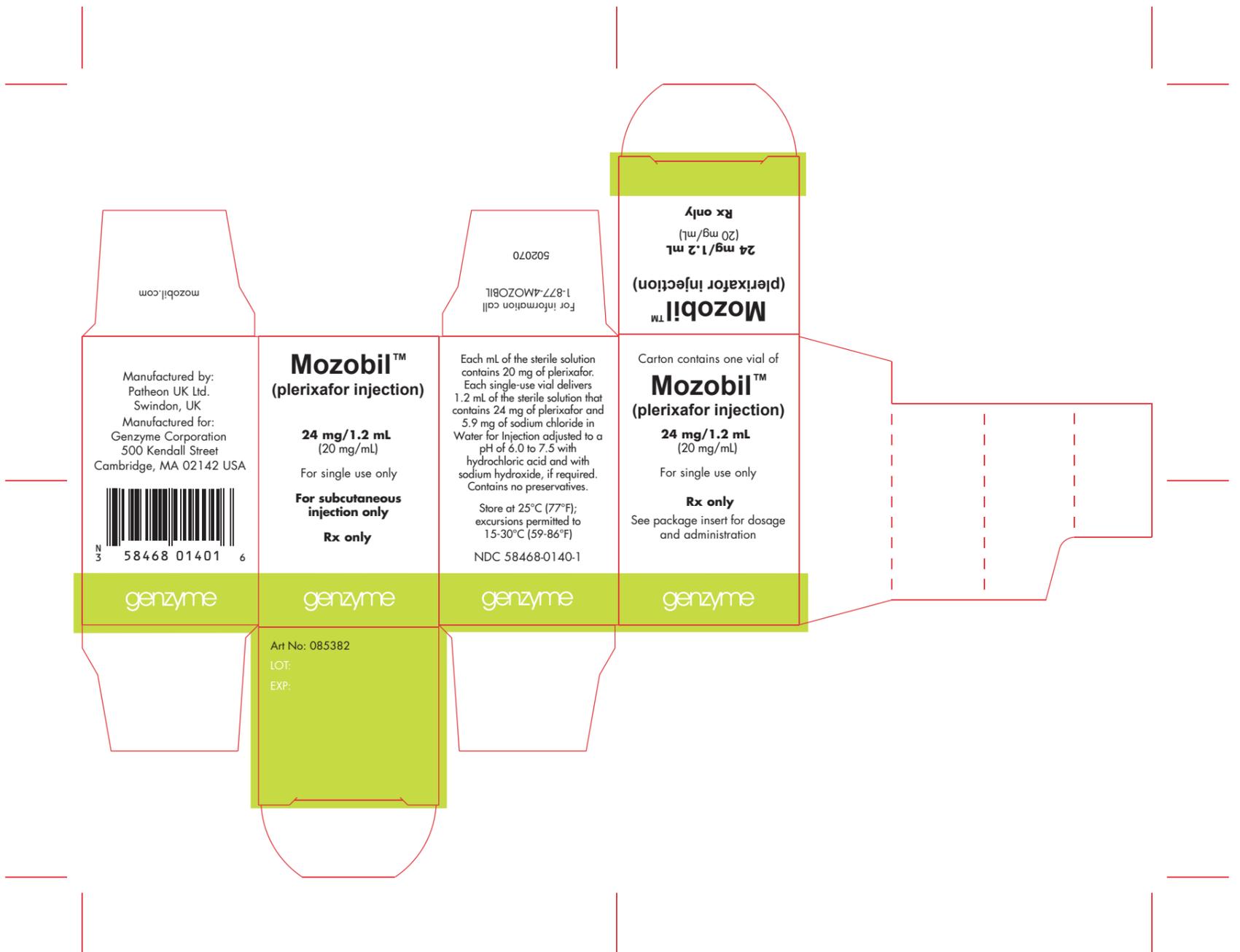
Inform patients that Mozobil may cause gastrointestinal disorders, including diarrhea, nausea, vomiting, flatulence, and abdominal pain. Patients should be told how to manage specific gastrointestinal disorders and to inform their health care professional if severe events occur following Mozobil injection. *[see Adverse Reactions (6.1)]*

Advise female patients with reproductive potential to use effective contraceptive methods during Mozobil use. *[see Warnings and Precautions (5.5) and Use In Specific Populations (8.1)]*

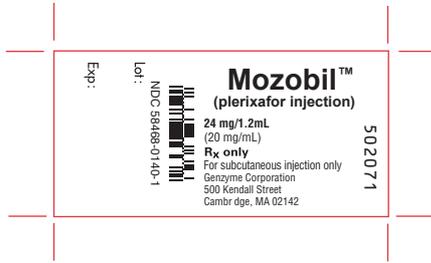
Manufactured by: Patheon UK Ltd., Swindon, UK

Manufactured for: Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
USA

©2008 Genzyme Corporation. All rights reserved.
Mozobil is a trademark of Genzyme Corporation.



(b) (4)



(b) (4)



**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 03:40:35 PM