MOZOBIL- plerixafor solution
sanofi-aventis U.S. LLC

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 (HSCs) 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)
• Dose based on patient weight
  - ≤ 83 kg: 20 mg dose or select dose based on 0.24 mg/kg actual body weight. (2.1)
  - > 83 kg: 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 ≤ 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

• History of hypersensitivity to Mozobil. (4)

WARNINGS AND PRECAUTIONS

• Anaphylactic shock and Serious Hypersensitivity Reactions have occurred. Monitor patients during and after completion of Mozobil administration. (5.1)
• Tumor Cell Mobilization in Leukemia Patients: Mozobil may mobilize leukemic cells and should not be used in leukemia patients. (5.2)
• Hematologic Effects: Increased circulating leukocytes and decreased platelet counts have been observed. Monitor blood cell counts and platelet counts during Mozobil use. (5.3)
• 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. (5.4)
• Splenic Rupture: Evaluate patients who report left upper abdominal and/or scapular or shoulder pain. (5.5)
• Embryo-fetal Toxicity: May cause fetal harm. Advise women not to become pregnant when taking Mozobil. (5.6, 8.1)

ADVERSE REACTIONS

Most common adverse reactions (≥ 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: 12/2017

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1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
   2.1 Recommended Dosage and Administration
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 (HSCs) 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
Administer Mozobil approximately 11 hours prior to initiation of each apheresis for up to 4 consecutive days.

The recommended dose of Mozobil by subcutaneous injection is based on body weight:
- 20 mg fixed dose or 0.24 mg/kg of body weight for patients weighing ≤83 kg. [see Clinical Pharmacology (12.3)]
- 0.24 mg/kg of body weight for patients weighing >83 kg.

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 Mozobil 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\textsubscript{CR}) ≤50 mL/min), reduce the dose of Mozobil by one-third based on body weight category as shown in Table 1. If CL\textsubscript{CR} is ≤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 Mozobil in Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Estimated Creatinine Clearance (mL/min)</th>
<th>Dose</th>
<th>Body Weight ≤83 kg</th>
<th>Body Weight &gt;83 kg and &lt;160 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td></td>
<td>20 mg or 0.24 mg/kg once daily</td>
<td>0.24 mg/kg once daily (not to exceed 40 mg/day)</td>
</tr>
<tr>
<td>≤50</td>
<td></td>
<td>13 mg or 0.16 mg/kg once daily</td>
<td>0.16 mg/kg once daily (not to exceed 27 mg/day)</td>
</tr>
</tbody>
</table>

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

Males:

\[
\text{Creatinine clearance (mL/min) = weight (kg) \times (140 - age in years) \over 72 \times \text{serum creatinine (mg/dL)}}
\]
Females:
Creatinine clearance (mL/min) = 0.85 × 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
History of hypersensitivity to Mozobil [see Warnings and Precautions (5.1)]. Anaphylactic shock has occurred with use of Mozobil.

5 WARNINGS AND PRECAUTIONS
5.1 Anaphylactic Shock and Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening with clinically significant hypotension and shock have occurred in patients receiving Mozobil [see Adverse Reactions (6.2)]. Observe patients for signs and symptoms of hypersensitivity during and after Mozobil administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer Mozobil when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

In clinical studies, mild or moderate allergic reactions occurred within approximately 30 minutes after Mozobil administration in less than 1% of patients [see Adverse Reactions (6.1)].

5.2 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.

5.3 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 [see Adverse Reactions (6.1)].

Thrombocytopenia
Thrombocytopenia has been observed in patients receiving Mozobil. Monitor platelet counts in all patients who receive Mozobil and then undergo apheresis.

5.4 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.

5.5 Splenic Enlargement and 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. Cases of splenic enlargement and/or rupture have been reported following the administration of Mozobil in conjunction
with growth factor G-CSF. Evaluate individuals receiving Mozobil in combination with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain for splenic integrity.

5.6 Embryo-fetal Toxicity
Mozobil may cause fetal harm when administered to a pregnant woman. Plerixafor is teratogenic in animals. There are no adequate and well-controlled studies in pregnant women using Mozobil. Advise women of childbearing potential 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
The following serious adverse reactions are discussed elsewhere in the labeling:

- Anaphylactic shock and hypersensitivity reactions [see Warnings and Precautions (5.1)]
- Potential for tumor cell mobilization in leukemia patients [see Warnings and Precautions (5.2)]
- Increased circulating leukocytes and decreased platelet counts [see Warnings and Precautions (5.3)]
- Potential for tumor cell mobilization [see Warnings and Precautions (5.4)]
- Splenic enlargement [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience
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.

The most common adverse reactions (≥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 randomized placebo-controlled studies (301 patients) and 10 uncontrolled studies (242 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 ≥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.

<p>| Table 2: Adverse Reactions in ≥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) |</p>
<table>
<thead>
<tr>
<th>All Grades *</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 allergic reactions were observed in less than 1% of patients within approximately 30 min after Mozobil administration, including 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 in the randomized studies 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.

Hyperleukocytosis: In clinical trials, white blood cell counts of 100,000/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.

### 6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported from postmarketing 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:** Splenomegaly and splenic rupture
Immune System Disorders: Anaphylactic reactions, including anaphylactic shock
Psychiatric disorders: Abnormal dreams and nightmares

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. At concentrations similar to what are seen clinically, plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an in vitro study [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D
Risk Summary
Mozobil may cause fetal harm when administered to a pregnant woman. Plerixafor is teratogenic in animals.
Animal Data
Plerixafor administered to pregnant rats induced embryo-fetal toxicities including fetal death, increased resorptions and postimplantation 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/m² (approximately 10 times the recommended human dose of 0.24 mg/kg when compared on a mg/m² 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 $\text{CL}_{\text{CR}} \leq 50 \text{ mL/min}$ 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} ≤ 50 mL/min), reduce the dose of Mozobil 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

![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-1α (SDF-1α). SDF-1α 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-1α 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/mcL) 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/mcL) 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>
<thead>
<tr>
<th>Study</th>
<th>Mozobil® and G-CSF</th>
<th>Placebo and G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Study 1</td>
<td>5.0</td>
<td>6.1 (5.4)</td>
</tr>
<tr>
<td>Study 2</td>
<td>4.8</td>
<td>6.4 (6.8)</td>
</tr>
</tbody>
</table>

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

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.

QT/QTc Prolongation

There is no indication of a QT/QTc prolonging effect of Mozobil in single doses up to 0.40 mg/kg. In a randomized, double-blind, crossover study, 48 healthy subjects were administered a single subcutaneous dose of plerixafor (0.24 mg/kg and 0.40 mg/kg) and placebo. 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.

12.3 Pharmacokinetics

The single-dose pharmacokinetics of plerixafor 0.24 mg/kg were evaluated in patients with NHL and MM following pretreatment 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 was 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\text{CR}), as well as between central volume of distribution and body weight were observed. The distribution half-life \(t_{\frac{1}{2}\alpha}\) was estimated to be 0.3 hours and the terminal population half-life \(t_{\frac{1}{2}\beta}\) 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\text{0–24h}) with increasing body weight. 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. The fixed 20 mg
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 \( \geq 5 \times 10^6 \) CD34+ cells/kg than the mg/kg-based dose. However, the median time to reach \( \geq 5 \times 10^6 \) CD34+ cells/kg was 3 days for both treatment groups, and the safety profile between the groups was similar. Based on these results, further analysis was conducted by FDA reviewers and a body weight of 83 kg was selected as an appropriate cut-off point to transition patients from fixed to weight based dosing.

### Table 4: Systemic Exposure (AUC\(_{0-10h}\)) Comparisons of Fixed and Weight-Based Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Geometric Mean AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed 20 mg (n=30)</td>
<td>3991.2</td>
</tr>
<tr>
<td>0.24 mg/kg (n=31)</td>
<td>2792.7</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>1.43 (1.32,1.54)</td>
</tr>
</tbody>
</table>

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\(_{\text{CR}}\) is \( >50 \) mL/min and 27 mg/day if CL\(_{\text{CR}}\) is \( \leq 50 \) mL/min) [see Dosage and Administration (2.1, 2.3)].

**Absorption**

Peak plasma concentrations occurred at approximately 30 to 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, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 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. At concentrations similar to what are seen clinically, plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an in vitro study with MDCKII and MDCKII-MDR1 cell models.

**Special Populations**

**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\(_{\text{CR}}\). The mean AUC\(_{0-24h}\) of plerixafor in subjects with mild (CL\(_{\text{CR}}\) 51–80 mL/min), moderate (CL\(_{\text{CR}}\) 31–50 mL/min), and severe (CL\(_{\text{CR}}\) <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\(_{\text{max}}\). A population pharmacokinetic analysis indicated an increased exposure (AUC\(_{0-24h}\)) in patients with moderate and severe renal
impairment compared to patients with CL\textsubscript{CR} >50 mL/min. These results support a dose reduction of one-third in patients with moderate to severe renal impairment (CL\textsubscript{CR} ≤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\textsubscript{0–24h}) with increasing body weight; therefore, if CL\textsubscript{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\textsuperscript{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 years (range 29–75) and 58 years (range 22–75) in the Mozobil and placebo groups, respectively, and 93% of subjects were Caucasian. In study 2, 302 patients with MM were included in the primary efficacy analyses. The mean age (58 years) and age range (28–75) were similar in the Mozobil and placebo groups, and 81% of subjects were Caucasian.

In Study 1, 59% of NHL patients who were mobilized with Mozobil and G-CSF collected ≥5 × 10\textsuperscript{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 5).
Table 5: Study 1 Efficacy Results - CD34+ Cell Mobilization in NHL Patients

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>Mozobil® and G-CSF (n=150)</th>
<th>Placebo and G-CSF (n=148)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients achieving ≥5 × 10^6 cells/kg in ≤4 apheresis days</td>
<td>89 (59%)</td>
<td>29 (20%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients achieving ≥2 × 10^6 cells/kg in ≤4 apheresis days</td>
<td>130 (87%)</td>
<td>70 (47%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* p-value calculated using Pearson's Chi-Squared test

The median number of days to reach ≥5 × 10^6 CD34+ cells/kg was 3 days for the Mozobil group and not evaluable for the placebo group. Table 6 presents the proportion of patients who achieved ≥5 × 10^6 CD34+ cells/kg by apheresis day.

Table 6: Study 1 Efficacy Results – Proportion of Patients Who Achieved ≥5 × 10^6 CD34+ cells/kg by Apheresis Day in NHL Patients

<table>
<thead>
<tr>
<th>Days</th>
<th>Proportion* in Mozobil® and G-CSF (n=147†)</th>
<th>Proportion* in Placebo and G-CSF (n=142†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>2</td>
<td>49.1%</td>
<td>14.2%</td>
</tr>
<tr>
<td>3</td>
<td>57.7%</td>
<td>21.6%</td>
</tr>
<tr>
<td>4</td>
<td>65.6%</td>
<td>24.2%</td>
</tr>
</tbody>
</table>

* Percents determined by Kaplan Meier method
† n 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 ≥6 × 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 7).

Table 7: Study 2 Efficacy Results – CD34+ Cell Mobilization in Multiple Myeloma Patients

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>Mozobil® and G-CSF (n=148)</th>
<th>Placebo and G-CSF (n=154)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients achieving ≥6 × 10^6 cells/kg in ≤2 apheresis days</td>
<td>106 (72%)</td>
<td>53 (34%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients achieving ≥6 × 10^6 cells/kg in ≤4 apheresis days</td>
<td>112 (76%)</td>
<td>79 (51%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients achieving ≥2 × 10^6 cells/kg in ≤4 apheresis days</td>
<td>141 (95%)</td>
<td>136 (88%)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

* p-value calculated using Pearson's Chi-Squared test

The median number of days to reach ≥6 × 10^6 CD34+ cells/kg was 1 day for the Mozobil group and 4
days for the placebo group. Table 8 presents the proportion of patients who achieved ≥6 × 10^6 CD34+ cells/kg by apheresis day.

Table 8: Study 2 – Proportion of Patients Who Achieved ≥6 × 10^6 CD34+ cells/kg by Apheresis Day in MM Patients

<table>
<thead>
<tr>
<th>Days</th>
<th>Proportion* in Mozobil® and G-CSF (n=144†)</th>
<th>Proportion* in Placebo and G-CSF (n=150†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54.2%</td>
<td>17.3%</td>
</tr>
<tr>
<td>2</td>
<td>77.9%</td>
<td>35.3%</td>
</tr>
<tr>
<td>3</td>
<td>86.8%</td>
<td>48.9%</td>
</tr>
<tr>
<td>4</td>
<td>86.8%</td>
<td>55.9%</td>
</tr>
</tbody>
</table>

* Percents determined by Kaplan Meier method
† n 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: 0024-5862-01

- Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–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 potential for anaphylactic reactions, including signs and symptoms such as urticaria, periorbital swelling, dyspnea, or hypoxia during and following Mozobil injection and to report these symptoms immediately to a health care professional [see Adverse Reactions (6.1), (6.2)].

Advise patients to contact health care professional immediately if they experience left upper abdominal pain and/or scapular or shoulder pain [see Adverse Reactions (6.1, 6.2)].

Advise patients to 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)].

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

Advise 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 (5.6) and Use In Specific Populations (8.1)].
PRINCIPAL DISPLAY PANEL - 1.2 mL Vial Carton

Carton contains one vial of

**Mozobil®**
*(plerixafor injection)*

24 mg/1.2 mL
(20 mg/mL)

For single use only

Rx only

See package insert for dosage and administration
MOZOBIL
plerixafor solution

Product Information

<table>
<thead>
<tr>
<th>Product Type</th>
<th>HUMAN PRESCRIPTION DRUG</th>
<th>Item Code (Source)</th>
<th>NDC:0024-5862</th>
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</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>SUBCUTANEOUS</td>
<td></td>
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</table>

Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLERIXAFOR (UNII: S915P5499N)</td>
<td>PLERIXAFOR</td>
<td>24 mg in 1.2 mL</td>
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## Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
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</thead>
<tbody>
<tr>
<td>SODIUM CHLORIDE (UNII: 451W47IQ8X)</td>
<td>5.9 mg in 1.2 mL</td>
</tr>
<tr>
<td>HYDROCHLORIC ACID (UNII: QTT17582CB)</td>
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</tr>
<tr>
<td>WATER (UNII: 059QF0KO0R)</td>
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</tr>
<tr>
<td>SODIUM HYDROXIDE (UNII: 55X04QC32I)</td>
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</tbody>
</table>

## Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:0024-5862-01</td>
<td>1 in 1 CARTON</td>
<td>09/01/2013</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>1.2 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
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<tbody>
<tr>
<td>NDA</td>
<td>NDA022311</td>
<td>09/01/2013</td>
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</tbody>
</table>

**Labeler** - sanofi-aventis U.S. LLC (824676584)

## Establishment

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
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</thead>
<tbody>
<tr>
<td>Genzyme Limited</td>
<td></td>
<td>229522842</td>
<td>MANUFACTURE(0024-5862) , ANALYSIS(0024-5862) , LABEL(0024-5862) , PACK(0024-5862)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patheon UK Limited</td>
<td></td>
<td>237710418</td>
<td>MANUFACTURE(0024-5862) , ANALYSIS(0024-5862)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genzyme Corporation</td>
<td></td>
<td>098066215</td>
<td>ANALYSIS(0024-5862) , LABEL(0024-5862) , MANUFACTURE(0024-5862) , PACK(0024-5862)</td>
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</tbody>
</table>

Revised: 12/2017