PRODUCT MONOGRAPH

^{Pr} MOZOBIL®

Plerixafor Injection

Solution, 24 mg/1.2 mL (20 mg/mL), Single Use Vial

Subcutaneous use only

Professed Standard

Hematopoietic Agent

ATC Code: L03AX16

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MOZOBIL®

plerixafor injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Subcutaneous	Single use vial solution for injection/20 mg/mL	Each 1.2 mL contains 5.9 mg sodium chloride in sterile Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required

INDICATIONS AND CLINICAL USE

Adult
MOZOBIL (plerixafor) is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). Some patients with NHL and MM are able to meet minimal and target HSC collection criteria with G-CSF alone. (See CLINICAL TRIALS)

MOZOBIL should only be administered under the supervision of a qualified health professional who is experienced in oncology and/or hematology and in the management of cancer patients undergoing mobilization of hematopoietic stem cells to the peripheral blood. (See DOSAGE AND ADMINISTRATION)

Geriatrics (≥ 65 years of age):
Of the total number of subjects in two placebo-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 with normal renal function or mild-moderate renal impairment. In general, care should be taken in dose selection for elderly patients due to the greater frequency of decreased renal function with advanced age. (See WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment)

Pediatrics (1 to less than 18 years of age):
MOZOBIL is indicated in combination with G-CSF to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumors and either:

- low circulating stem cell count on the predicted date of collection after mobilization with G-CSF (with or without chemotherapy), or

- who previously failed to collect sufficient hematopoietic stem cells (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions: MOZOBIL (plerixafor) should only be administered under the supervision of a qualified health professional who is experienced in oncology and/or hematology and in the management of cancer patients undergoing mobilization of hematopoietic stem cells to the peripheral blood. (See INDICATIONS AND CLINICAL USE)

General

No studies on the effect of MOZOBIL on the ability to drive and use machines have been conducted. Some patients have experienced dizziness, fatigue or vasovagal reactions (orthostatic hypotension and/or syncope). Appropriate precautions should be taken because of the potential for these reactions. (See ADVERSE REACTIONS)

Carcinogenesis and Mutagenesis

Carcinogenicity studies with plerixafor have not been conducted. (See Part II: Scientific Information, TOXICOLOGY, Carcinogenesis)

Cardiovascular

Patients with an abnormal ECG with clinically significant rhythm disturbance or other conduction abnormality were excluded from the Phase 3 clinical trials. Arrhythmias are a known risk following citrate anticoagulation and apheresis which induce low Ca/Mg levels and blood volume. In the Phase 3 clinical studies, examination of all clinical cardiovascular adverse events does not identify any rhythm related cardiac safety signals attributable to plerixafor treatment in the populations studied.

Decreases in Blood Pressure: In Phase 3 trials, the incidence of hypotension during mobilization and apheresis was increased in patients receiving MOZOBIL and G-CSF (3.7%) as compared to patients receiving placebo and G-CSF (2.4%). In MOZOBIL oncology and non-oncology clinical studies, 0.8% of subjects experienced vasovagal reactions (orthostatic hypotension and/or syncope) following SC administration of MOZOBIL doses ≤ 0.40 mg/kg (see ACTION AND CLINICAL PHARMACOLOGY, Electrocardiography and Hemodynamics). The majority of these events occurred within 1 hour of MOZOBIL administration. Appropriate precautions should be taken because of the potential for these reactions to occur following treatment with MOZOBIL (see WARNINGS AND PRECAUTIONS, General).

Disorders of Atrioventricular Conduction: In a randomized, double-blind, placebo-controlled crossover study in healthy subjects, MOZOBIL was associated with an asymptomatic shortening of the PR interval (see ACTION AND CLINICAL PHARMACOLOGY, Electrocardiography and Hemodynamics). Caution should be observed in patients with pre-excitation syndromes such as Wolff-Parkinson-White syndrome or Lown-Ganong-Levine syndrome, or atrioventricular nodal rhythm disorders, such as AV junctional rhythms with retrograde activation or ectopic atrial rhythms originating near the AV node.

Myocardial infarctions: In clinical studies, 0.9% of oncology patients experienced myocardial infarctions after HSC mobilization with MOZOBIL and G-CSF as compared with 0.3% of oncology patients after mobilization with placebo and G-CSF. All events occurred at least 14 days after last MOZOBIL administration. Two additional oncology patients in the compassionate use program experienced myocardial infarctions following HSC mobilization with MOZOBIL and G-CSF. One of these events occurred 4 days after last MOZOBIL administration and the other occurred 67 days after last MOZOBIL administration.

Hematologic

Leukocytosis: Administration of MOZOBIL in conjunction with G-CSF increases circulating leukocytes as well as HSC populations. White blood cell counts should be monitored during MOZOBIL use. Clinical judgment should be exercised when administering MOZOBIL to patients with peripheral blood neutrophil counts above 50,000 cells/µL.

Thrombocytopenia: Thrombocytopenia has been observed in patients receiving MOZOBIL. Platelet counts should be monitored in all patients who receive MOZOBIL.

Potential Effect on Spleen Size: Higher absolute and relative spleen weights associated with extramedullary hematopoiesis were observed following prolonged (2 to 4 weeks) daily plerixafor subcutaneous 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 has not been specifically evaluated in clinical studies. Cases of splenic enlargement and/or rupture have been reported following the administration of MOZOBIL in conjunction with growth factor G-CSF. Individuals receiving MOZOBIL in conjunction with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity.

Immune

Allergic Reactions: In MOZOBIL oncology clinical studies, 0.7% of patients experienced mild or moderate systemic reactions within approximately 30 minutes 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. Cases of anaphylactic reactions, including anaphylactic shock, have been reported from world-wide post-marketing experience. Appropriate precautions should be taken because of the potential for these reactions.

Psychiatric

An *in vitro* general receptor screen identified moderate or strong affinity of plerixafor for a number of receptors of the central and/or peripheral nervous systems (CNS and PNS) (see DETAILED PHARMACOLOGY, Safety Pharmacology). In Phase 3 trials, the incidence of psychiatric disorders during mobilization and apheresis was 14.8% in the MOZOBIL + G-CSF treatment arm and 10.2% in the placebo + G-CSF treatment arm. Insomnia and anxiety were the most common events (see ADVERSE REACTIONS). Related events of insomnia during the same period occurred in 1.0% of MOZOBIL-treated patients compared to 0% of placebo-treated patients in the Phase 3 studies. Related events of anxiety occurred in 0.7% of MOZOBIL-treated patients compared to 0.3% of placebo-treated patients in the Phase 3 studies. Vivid dreams and nightmares have been described in post marketing reports.

Other

Potential for Tumor Cell Mobilization in Lymphoma and Multiple Myeloma Patients: When MOZOBIL is used in conjunction with G-CSF for HSC mobilization in patients with NHL or MM, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. Based on limited laboratory investigations conducted in clinical studies of patients with NHL and MM, an increase in mobilization of tumor cells above that which occurs with G-CSF mobilization alone has not been observed with MOZOBIL.

The effect of potential reinfusion of tumor cells has not been well studied.

Tumor Cell Mobilization in Leukemia Patients: MOZOBIL and G-CSF have been administered to patients with acute myelogenous leukemia and plasma cell leukemia. In some instances, these patients experienced an increase in the number of circulating leukemia cells. For the purpose of HSC mobilization, MOZOBIL may cause mobilization of leukemic cells and subsequent contamination of the apheresis product. Therefore, MOZOBIL should not be used for HSC mobilization and harvest in patients with leukemia.

Special Populations

Pregnant Women: MOZOBIL may cause fetal harm when administered to a pregnant woman. Studies in animals have shown teratogenicity (see TOXICOLOGY). There are no adequate and well-controlled studies in pregnant women using MOZOBIL. Because CXCR4 plays an essential role in fetal development and plerixafor is a selective antagonist of CXCR4, plerixafor is suggested to cause congenital malformations when administered during pregnancy. The use of MOZOBIL is not recommended in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. Advise women of childbearing potential to use effective contraception during treatment.

Nursing Women: It is not known whether plerixafor is excreted in human milk. Because many drugs are excreted in human milk, 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.

Pediatrics (1 to less than 18 years of age): The safety and efficacy of MOZOBIL in pediatric patients (1 to less than 18 years) were studied in an open-label, multicentre, randomized, controlled clinical study (see ADVERSE REACTIONS; ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics; CLINICAL TRIALS). No new safety concerns were identified in this study.

Another single site study evaluating plerixafor in young patients (< 6 years of age) was stopped when 9 of 10 planned patients were enrolled, due to the occurrence of nightmares, nyctophobia, and visual hallucinations reported in some patients following the third or fourth dose of plerixafor. Comparable adverse events have not been observed in a larger, randomized, and comparative multiple site pediatric study.

Geriatrics (≥ 65 years of age): In general, care should be taken in dose selection for elderly patients due to the greater frequency of decreased renal function with advanced age. (See Renal Impairment, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY)

Hepatic Impairment: No studies in patients with hepatic impairment have been conducted. Patients with serum alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin values >2.5 x upper limit of normal were excluded from placebo-controlled clinical studies of MOZOBIL. MOZOBIL is not metabolized by the liver.

Renal Impairment: Renal impairment was associated with a prolongation of MOZOBIL half-life and increased exposure due to impaired clearance. Patients with an estimated creatinine clearance (Cl_{CR}) 20-50 mL/min should have their dose of plerixafor reduced to 0.16 mg/kg/day. Clinical data with this dose adjustment are limited. There are insufficient clinical data to make dosing recommendations for patients with a creatinine clearance <20 mL/min or for patients on dialysis. (See DOSAGE AND ADMINISTRATION; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency)

Monitoring and Laboratory Tests

White blood cell and platelet counts should be monitored during MOZOBIL use and apheresis.

Electrolytes, including calcium and magnesium, should be monitored during MOZOBIL use (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See WARNINGS AND PRECAUTIONS regarding Decreases in Blood Pressure, Disorders of

Atrioventricular Conduction, Myocardial Infarctions, Leukocytosis, Thrombocytopenia, Potential Effect on Spleen Size, Allergic Reactions, and Tumor Cell Mobilization in Leukemia Patients.

Safety data for MOZOBIL in conjunction with G-CSF were obtained from two randomized placebo-controlled studies (301 patients) and 10 uncontrolled studies (242 patients). Patients were primarily treated with MOZOBIL (plerixafor) at daily doses of 0.24 mg/kg by subcutaneous (SC) injection. Median exposure to MOZOBIL in these studies was 2 days (range 1 to 7 days).

The number of patients in the two treatment groups in the pooled Phase 3 studies changed considerably over the course of the studies, primarily due to the difference in the number who entered the rescue procedure. The Primary Safety Population comprised 301 patients during mobilization and apheresis, 279 from the first dose of ablative chemotherapy until engraftment, and 278 post-engraftment in the MOZOBIL group; 292 patients during the mobilization and apheresis period and 216 from the start of ablative chemotherapy onwards, in the placebo group.

In the Phase 3 studies, all AEs that occurred from the first dose of G-CSF until 30 days after the last apheresis or until the first dose of ablative chemotherapy, whichever occurred first, were documented. Subsequently, from the first dose of ablative chemotherapy until polymorphonuclear (PMN) engraftment, data were collected only for serious adverse events (SAEs) and AEs that were Grade 3 or greater, except for febrile neutropenia and hemorrhage (data were collected only if Grade 4 or Grade 5) and neutropenia, thrombocytopenia, and anemia (data were collected only if the outcome was death). From the first day following engraftment through the follow-up period, all SAEs up to 6 months post-transplantation or until relapse, whichever occurred first, graft failures that occurred within 12 months post-transplantation, and myelodysplastic syndrome that occurred after 6 months post-transplantation were documented.

The adverse reactions reported in oncology patients who received MOZOBIL (plerixafor) in controlled Phase 3 studies and uncontrolled studies, including a Phase 2 study of MOZOBIL as monotherapy for HSC mobilization, were similar. No notable differences in the incidence of adverse reactions were observed for oncology patients by disease, age, or sex.

The most common (≥ 10%) adverse events (AEs) reported during HSC mobilization and apheresis in pooled Phase 3 results from patients who received MOZOBIL in conjunction with G-CSF regardless of causality and more frequent with MOZOBIL than placebo, were: diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting.

Rescue patients: In the Phase 3 studies, 59 patients who had received G-CSF + placebo as their original randomized treatment received a 4-day course of G-CSF followed by G-CSF + MOZOBIL rescue. The AE profile of these patients was consistent with that of the non-rescue patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and *should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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 majority of AEs were reported during mobilization and apheresis, 96% in patients receiving G-CSF + MOZOBIL compared to 94% in patients receiving G-CSF + placebo. The majority of AEs were mild or moderate. The incidence of AEs considered related to study treatment was 65% in the MOZOBIL group and 43% in the placebo group during the period of mobilization and apheresis, and overall.

The adverse events that occurred in ≥ 5% of the pooled Phase 3 patients who received MOZOBIL regardless of causality and were more frequent with MOZOBIL than placebo during HSC mobilization and apheresis are shown in Table 1.

Table 1: **Adverse Events in ≥ 5% of Non-Hodgkin's Lymphoma and Multiple Myeloma Patients Receiving MOZOBIL and More Frequent than Placebo During HSC Mobilization and Apheresis in Phase 3 Studies**

	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

[a]Grades based on criteria from the World Health Organization (WHO)

The incidence of anxiety during HSC mobilization and apheresis was 5.3% versus 4.5%, MOZOBIL versus placebo, respectively.

General disorders and administration site conditions:

Injection site reactions: 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. (see Table 1)

Paresthesia was considered an AE related to study treatment in 7.0% of patients in the MOZOBIL group and 5.1% of patients in the placebo group in the pooled Phase 3 data.

The majority of SAEs were severe and were considered unrelated to study treatment. The incidence of SAEs in the pooled Phase 3 data (MOZOBIL versus placebo, respectively) was 112/301 (37.2%) versus 84/292 (28.8%) overall, 13/301 (4.3%) versus 16/292 (5.5%) during mobilization and apheresis, 62/279 (22.2%) versus 44/216 (20.4%) from the start of ablative chemotherapy through engraftment, and 45/278 (16.2%) versus 34/216 (15.7%) post-engraftment.

In the pooled Phase 3 data, the incidence of bacteremia was 6.0% versus 4.4%, MOZOBIL versus placebo, respectively. The difference between the 2 groups was largely due to the greater incidence of staphylococcal bacteremia in the MOZOBIL group (7 patients, versus 0 patients in the placebo group). The incidence of lung infections was 5.0% versus 3.4%, MOZOBIL versus placebo, respectively. The incidence of febrile neutropenia was 10.1% versus 6.1%, MOZOBIL versus placebo, respectively. The majority of events of bacteremia, lung infection, and febrile neutropenia occurred following myeloablative chemotherapy and were considered by the investigator to be unrelated to MOZOBIL administration.

The incidence, cause, and timing of deaths, as well as the incidence of study or treatment discontinuations due to AEs were similar in both treatment groups. The majority of deaths occurred post-engraftment.

Less Common Clinical Trial Adverse Drug Reactions

Less common AEs occurring more frequently with MOZOBIL than placebo and considered related to study treatment in ≥ 1% and < 5% of patients during mobilization and apheresis in the randomized trials were as follows:

Allergic Reactions
In MOZOBIL oncology clinical studies, 0.7% of patients experienced mild or moderate allergic reactions within approximately 30 minutes after MOZOBIL administration, including one or more of the following: urticaria (n = 2), periorbital swelling (n =2), dyspnea (n =1) or hypoxia (n=1).

Gastrointestinal disorders: abdominal distention, abdominal pain, constipation, dyspepsia, hypoesthesia oral, stomach discomfort

General disorders and administration site conditions: malaise

Musculo-skeletal and connective tissue disorders: musculoskeletal pain

Skin and subcutaneous tissue disorders: erythema, hyperhidrosis

Vasovagal Reactions
In MOZOBIL oncology and healthy volunteer clinical studies, less than 1% of subjects experienced vasovagal reactions (orthostatic hypotension and/or syncope) following subcutaneous administration of plerixafor doses ≤ 0.24 mg/kg. The majority of these events occurred within 1 hour of MOZOBIL administration.

Abnormal Hematologic and Clinical Chemistry Findings

Hypokalemia and hypomagnesemia
Hypokalemia (2.3% versus 0.7%, MOZOBIL versus placebo, respectively) and hypomagnesemia (2.0% versus 0.3%, MOZOBIL versus placebo, respectively) were reported as treatment related AEs more frequently with MOZOBIL than with placebo during mobilization and apheresis in the pooled Phase 3 data. (See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests)

Hyperleukocytosis
In the phase 3 clinical studies, white blood cell counts of 100,000 cells/mcl or greater were observed, on the day prior to or any day of apheresis, in 7% of patients receiving MOZOBIL and in 1% of patients receiving placebo. No complications or clinical symptoms of leukostasis were observed.

Clinical Trial Adverse Reactions (Pediatrics)
Thirty patients (1 to less than 18 years) with lymphoma or solid tumours were treated with 0.24 mg/kg of MOZOBIL plus standard mobilization in the stage 2 of an open label, multicenter, randomized, controlled study (see CLINICAL TRIALS). In this study, 23 of 30 (76.7%) patients in the MOZOBIL arm and 10 of 15 (66.7%) patients in the control arm experienced adverse events.

The most common adverse events (≥10% of patients) in the MOZOBIL arm were anemia, decreased platelet count, rhinitis, febrile neutropenia, abdominal pain, hypoalbuminemia, diarrhea, vomiting, and pyrexia.

The most common adverse events (> 10% of patients) in the control arm were hypokalemia, increased alanine aminotransferase, febrile neutropenia, vomiting, decreased platelet count, fatigue, nausea, and anemia.

Serious adverse events were reported in 9 of 30 (30.0%) patients in the MOZOBIL arm and in 4 of 15 (26.7%) patients in the control arm. The most common treatment-emergent serious adverse events (>2%) in the MOZOBIL arm were febrile neutropenia, pancytopenia, pyrexia,and bone marrow failure.

The most common treatment-emergent serious adverse events (>2%) in the control arm were febrile neutropenia, abdominal infection, Enterobacter bacteremia, leukopenia, and pulmonary embolism.

No new safety concerns were identified in this study.

Post-marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported from worldwide post-marketing experience with MOZOBIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Splenomegaly and splenic rupture (see WARNINGS AND PRECAUTIONS, Hematologic).

Immune system disorders: Anaphylactic reactions, including anaphylactic shock (See WARNINGS AND PRECAUTIONS, Immune, Allergic Reactions).

Psychiatric disorders: abnormal dreams, nightmares.

DRUG INTERACTIONS

Drug-Drug Interactions

Based on *in vitro* studies, plerixafor is not a substrate, inhibitor, or inducer of human cytochrome P450 enzymes. Formal drug interaction studies have not been conducted. Plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an *in vitro* study. (See PHARMACOKINETICS)

The effects of coadministration of MOZOBIL with other drugs that are renally eliminated or are known to affect renal function have not been evaluated in formal drug interaction studies. Since MOZOBIL is primarily eliminated by the kidneys, co-administration of MOZOBIL with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of MOZOBIL or the co-administered drug.

In the absence of compatibility studies, MOZOBIL should not be mixed with other medicinal products in the same injection.

Drug-Food Interactions

MOZOBIL is administered parenterally, and interactions with food and drink are considered unlikely.

Drug-Herb Interactions

No drug-herb interaction studies have been conducted with MOZOBIL.

Drug-Laboratory Interactions

MOZOBIL has not been shown to interfere with any routine clinical laboratory tests.

Drug-Lifestyle Interactions

Some patients have experienced dizziness, fatigue or vasovagal reactions (orthostatic hypotension and/or syncope) with MOZOBIL treatment which may affect their ability to drive and use machines (see WARNINGS AND PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available. (See INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS)

Dosing Considerations

Recommended Concomitant Medications
Administer daily morning doses of G-CSF 10 μg/kg for 4 days prior to the first evening dose of MOZOBIL (plerixafor) and on each day prior to apheresis. (See CLINICAL TRIALS)

Dosing in Patients with Renal Impairment
Patients with serum creatinine values >2.2 mg/dL were excluded from the placebo-controlled clinical studies of MOZOBIL in combination with G-CSF. A total of 60 patients with an estimated creatinine clearance (CrCl) 51-80 mL/min, 11 patients with CrCl 31-50 mL/min, and none with CrCl ≤ 30 mL/min were enrolled and received at least one dose of MOZOBIL (0.24 mg/kg body weight subcutaneously (SC)).

Dose adjustments are recommended for patients with an estimated CL_{CR} 20-50 mL/min. (See Recommended Dose and Dosage Adjustment, Dosage Adjustment For Renal Impairment) There are insufficient clinical data to make dosing recommendations for patients with a creatinine clearance <20 mL/min or for patients on dialysis.

Recommended Dose and Dosage Adjustment

A. Adult Patients

Recommended Dose:
Begin treatment with MOZOBIL after the patient has received G-CSF once daily for four days.

The recommended dose of MOZOBIL by subcutaneous (SC) injection in the abdominal region is:

- 20 mg fixed dose or 0.24 mg/kg of body weight for patients weighing ≤ 83 kg (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics)
- 0.24 mg/kg of body weight for patients weighing > 83 kg.

MOZOBIL should be administered 10 - 11 hours prior to initiation of each apheresis. MOZOBIL has been used as a single course for up to 4 consecutive days in two randomized clinical trials.

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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics)

Dosage Adjustment For Renal Impairment:

In patients with CL_{CR} 20-50 mL/min, reduce the dose of MOZOBIL to 0.16 mg/kg. This will reduce the increased systemic exposure in these patients when compared to patients with CL_{CR} >50 mL/min receiving the 0.24 mg/kg dose. In patients with CL_{CR} ≤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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Table 2: 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)
20-50	0.16 mg/kg once daily (not to exceed 27 mg/day)

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

Males:

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

Females:

Creatinine clearance (mL/min) = 0.85 X value calculated for males

B. Pediatric Patients (1 to less than 18 years)

Recommended dose

Begin treatment with MOZOBIL after the patient has received G-CSF once daily for four days. The recommended dose of MOZOBIL is 0.24 mg/kg body weight by subcutaneous (SC) injection in the abdominal region. MOZOBIL should be administered 8-12 hours prior to initiation of each apheresis (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). MOZOBIL has been used as a single course for up to 3 consecutive days in a pediatric clinical trial.

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.

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 X patient’s actual body weight (in kg) = volume to be administered (in mL)

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Based on limited data at doses above the recommended dose of 0.24 mg/kg SC and up to 0.48 mg/kg SC, the frequency of gastrointestinal disorders, vasovagal reactions, orthostatic hypotension, and/or syncope may be higher.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Plerixafor is a selective antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α), also known as CXCL12. SDF-1α and CXCR4 are recognized to play key regulatory roles in the trafficking and homing of human HSCs to the marrow compartment. Stem cells express CXCR4 and are known to migrate to the bone marrow through a chemoattractant effect of SDF-1α that is produced locally by bone marrow stromal cells. Once in the marrow, it is postulated that stem cell CXCR4 can act to help “anchor” these cells to the marrow matrix, either directly via SDF-1α or through the induction of other adhesion molecules. Plerixafor-induced leukocytosis and elevations in circulating hematopoietic progenitor cell levels are thought to result from a disruption of CXCR4 binding to its cognate ligand, resulting in the appearance of both mature and pluripotent cells in the systemic circulation.

CD34+ cells mobilized by MOZOBIL (plerixafor) are functional and capable of engraftment with long-term repopulating capacity.

Pharmacodynamics

Fold increase in peripheral blood CD34+ cell count (cells/µL) by apheresis day was evaluated in two placebo-controlled clinical studies in patients with lymphoma and MM (Studies 1 and 2, respectively). Fold increase over the 24-hour period from the day prior to the first apheresis to just before the first apheresis is summarized in Table 3. During that 24-hour period, the first dose of MOZOBIL 0.24 mg/kg or placebo was administered 10-11 hours prior to apheresis.

Table 3: Fold Increase in Peripheral Blood CD34+ Cell Count Following MOZOBIL Administration

Study	MOZOBIL and G-CSF		Placebo and G-CSF	
	Median	Mean (SD)	Median	Mean (SD)
1	5.0	6.1 (5.4)	1.4	1.9 (1.5)
2	4.8	6.4 (6.8)	1.7	2.4 (7.3)

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

Pharmacokinetics

The pharmacokinetics of plerixafor have been evaluated in lymphoma and MM patients at the clinical dose level of 0.24 mg/kg following pre-treatment with G-CSF (10 mcg/kg once daily for 4 consecutive days).

Table 4: Comparison of Mean Pharmacokinetic Parameters in Healthy Subjects and Oncology Patients Treated With 0.24 mg/kg Plerixafor With or Without G-CSF[a]

Diagnosis	G-CSF Administered?	N	Cmax (ng/mL)	Tmax (hr)	AUC_{0-10} (ng*hr/mL)	$t_{1/2}$ (hr)
HD	Yes	9	831 ± 183	0.5 (0.3, 1.3)	3572 ± 772	3.5 ± 0.7
MM	Yes	8	1029 ± 242	0.5 (0.3, 1.0)	3945 ± 610	5.6 ± 2.6
NHL	Yes	5	761 ± 101	0.5 (0.5, 1.0)	3035 ± 412	4.4 ± 1.1
Healthy	No	42	729 ± 101	0.65 (0.35, 1.60)	3108 ± 335	4.6 ± 0.8

[a] Values are reported as mean ± standard deviation, except T_{max} is reported as median (min, max).

A 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 clinical experience with treating patients above 160 mg and therefore the dose should not exceed 40 mg/day for patients with a CL_{CR} > 50 mL/min and 27 mg/day for patients with a CL_{CR} 20-50 mL/min.

In order to compare the pharmacokinetics and pharmacodynamics of plerixafor following 0.24 mg/kg-based and fixed (20 mg) doses, a follow-up trial was conducted in patients with NHL (N=61) who were treated with 0.24 mg/kg or 20 mg of plerixafor. The trial was conducted in patients weighing 70 kg or less (median: 63.7 kg, range of 34.2 to 70 kg). The study population was primarily Asian (91.8%). The fixed 20 mg dose showed 1.43-fold higher exposure (AUC_{0-10h}) than the 0.24 mg/kg dose (Table 5). The fixed 20 mg dose also showed numerically higher response rate (5.2% [60.0% vs 54.8%] based on the local lab data and 11.7% [63.3% vs 51.6%] based on the central lab data) in attaining the target of ≥ 5 × 10^6 CD34+ cells/kg than the mg/kg-based dose. The median time to reach ≥ 5 × 10^6 CD34+ cells/kg was 3 days for both treatment groups, and the safety profile between the groups was similar. Body weight of 83 kg was selected as a cut-off point to transition patients from fixed to weight based dosing (83 kg x 0.24 mg = 19.92 mg/kg).

Table 5 - Systemic exposure (AUC_{0-10h}) comparison of fixed and weight based regimens

Regimen	Geometric Mean AUC
Fixed 20 mg (n=30)	3991.2
0.24 mg/kg (n=31)	2792.7
Ratio (90% CI)	1.43 (1.32-1.54)

Absorption: Plerixafor is rapidly absorbed following SC injection with peak concentrations reached in approximately 30-60 minutes.

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

Metabolism: Plerixafor is not metabolized *in vitro* using human liver microsomes or human primary hepatocytes and does not exhibit inhibitory activity *in vitro* towards the major drug metabolizing CYP450 enzymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5). In *in vitro* studies with human hepatocytes, plerixafor does not induce CYP1A2, CYP2B6, and CYP3A4 enzymes. These findings suggest that plerixafor has a low potential for involvement in P450-dependent drug-drug interactions.

Excretion: 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. The amount of MOZOBIL excreted in the feces is not known. The half-life in plasma is 3-5 hours. Plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an *in vitro* study with MDCKII and MDCKII-MDR1 cell models.

Electrocardiography and Haemodynamics: In a randomized, double-blind, placebo-controlled crossover study, 46 healthy subjects were administered single subcutaneous doses of MOZOBIL at a therapeutic dose of 0.24 mg/kg or a supratherapeutic dose of 0.40 mg/kg. Peak concentrations for 0.40 mg/kg MOZOBIL were approximately 1.8-fold higher than the peak concentrations following the 0.24 mg/kg single subcutaneous dose.

There was no treatment-related effect on the QTc interval or QRS duration, indicating no impact in ventricular repolarization, depolarization and conduction, at the MOZOBIL doses tested.

The PR interval was shortened during the period from 15 min to 12 h post-dosing at both doses of MOZOBIL, with maximum decreases of mean -9.8 (90% CI -12.3, -7.2) at the 0.24 mg/kg dose and -9.5 (90% CI -12.0, -6.9) ms at the 0.40 mg/kg dose, both at 2.5 h post-dosing (see WARNINGS AND PRECAUTIONS, Disorders of Atrioventricular Conduction). The PR interval changes were not dose-dependent over the 0.24-0.40 mg/kg dose range studied.

Sitting diastolic blood pressure was decreased from 1 h to 10 h post-dosing with MOZOBIL 0.24 mg/kg, with a maximum decrease of mean -5.8 (90% CI -8.6, -3.0) mmHg at 8 h post-dosing. Systolic blood pressure was decreased by mean -3.2 (90% CI -6.4, -0.1) mmHg at this time point.

At the 0.40 mg/kg dose, the maximum decrease in sitting diastolic blood pressure was mean -6.1 (90% CI -9.9, -2.2) mmHg at 1 h post-dosing, whilst the maximum decrease in systolic blood pressure was mean -3.5 (90% CI -6.4, -0.5) mmHg at 2 h post-dosing.

The incidence of syncope was 4.8% for the 0.24 mg/kg dose and 6.7% for the 0.40 mg/kg dose. There were no events of syncope in the placebo arm of this crossover study (see WARNINGS AND PRECAUTIONS, Vasovagal Reactions).

Special Populations and Conditions

Pediatrics: The pharmacokinetics of MOZOBIL were evaluated at doses of 0.16, 0.24 and 0.32 mg/kg in 27 pediatric patients (2 to less than 18 years) with solid tumors participating in the stage 1 of an open-label, multicenter, randomized study (see CLINICAL TRIALS). Plerixafor exposures (C_{max} and $AUC_{0\text{-}9h}$) generally increased with age and with dose over the range of 0.16 to 0.32 mg/kg. At the same weight-based dosing regimen of 240 µg/kg, plerixafor mean $AUC_{0\text{-}9h}$ in pediatric patients aged 2 to < 6 years (1740 ng.h/mL), 6 to <12 years (2270 ng.h/mL), and 12 to <18 years (2600 ng.h/mL) were consistently lower than those in healthy adults ($AUC_{0\text{-}10}$: 3108 ng.h/mL) and adult patients ($AUC_{0\text{-}10}$ range: 3035 to 3945 ng.h/mL). However, even with the lower exposure than adults, exposure was sufficient to enhance mobilization of PB CD34+ count in stage 2 of the trial (see CLINICAL TRIALS).

Geriatrics: No specific studies have been conducted to investigate pharmacokinetics in geriatric patients. However a population pharmacokinetic analysis showed no effect of age on plerixafor pharmacokinetics.

Gender: A population pharmacokinetic analysis showed no effect of gender on plerixafor pharmacokinetics.

Race: Clinical data show similar plerixafor pharmacokinetics for Whites and Blacks, and the effect of other racial/ethnic groups has not been studied.

Hepatic Insufficiency: No specific pharmacokinetics studies have been conducted in hepatically impaired patients.

Renal Insufficiency: Following a single 0.24 mg/kg dose of MOZOBIL, plerixafor clearance was reduced in subjects with varying degrees of renal dysfunction and was positively correlated with CL_{CR}. Mean values of AUC_{0-24} of plerixafor in subjects with CL_{CR} 51-80 mL/min, CL_{CR} 31-50 mL/min and $CL_{CR} \leq 30$ mL/min were higher than the exposure observed in healthy subjects with normal renal function (CL_{CR} >80 mL/min) (Table 6). Renal impairment had no effect on C_{max}. (See DOSAGE AND ADMINISTRATION)

Table 6 : Human Pharmacokinetic Data for Subjects Enrolled in a Phase I Renal Impairment Study

		Creatinine Clearance (mL/min)*			
		>80 (n=6)	**51-80 (n=5)**	**31-50 (n=6)**	**≤30 (n=6)**
T_{max} (h)	Median	0.56	0.50	0.50	0.75
	Min, Max	0.50, 1.02	0.50, 1.00	0.25, 1.00	0.50, 1.00
C_{max} (ng/mL)	Mean ± SD	980 ± 196	739 ± 76.1	936 ± 280	861 ± 193
	Min, Max	812, 1260	640, 845	559, 1270	609, 1140
AUC_{0-24h} (ng×h/mL)	Mean ± SD	5070 ± 979	5410 ± 1070	6780 ± 1660	6990 ± 1010
	Min, Max	3900, 6240	3970, 6540	4680, 8410	5700, 8050
Cl/F (mL/h)	Mean ± SD	4380 ± 821	3500 ± 1690	2420 ± 1110	1820 ± 380
	Min, Max	3700, 5730	2430, 6410	1750, 4670	1520, 2550

* Values were based on 24 h urine collection.

A population PK analysis simulated the effect of CL_{CR} (as determined by the Cockcroft-Gault formula) on plasma clearance of MOZOBIL. These results support a dose reduction to 0.16 mg/kg in patients with a CL_{CR} of 20-50 mL/min to reduce the increased exposure in these patients when compared to patients with CL_{CR} >50 mL/min receiving a 0.24 mg/kg dose of MOZOBIL.

Tissue accumulation of MOZOBIL in patients with renal impairment has not been studied.

Genetic Polymorphism: Based on *in vitro* data, plerixafor is not a substrate, inhibitor or inducer of human cytochrome P450 isozymes, nor is it an *in vitro* substrate or inhibitor of P-glycoprotein. Therefore, no specific drug metabolism or transporter genetic polymorphism studies have been conducted with MOZOBIL.

STORAGE AND STABILITY

- Store at 25°C; excursions permitted to 15°-30°C
- DO NOT USE MOZOBIL (plerixafor) after the expiration date indicated on the label.
- Each vial of MOZOBIL is intended for single use only. Any unused drug remaining after injection must be discarded.

SPECIAL HANDLING INSTRUCTIONS

MOZOBIL (plerixafor) is supplied as a ready-to-use formulation. The contents of the vial must be transferred to a suitable syringe for SC 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MOZOBIL (plerixafor) is supplied as a sterile, preservative-free, clear, colorless to pale yellow, pH neutral, isotonic solution in a single-use 2.0 mL clear glass (Type I) vial, sealed with a rubber stopper and aluminum seal with a plastic flip-off cap.

Active ingredient: Each 2.0 mL vial is filled to deliver 1.2 mL of 20 mg/mL solution, containing 24.0 mg of plerixafor.

Non-medicinal ingredients: Each 1.2 mL contains 5.9 mg sodium chloride in sterile Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

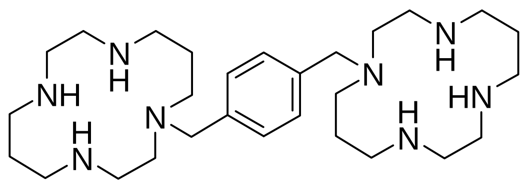
Drug Substance

Common name: plerixafor

Chemical name: l, 1'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11-tetraazacyclotetradecane

Molecular formula and molecular mass: $C_{28}H_{54}N_8$; 502.79 g/mol

Structural formula:



Physicochemical properties:

Table 7: Physicochemical Properties

Physical Property	**Result**
Description	White to off-white crystalline solid
Melting point by differential scanning calorimetry	Typical = 131.5°C Observed Range = 130–135°C
Solubility	Freely soluble in alcohols, glycol, and aqueous solutions of less than pH 10; sparing soluble in pH 11 aqueous solutions and in 0.l M HCl; slightly soluble in water, saline; and very slightly soluble in acetonitrile, acetone, ethyl and isopropyl acetate, and *tert*-butyl methyl ether.
pH	11.20 (2.6 mg/mL solution at ambient conditions)
Partition coefficient between 1-octanol and pH 7 aqueous buffer	< 0.1

CLINICAL TRIALS

ADULT PATIENTS

Study demographics and trial design

Table 8: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (M/F)
Study 1	Randomized, double-blind, placebo controlled, parallel group, multicentre	0.24 mg/kg or placebo subcutaneous single daily dose for up to 4 days	298	MOZOBIL: 55.1 years (29-75) Placebo: 57.5 years (22-75)	202/96
Study 2	Randomized, double-blind, placebo controlled, parallel group, multicentre	0.24 mg/kg or placebo subcutaneous single daily dose for up to 4 days	302	MOZOBIL: 58.2 years (28-75) Placebo: 58.5 years (28-75)	207/95

Trial Design

The efficacy and safety of MOZOBIL (plerixafor) in conjunction with G-CSF in non-Hodgkin's lymphoma (NHL) patients and multiple myeloma (MM) patients who were eligible for autologous hematopoietic stem cell transplant were evaluated in two placebo-controlled studies (Studies 1 and 2).

On the evening of Day 4 of daily morning doses of G-CSF 10 µg/kg, the first dose of assigned study treatment, either MOZOBIL 0.24 mg/kg or placebo was administered. On Day 5, patients received a morning dose of G-CSF 10 µg/kg and underwent apheresis approximately 10 to 11 hours after the first dose of study treatment (within 60 minutes after administration of G-CSF). Patients continued to receive an evening dose of study treatment followed the next day by a morning dose of G-CSF and apheresis for up to a maximum of 4 aphereses or until the target collection of CD34+ HSCs was achieved.

In both studies, patients who failed to collect $\geq 0.8 \times 10^6$ CD34+ cells/kg after 2 days of apheresis or at least 2×10^6 CD34+ cells/kg in 4 or fewer days of apheresis had the option of entering an open-label rescue procedure. After a minimum 7-day rest period, they received another 4-day course of G-CSF followed by a course of MOZOBIL (0.24 mg/kg) in combination with G-CSF for repeat mobilization.

Following the last apheresis, patients underwent a rest period, then pre-transplant ablative chemotherapy followed by autologous transplantation within 5 weeks after the last apheresis. Transplantation was performed according to standard of care at each study center.

Patients received G-CSF (5 µg/kg once daily) beginning on the fifth or sixth day after transplantation and continuing until the absolute neutrophil count (ANC) was $\geq 0.5 \times 10^9$/L for 3 days or $\geq 1.0 \times 10^9$/L for 1 day. Platelet (PLT) engraftment was defined as a PLT count $\geq 20 \times 10^9$/L without transfusion for the preceding 7 days.

Graft durability was assessed at 100 days, 6 months, and 12 months post-transplantation.

The primary objective of Study 1 was to determine if NHL patients mobilized with G-CSF plus MOZOBIL 0.24 mg/kg were more likely to achieve a target number of $\geq 5 \times 10^6$ CD34+ cells/kg in 4 or fewer days of apheresis than NHL patients mobilized with G-CSF plus placebo. The primary objective of Study 2 was to determine if MM patients mobilized with G-CSF plus MOZOBIL 0.24 mg/kg were more likely to achieve a target number of $\geq 6 \times 10^6$ CD34+ cells/kg in 2 or fewer days of apheresis than MM patients mobilized with G-CSF plus placebo.

Secondary efficacy objectives common to both studies were to compare the two treatment arms with respect to the number of patients who achieved a minimum of 2×10^6 CD34+ cells/kg (minimum number required for transplantation) in 4 or fewer days of apheresis, the number of days of apheresis required to reach target cell numbers, the time to engraftment of PMNs and PLTs, and the durability of the graft at prespecified times post-transplantation. A secondary objective unique to Study 2 was to compare the two treatment arms with respect to the number of MM patients who achieved the target number of cells in 4 or fewer apheresis days.

Subsequent to the completion of both studies, enrolled patients were asked to participate in observational long-term follow-up with the primary objective of assessing any differences in clinical outcome (progression-free survival [PFS] and overall survival [OS]) in patients treated with at least 1 dose of study treatment (MOZOBIL or placebo). These patients are to be followed for up to 5 years post-transplantation and the data is not yet mature.

Study demographics

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, 52 NHL patients in the placebo + G-CSF group entered into the open-label rescue procedure. In Study 2, 7 MM patients from the placebo + G-CSF group entered the rescue procedure.

Study results

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 ($p < 0.001$). The achievement of the minimum CD34+ cell collection required for transplantation in 4 or fewer days of apheresis is included in Table 9.

Table 9 : Study 1 Efficacy Results - CD34+ Cell Mobilization in NHL Patients (Primary ITT Population)

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

[a]p-value calculated using Pearson's Chi-Squared test

The number of apheresis days required to achieve $\geq 5 \times 10^6$ CD34+ cells/kg are summarized in Table 10. 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 10: Study 1 Efficacy Results – Number of Apheresis Days Required to Achieve $\geq 5 \times 10^6$ CD34+ cells/kg in NHL Patients (Primary ITT Population)

Apheresis Day	Patients Reaching Target by Apheresis Day, n (%)[a]	
	MOZOBIL and G-CSF (n=147)	Placebo and G-CSF (n=142)
1	41 (27.9%)	6 (4.2%)
2	71 (49.1%)	20 (14.2%)
3	81 (57.7%)	27 (21.6%)
4	89 (65.6%)	29 (24.2%)

[a] Patient counts are cumulative across day numbers. Percentages were determined by Kaplan-Meier method.

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 ($p < 0.001$). Patients achieving the target and minimum CD34+ cell collections within four or fewer apheresis sessions are presented in Table 11.

Table 11 : 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 ≥ 6 X 10^6 cells/kg in ≤ 2 apheresis days	106 (72%)	53 (34%)	< 0.001
Patients achieving ≥ 6 X 10^6 cells/kg in ≤ 4 apheresis days	112 (76%)	79 (51%)	< 0.001
Patients achieving ≥ 2 X 10^6 cells/kg in ≤ 4 apheresis days	141 (95%)	136 (88%)	0.028

[a]p-value calculated using Pearson's Chi-Squared test

The number of apheresis days required to achieve target cell collection are summarized in Table 12. The median number of days to reach ≥ 6 x 10^6 CD34+ cells/kg was 1 day for the MOZOBIL group and 4 days for the placebo group.

Table 12 : Study 2 Efficacy Results – Number of Apheresis Days Required to Achieve ≥ 6 × 10^6 CD34+ cells/kg in MM Patients (Primary ITT Population)

Apheresis Day	Patients Reaching Target by Apheresis Day, n (%)[a]	
	MOZOBIL and G-CSF (n=144)	Placebo and G-CSF (n=150)
1	78 (54.2%)	26 (17.3%)
2	106 (77.9%)	53 (35.3%)
3	112 (86.8%)	71 (48.9%)
4	112 (86.8%)	79 (55.9%)

[a] Patient counts are cumulative across day numbers. Percentages are determined by Kaplan-Meier method.

Rescue patients

In Study 1, 52 NHL patients in the placebo + G-CSF group entered into the rescue procedure with MOZOBIL and G-CSF. Of these patients, 60% (31 out of 52) mobilized ≥ 2 x10^6/kg CD34+ cells and had successful engraftment. In Study 2, 7 MM patients in the placebo + G-CSF group entered the rescue procedure, all of whom mobilized ≥ 2 x10^6/kg CD34+ cells and had successful engraftment.

For transplanted patients in the Phase 3 studies, time to neutrophil engraftment (10-11 days) and platelet engraftment (18-20 days) were similar across the treatment groups.

Based on an adjusted analysis which used laboratory measurements and clinical criteria to assess graft durability, results were similar in both treatment groups, specifically, 128/135 (94.8%) versus 78/82 (95.1%) at 100 days, 120/123 (97.6%) versus 77/78 (98.7%) at 6 months, and 110/112 (98.2%) versus 65/65 (100%) at 12 months in Study 1 and 140/142 (98.6%) versus 133/136 (97.8%) at 100 days, 133/135 (98.5%) versus 125/127 (98.4%) at 6 months, and 127/128 (99.2%) versus 119/120 (99.2%) at 12 months in Study 2, MOZOBIL versus placebo, respectively.

For transplanted patients, the frequency of graft failure was low in Phase 3 studies, 3 events in MOZOBIL-treated NHL patients in Study 1 and none in MM patients in Study 2. None of these graft failures were considered by the investigator as related to MOZOBIL.

Final 5-year PFS and OS data are not yet available. However, OS at 12 months post-transplantation for the primary ITT population was 132/150 (88.0%) in the MOZOBIL group and 129/148 (87.2%) in the placebo in Study 1, and 141/148 (95.3%) in the MOZOBIL group and 148/154 (96.1%) in the placebo group in Study 2.

PEDIATRIC PATIENTS

The table below summarizes the demographic and baseline characteristics data in stage 2 of the pediatric study DFI12860, including the baseline imbalance in peripheral blood CD34+ counts between patient groups that was observed.

Table 13: Summary of the demographic and baseline data for DFI12860 (Stage 2)

DFI 12860		**Standard Mobilization Alone (N=15)**	**Plerixafor + Standard Mobilization (N=30)**
Gender	Male	7 (46.7%)	19 (63.3%)
	Female	8 (53.3%)	11 (36.7%)
Age (years)	Mean (SD)	5.4 (4.3)	7.0 (4.7)
	Median	4.7	5.3
	Min : Max	2 : 17	1 : 18
Age category	1 to <2 years	3 (20.0%)	1 (3.3%)
	2 to <6 years	7 (46.7%)	15 (50.0%)
	6 to <12 years	3 (20.0%)	9 (30.0%)
	12 to <18 years	2 (13.3%)	5 (16.7%)
Tumor type	Lymphoma	1 (6.7%)	2 (6.7%)
	Neuroblastoma	7 (46.7%)	14 (46.7%)
	Sarcoma	4 (26.7%)	8 (26.7%)
	Other	3 (20.0%)	6 (20.0%)
Baseline PB CD34+ count on the day prior to first apheresis*		**N=14**	**N=28**
	Mean (SD)	84.0 (94.5)	31.4 (56.1)
	Median	35.0	15.0
	Min : Max	5.0 : 300.0	1.0 : 306.0

The efficacy and safety of MOZOBIL were evaluated in an open label, multi-center, controlled study in pediatric patients with solid tumors (including neuroblastoma, sarcoma, Ewing sarcoma), or lymphoma who were eligible for autologous hematopoietic stem cell transplantation. Patients with leukemia, persistent high percentage marrow involvement prior to mobilization, or previous stem cell transplantation were excluded. This study consisted of an initial dose escalation study (Stage 1, N=27, age 2 to <18 years) followed by a randomized, comparative study extension (Stage 2, N=45, age 1 to <18 years) at the dose identified as most appropriate in the dose escalation part of the study.

Study patients (N=45) were started on standard mobilization (G-CSF ± chemotherapy as per site standard practice). Upon reaching the trigger point minimum of 7 CD34+ cells/µL in peripheral blood (PB), patients were randomized 2:1 to either receive 0.24 mg/kg of MOZOBIL plus standard mobilization (G-CSF plus or minus chemotherapy) or standard mobilization alone. Apheresis was to occur if, on the scheduled day of apheresis, the PB CD34+ count was ≥20 cells/µL.

The primary efficacy analysis showed that 80% of patients in the MOZOBIL arm experienced at least a doubling of the PB CD34+ count, observed from the morning of the day preceding the first planned apheresis to the morning prior to apheresis versus 28.6 % of patients in the control arm (p=0.0019).

The table below summarizes the secondary endpoints that relate to mobilization and cell collection:

Table 14: Secondary Endpoints Related to Mobilization and Cell Collection

DFI 12860	Standard Mobilization Alone (N=15)	Plerixafor + Standard Mobilization (N=30)
Proportion of patients reaching ≥2 x 10^6 CD34+ cells/kg	92.9%	89.7%
Median Number of apheresis	1	1
Cumulative CD34+ Collection (10^6 cells/kg),		
Mean (SD)	17.61 (20.76)	19.44 (36.69)
Median	10.15	9.13
Min: Max	0.7 : 66.0	0.1 : 200.4
% Increase in PB CD 34+ Counts from day prior to first apheresis to day of first apheresis (Exploratory)		
Mean (SD)	133.35 (264.00)	496.16 (587.89)
Median	39.03	220.83
Min : Max	-19.10 : 1010.00	-100.00 : 2042.86
Median Fold increase	1.39	3.2

DETAILED PHARMACOLOGY

<u>Nonclinical Pharmacology</u>

The activity of plerixafor at the human CXCR4 receptor was demonstrated *in vitro* using the CCRF-CEM cell line which endogenously expresses CXCR4. Plerixafor was shown to inhibit SDF-1α ligand binding to CXCR4, and to inhibit SDF-1-mediated calcium flux, G-protein activation, and chemotaxis with IC_{50} values of 651 ± 37 nM, 572 ± 190 nM, 15.4 ± 4.4 nM, and 51 ± 17 nM respectively. The selectivity of plerixafor's inhibitory activity was demonstrated in similar studies with cells expressing different chemokine receptors. In these studies plerixafor did not inhibit calcium flux against the following receptors: CXCR1, CXCR2, CXCR3, CCR1, CCR2b, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, or CCR9. In addition plerixafor did not inhibit the binding of leukotriene B4 (chemoattractant for granulocytes) to its receptor, BLTR., nor did it inhibit binding of SDF-1 to CXCR7, an alternative receptor for SDF-1. The molecular interactions of plerixafor with the CXCR4 chemokine receptor were investigated using receptor site directed mutagenesis studies. Receptor mutagenesis identified Asp171 and Asp262 as being essential for the ability of plerixafor to block the receptor. These studies showed that plerixafor acts on the CXCR4 receptor through binding to the negatively charged amino acids Asp171 and Asp262 with each of its cyclam moieties.

The ability of plerixafor to mobilize HSC and HPC capable of long term engraftment was demonstrated in three species.

The administration of single SC injection of plerixafor (5 mg/kg) to C3H/HeJ mice induced a rapid and dose-dependent mobilization of HPC to blood with peak mobilization occurring at 1 hour post dosing. Repeat daily dosing (3 days) with plerixafor gave consistent HPC mobilization after each dose, indicating that there was no desensitization with repeated administration. Plerixafor was shown to be a potent HPC mobilizer in other strains of mice where G-CSF is a poor HPC mobilizer, such as DBA/2 and $Fanc^{-/-}$. Plerixafor was also shown to augment G-CSF-induced mobilization in DBA/2, C57Bl6 and C3H/HEJ mice. Long-term engraftment in bone marrow was demonstrated using a competitive repopulating assay with $CD45^{+}$ congenic mice. Donor blood cells collected from plerixafor-treated C57B1/6 ($CD45.2^{+}$) mice competed with recipient bone marrow cells for engraftment in lethally irradiated transplant recipient B6.BoyJ ($CD45.1^{+}$) mice. A greater than 8-fold higher chimerism (ratio of donor cells:recipient cells) was observed with plerixafor-mobilized donor cells compared with a saline control. Self-renewal of plerixafor-mobilized HSC was demonstrated using a secondary repopulating assay in which donor cells obtained from the competitively engrafted mice above were re-injected into lethally-irradiated secondary mice. All secondary mice survived with > 50 % engrafted cells of donor origin. The repopulating potential of plerixafor–mobilized human HSC was also evaluated in a NOD/SCID mouse repopulation assay. $CD34^{+}$ blood cells collected during apheresis from healthy human volunteers administered plerixafor, G-CSF, or plerixafor plus G-CSF were able to repopulate the bone marrow of lethally irradiated NOD/SCID mice, as demonstrated by the presence of chimerism (human $CD45^{+}$ cells) in the bone marrow after eight weeks.

The ability of plerixafor to mobilize $CD34^{+}$ stem cells which, following transplantation, result in timely and durable engraftment and reconstitution of the bone marrow has been demonstrated in dogs and monkeys. In these studies, $CD34^{+}$ cells were collected from plerixafor-treated animals by apheresis. Prior to transplantation, the recipient animals received myeloablative total body irradiation followed by infusion of autologous plerixafor-mobilized peripheral blood mononuclear cells. Engraftment was monitored by peripheral blood counts. In dogs, neutrophil and platelet engraftment occurred at medians of 8 and 25 days. In rhesus macaque monkeys, rapid engraftment measured by gene marking was observed within 7- 14 days, with persistent long-term retrovirally marked myeloid and lymphoid cells present up to 32 months after transplantation.

Safety Pharmacology

The effect on the cardiovascular system of SC administration was evaluated in anesthetized rats at a single dose (20 mg/kg). Similarly to plerixafor after IV administration in the rats, there were decreases in mean arterial blood pressure, heart rate, +dP/dt, dP/dt and cardiac output. In addition, a visual inspection of the ECG tracing showed that the P wave became flat, negative or undetectable. Continuous IV infusion of plerixafor for 8 hours to conscious dogs delivering plasma steady state levels between 6.4 and 7.4 µg/ml (significantly higher than the approximate peak plasma level observed in humans at the recommended dose for HSC mobilization, i.e. approximately 1.0 µg/ml) showed no treatment-related changes in ECG tracings, heart rate, cardiac function, or blood pressure. Continuous IV infusion at a 2-fold higher rate with plasma levels between 10.9 and 14.3 µg/ml (measured between 3 and 8 hours of infusion) produced an increase in heart rate with associated decrease in PR interval, increased systemic blood pressure and clinical signs of frank toxicity. There were no effects on QRS interval duration or QTc interval.

An *in vitro* general receptor activity screen showed that plerixafor at a concentration of 5 µg/ml has moderate or strong binding affinity for a number of different receptors predominantly located on pre-synaptic nerve endings in the CNS and/or the PNS (N-type calcium channel, potassium channel SKCA, histamine H3, acetylcholine muscarinic M1 and M2, adrenergic α1B and α2C, neuropeptide Y/Y1 and glutamate NMDA polyamine receptors). The clinical relevance of these findings is not known.

Nonclinical Pharmacokinetics

Distribution studies conducted with radiolabeled MOZOBIL in rat following SC administration demonstrated that plerixafor distributed readily into the majority of tissues evaluated, with the exception of brain, muscle, pancreas, renal fat, salivary gland, spinal chord, and testes tissues. Tissues with the highest radioactivity concentrations were the renal medulla, thymus, epididymis, kidney, renal cortex, and liver. Overall low concentrations (ratio of tissue to plasma of <1) of radioactivity were detected in the brain, muscle, pancreas, renal fat, salivary gland, spinal cord, and testes at up to 4 hours post dose. Elimination of MOZOBIL from most tissues occurred between 4 and 24 hours, however retention of drug-derived material in bone marrow, cartilage, spleen, liver, and kidney tissues was noted at up to 144 hours post SC administration. After 168 hours following SC administration to rat and dog up to 30% of drug-derived material remained in the body. The primary route of elimination of MOZOBIL in rat and dog is via renal excretion. Following SC and IV administration in rat and dog the majority of the radioactivity

(63–72 % of the dose) was excreted in the urine within 48 hours. Elimination in the feces accounted for < 12 % of total radioactivity in rat and dog.

Human Pharmacology

Pharmacodynamics

Plerixafor reversibly and selectively blocks the binding of the CXCR4 chemokine receptor to its cognate ligand SDF-1α. The interruption of the CXCR4/SDF-1α interaction results in the mobilization of bone marrow HSCs to the peripheral blood. A close correlation exists between the number of CD34+ cells, a well-established surrogate marker for HSCs, and the number of colony forming units (which indicate functional HSCs) in peripheral blood HSC collections. Based upon this information, pharmacodynamic activity of plerixafor was assessed by measuring the number of PB CD34+ cells using fluorescence activated cell sorting (FACS) analysis. The pharmacodynamics of plerixafor were also assessed by colony forming units, as a confirmation that CD34+ cell count by FACS analysis was an adequate proxy measure of functional HSCs.

In all studies in both healthy subjects and patients with NHL and MM, the pharmacodynamic effect of plerixafor produces a consistent and marked increase in PB CD34+ cell counts from baseline.

In healthy subjects, the administration of a single dose of plerixafor (0.040 to 0.24 mg/kg) with no G-CSF led to dose-proportional increases from baseline of PB CD34+ cell counts. The pharmacodynamic response to plerixafor 0.24 mg/kg (no G-CSF) in healthy subjects occurs 6 to 10 hours after dosing. The median peak fold-increase was 15.8 over baseline. The pharmacodynamic response to 0.24 mg/kg plerixafor alone was higher than after 0.16 mg/kg plerixafor, yet similar to after 0.32 mg/kg.

The administration of plerixafor to healthy subjects (0.24 mg/kg) in conjunction with G-CSF produced a sustained elevation in the PB CD34+ cell count from 4 to 18 hours after plerixafor administration, with peak response between 10 to 14 hours. Following 4 days of G-CSF, administration of plerixafor (0.16 mg/kg) and G-CSF produced higher peak PB CD34+ cell counts (a 3.8-fold increase over the G-CSF alone baseline) than treatment with either plerixafor (0.16 mg/kg) alone (a 3.2-fold increase over baseline) or G-CSF alone (a 1.2-fold increase over baseline) on the 5^{th} day.

The pharmacodynamics of plerixafor were also evaluated in oncology patients, either after a single SC administration or in combination with G-CSF. A single injection of plerixafor alone elicited an increase in PB CD34+ cell counts that was generally less than observed in healthy volunteers.

In combination with G-CSF, patients with MM, in general, had higher responses than patients with NHL in mobilizing CD34+ cells. In the NHL group, patients with higher baseline concentrations of PB CD34+ cell counts (cells/µL) had better responses than those with lower baseline PB CD34+ cell counts. Plerixafor increased the PB CD34+ count by 3- to 6-fold over the pre-plerixafor dose level after the first injection, which was similar to the 3- to 4-fold increase observed in healthy subjects.

Cumulatively, pharmacodynamic studies showed that in healthy subjects, the plerixafor dose of 0.24 mg/kg elicited a higher and later peak response compared with the 0.16- mg/kg dose. The increase in PB CD34+ cells with plerixafor following 4 days of pre-treatment with G-CSF was higher than with plerixafor or G-CSF alone. When added to a dosing regimen of G-CSF in healthy subjects, 0.16 mg/kg and 0.24 mg/kg plerixafor had similar magnitudes of fold-increases in PB CD34+ cells. In patients with MM and NHL, the 0.24 mg/kg dose with G-CSF elicited a greater response (greater fold-increase in apheresis yields) than the 0.16 mg/kg dose with G-CSF. Based upon the above data and given the difference in response rates of patients with MM and NHL, the recommended dose of MOZOBIL (plerixafor injection) is 0.24 mg/kg body weight by subcutaneous (SC) injection.

Pharmacokinetics
The pharmacokinetics of MOZOBIL are described under ACTION AND CLINICAL PHARMACOLOGY.

TOXICOLOGY

Single Dose Toxicology
Single IV or SC injection of plerixafor in rats and mice induced a rapid onset (< 2 hour) of transient, but severe, neuromuscular, sedative-like effects (hypoactivity), dyspnea, ventral or lateral recumbency and/or spasms. Complete recovery from most signs occurred within 4 hours following plerixafor administration. In mice, deaths were observed following doses of ≥ 14 mg/kg SC and ≥ 5 mg/kg IV. In rats, deaths were observed following doses of ≥ 40 mg/kg SC and ≥ 5 mg/kg IV.

Repeat Dose Toxicology
The repeat-dose general toxicology has been evaluated after subcutaneous (SC) administration in rats and dogs for up to 4 weeks. This duration of dosing supports clinical administration of plerixafor up to 2 weeks. There are no 6 month studies in rats and 9 month studies in dogs or monkeys that would support chronic clinical studies and/or long term administration in clinical practice.

In repeat dose studies in rats and dogs with once- or twice-daily SC dosing, severe adverse neuromuscular-like clinical signs were observed within the first 1 to 2 hours post dose and were dose-limiting. At non-lethal doses, daily SC treatment induced adverse clinical signs similar to those seen in the single dose mouse and rat studies. The onset of these clinical signs occurred within 15 min to 1 hr following SC plerixafor injection; however, unlike the single dose studies, the signs were generally not seen until after approximately 5 to 8 daily SC doses of plerixafor had been administered to rats or dogs. Plerixafor was associated with GI clinical signs in dogs (diarrhea, emesis, increased defecation) and neurological signs in dogs and rats (sedation, tremors, spasms, twitching, recumbency and ataxia and mydriasis). There were some minor decreases in body weight gain and food consumption.

Increases in white cell counts (predominantly due to neutrophils), and decreases in serum magnesium and increases in urinary calcium and/or magnesium were noted in both rats and dogs. Histopathology findings of extramedullary hematopoiesis were observed in the liver, spleen and occasionally in other organs of rats and/or dogs. Slightly higher spleen weights were observed in rats. These findings were considered to be an extension of the pharmacological action of plerixafor to mobilize hematopoietic and/or white blood cells and for its affinity to chelate cations.

Compared to control rats, increased injection site reactions were more pronounced at 12 mg/kg BID (24 mg/kg/day) in a 4 week SC study. At doses of ≥1 mg/kg/day (≥20 mg/m^2) plerixafor induced transient increases in heart rates in dogs with decreases in QT interval considered secondary to the effect on heart rate. The No Adverse Effect Dose Level (NOAEL) in 4 week SC studies were 0.6-1.2 mg/kg/day (3.6-7.2 mg/m^2) and 0.25-0.30 mg/kg/day (3.6-7.2 mg/m^2) in rats and dogs, respectively. Exposures (AUCs) at these doses were 0.1 to 5 times the clinical exposure. In the rat and dog, the Maximum Tolerated Dose (MTD) was 7.6-24 mg/kg/day (46-144 mg/m^2) and 4-8 mg/kg/day (80-160 mg/m^2), respectively. At the MTD, exposures (AUCs) are 7 to 18 times the clinical exposure.

Three nonclinical studies have been performed in juvenile animals. In a non-GLP dose range-finding study, Mozobil was administered to juvenile male miniature pigs at single subcutaneous (SC) doses from 1-12 mg/kg or repeat SC doses of 4.75 mg/kg/day for 4 days. In a non-GLP dose range-finding toxicity study and in a GLP toxicity study, Mozobil was administered SC daily to juvenile Sprague-Dawley rats from Postnatal Day (PND)21 to PND50 at 1.5-15 mg/kg/day. The results of the dose range-finding study in juvenile miniature pigs and the range-finding and definitive studies in juvenile rats were similar to those observed in adult mice, rats, and dogs. Clinical signs of lateral recumbence and discomfort were observed in miniature pigs at 8 mg/kg and mortality was seen at 12 mg/kg. Plerixafor produced the expected pharmacologically-mediated leukocytosis in pigs and rats. The organ weight effects observed in rats were considered pharmacologic (thymus) or an adaptive response (extramedullary hematopoiesis in the liver and spleen).

Dose margins in the juvenile rat study at the maximum tolerated dose (MTD) were 18-26-fold higher based on exposure when compared with the recommended clinical pediatric dose in children 2 to less than 18 years of age.

Carcinogenesis
Carcinogenicity studies with plerixafor have not been conducted.

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

Impairment of Fertility
The potential effects of plerixafor on male fertility and post-natal development have not been evaluated in non-clinical studies. In studies conducted to measure the distribution of ^{14}C-plerixafor, there was no evidence of accumulation in testes. The staging of spermatogenesis measured in a 28-day repeat-dose toxicity study in rats revealed no abnormalities considered to be related to plerixafor. There were no plerixafor related histopathological changes in male or female reproductive organs in rats and dogs administered plerixafor daily at doses 24 mg/kg (144 mg/m^2; 12 mg/kg BID) and 8 mg/kg (160 mg/m^2; 4 mg/kg BID), respectively for up to 4 weeks.

No adverse effects were observed in an investigative female fertility study in rats, even though concentrations of plerixafor in the ovaries were detectable up to the last days of cohabitation.

Reproductive Toxicity
SDF-1α and CXCR4 play major roles in embryo-fetal development. Plerixafor administered during organogenesis has been shown to cause fetal death, increased resorptions, and post-implantation loss, decreased fetal weights, retarded skeletal development and increased fetal abnormalities in rats and rabbits. Fetal abnormalities included cyst at the parietal/frontal bone, anophthalmia, globular heart dilation of the ascending aorta, ringed aorta, cardiac interventricular septal defect, dilation of pulmonary truncus and stenosis of descending aorta, omphalocele, anal atresia, intestinal stenosis, brachdactyly, and acaudia. Animal models also suggest modulation of fetal hematopoiesis, vascularization, and cerebellar development by SDF-1α and CXCR4. The no-observed-adverse-effect-levels (NOAEL) of plerixafor in rats and rabbits (3 mg/kg/day and 0.6 mg/kg/day, respectively) are approximately 2.0 and 0.8 times the recommended human dose of 0.24 mg/kg/day (8.9 mcg/m^2/day). The embryolethal, fetotoxic and teratogenic effects are likely due to the pharmacodynamic mechanism of action of plerixafor.

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PART III: CONSUMER INFORMATION

MOZOBIL®
Plerixafor injection

This leaflet is part III of a three-part "Product Monograph" published when MOZOBIL (plerixafor) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MOZOBIL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MOZOBIL in combination with granulocyte-colony stimulating factor (G-CSF) is used to help collect blood stem cells for transplantation in

- Adults with non-Hodgkin's lymphoma (a cancer of the white blood cells) and multiple myeloma (a cancer that affects plasma cells in the bone marrow).
- Children and adolescents (1 to less than 18 years of age) with lymphoma or solid cancerous tumors, where following G-CSF treatment:
    - Blood stem cell count is low on the predicted date of collection, or
    - Previous collection has failed to yield enough stem cells

What it does:
MOZOBIL contains the active substance plerixafor which blocks a protein on the surface of blood stem cells. This protein "ties" blood stem cells to the bone marrow. Plerixafor improves the release of stem cells into the blood stream (mobilization). The stem cells can then be collected by an apheresis machine, and subsequently frozen and stored until your transplant.

When it should not be used:
If you or your child are allergic (hypersensitive) to plerixafor or any of the other ingredients of MOZOBIL (see below for a list of important non-medicinal ingredients).

What the medicinal ingredient is:
Plerixafor

What the important nonmedicinal ingredients are:
Sodium chloride (typically less than 6 mg per dose). Other ingredients are hydrochloric acid (concentrated) and sodium hydroxide for pH adjustment and water for injections.

What dosage forms it comes in:
MOZOBIL is supplied as a clear colorless or pale yellow solution for injection in a glass vial with a non-latex rubber stopper. Each vial contains 1.2 mL solution.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions: MOZOBIL will be prescribed and managed by a healthcare professional experienced in oncology and/or hematology.

BEFORE you or your child are given MOZOBIL talk to your doctor or pharmacist if:

- you or your child have or have had any heart problems.
- you or your child have kidney problems.
- you or your child have high white blood cell counts.
- you or your child have low platelet counts.
- you or your child have a history of feeling faint or lightheaded on standing or sitting or have fainted following injections.
- you are pregnant or are planning to become pregnant. Female patients who can get pregnant should use an effective birth control while having treatment with MOZOBIL.
- you are breast feeding.

Your doctor may perform regular blood tests to monitor your blood cell count.

It is not recommended to use MOZOBIL for stem cell mobilization if you have leukemia (a cancer of the blood or bone marrow).

Driving and using machines
MOZOBIL may cause dizziness and fatigue. Therefore, you should avoid driving if you feel dizzy, tired or unwell.

INTERACTIONS WITH THIS MEDICATION

Before and during treatment with MOZOBIL tell your doctor or pharmacist about your other medicines, including medicines that you bought without a prescription.

PROPER USE OF THIS MEDICATION

You or your child will first receive a treatment with G-CSF once daily for 4 days.

Then MOZOBIL will be given 10 to 11 hours for adults and 8 to 12 hours for children and adolescents before each session of apheresis (a collection of stem cells).

The usual dose of MOZOBIL is 0.24 mg/kg body weight/day given to you as an injection under the skin (subcutaneous injection). For adults who weigh 83 kg or less, your doctor may prescribe a fixed dose of 20 mg of MOZOBIL.

MOZOBIL can be used for up to

- 4 consecutive days in **adults**
- 3 consecutive days in **children and adolescents (1 to less than 18 years of age).**

OVERDOSE

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, MOZOBIL can cause side effects. The following are potential side effects with the use of MOZOBIL:

- Injection site reactions, such as swelling, pain, irritation, bruising
- feeling tired
- stuffy and runny nose
- abnormal dreams, nightmares.

Please tell your doctor immediately if

- shortly after receiving MOZOBIL, you experience rash, swelling around the eyes, shortness of breath or lack of oxygen, feeling lightheaded on standing or sitting, feeling faint or fainting
- you have pain in the upper left abdomen (belly) or at the tip of your shoulder.

Heart attacks

In clinical trials, 0.9% of patients with risk factors for a heart attack suffered heart attacks after being given MOZOBIL and G-CSF. Please inform your doctor immediately if you experience chest discomfort.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very common			
Diarrhea, nausea (feeling sick), injection site redness or irritation	√		
Fever (pyrexia)	√		
Decreased level of protein in blood (hypoproteinemia)	√		
Decreased red blood cells (anemia) – fatigue, loss of energy, weakness, shortness of breath	√		
Decreased white blood cells (neutropenia or leukopenia) – infections, fatigue, fever, aches, pains and flu-like symptoms	√		
Decreased platelets (thrombocytopenia)– bruising, bleeding, fatigue and weakness	√		
Common			
Headache	√		
Dizziness, feeling tired or unwell	√		
Difficulty in sleeping, anxiety	√		
Flatulence, constipation, indigestion, vomiting	√		
Stomach symptoms such as pain, swelling or discomfort	√		
Numbness around the mouth, pins and needles and numbness	√		
Sweating, generalized redness of the skin	√		
Joint pains, pains in muscles and bones.	√		
Uncommon			
Systemic reactions such as skin rash, swelling around the eyes, shortness of breath		√	
Feeling faint, sudden drop in pulse and/or blood pressure, fainting		√	
Heart attack, chest discomfort		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and**
Fever with low white blood cell count (febrile neutropenia) – fever, signs of low white blood cell count and/or infection		√	
Decreased red and white blood cells and platelets (pancytopenia) –bruising, bleeding (gums), nose bleed, weakness, paleness of skin, fatigue, shortness of breath, rapid heart rate, and/or symptoms of infection		√	
Rare			
Severe diarrhea, vomiting, stomach pain and/or nausea.		√	
Unknown frequency			
Spleen enlargement and/or rupture: pain in the upper left abdomen (belly) or at the tip of your shoulder		√	

This is not a complete list of side effects. For any unexpected effects while taking MOZOBIL contact your doctor or pharmacist.

HOW TO STORE IT

You will not be given MOZOBIL to store. It will only be administered by a doctor or nurse.

Reporting Suspected Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345."

NOTE: Contact your health care professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.sanofi.ca or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-800-265-7927

This leaflet was prepared by sanofi-aventis Canada Inc.

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