APPROVED PACKAGE INSERT FOR MOZOBIL®

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

MOZOBIL® (solution for injection)

COMPOSITION:

Active ingredient: Each 1,2 ml vial contains 24,0 mg plerixafor (20 mg/ml).

Inactive ingredients:Sodium chloride, hydrochloric acid, sodium hydroxide, water for injection.

Each ml **MOZOBIL®** solution for injection contains about 5 mg sodium.

PHARMACOLOGICAL CLASSIFICATION:

A 32.2 Other substances (immunostimulant)

PHARMACOLOGICAL 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 hematopoietic stem cells (HSCs) to the marrow compartment. Stem cells express CXCR4 and are known to migrate to the bone marrow through a chemo-attractant 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 mobilised by 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 multiple myeloma (AMD3100-3101 and AMD3100-3102, respectively). Fold increase over the 24-hour period from the day prior to the first apheresis to just before the first apheresis is summarised in **Table 1**. During that 24-hour period, the first dose of plerixafor 0,24 mg/kg or placebo was administered 10-11 hours prior to apheresis.

Table 1: Fold increase in peripheral blood CD34+ cell count following Plerixafor administration

Study	**Plerixafor and G-CSF**		**Placebo and G-CSF**	
	Median	**Mean (SD)**	**Median**	**Mean (SD)**
AMD3100-3101	5,0	6,2 (5,4)	1,4	1,9 (1,5)
AMD3100-3102	4,8	6,4 (6,8)	1,7	2,4 (7,3)

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

A study in healthy volunteers at single doses of 0,24 and 0,40 mg/kg showed that plerixafor had no effects on QT interval, heart rate, PR interval, QRS interval duration, or ECG morphology.

Pharmacokinetics

The pharmacokinetics of plerixafor have been evaluated in lymphoma and multiple myeloma

patients at the clinical dose level of 0,24 mg/kg following pre-treatment with G-CSF (10 µg/kg once daily for 4 consecutive days).

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 demonstrating that plerixafor is largely confined to, but not limited to, the extravascular fluid space.

Metabolism

Plerixafor is not metabolised *in vitro* using human liver microsomes or human primary hepatocytes and does not exhibit inhibitory activity *in vitro* towards the major drug metabolising 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.

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. The half-life in plasma is 3 - 5 hours.

Renal impairment

Following a single 0,24 mg/kg dose of plerixafor clearance was reduced in subjects with varying degrees of renal dysfunction and was positively correlated with CrCl. Mean values of AUC_{0-24} of plerixafor in subjects with mild (CrCl 51-80 ml/min), moderate (CrCl 31-50 ml/min) and severe (CrCl ≤ 30 ml/min) renal impairment were 5410, 6780 and 6990 ng x h/ml, respectively, which were higher than the exposure observed in healthy patients with normal renal function (5070 ng x h/ml). Renal impairment had no effect on C_{max} (see **DOSAGE AND DIRECTIONS FOR USE**).

Gender

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

Age

A population pharmacokinetic analysis showed no effect of age on plerixafor pharmacokinetics.

INDICATIONS:

Mozobil® is indicated to enhance mobilisation of hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma (MM) (see **DOSAGE AND DIRECTIONS FOR USE**).

CONTRAINDICATIONS:

Hypersensitivity to any of the ingredients of this formulation.

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS:

Tumour cell mobilisation in leukemia patients

In a compassionate use program, **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 mobilisation, **Mozobil®** may cause mobilisation of leukemic cells and subsequent contamination of the apheresis product. Therefore, **Mozobil®** is not intended for HSC mobilisation and harvest in patients with leukemia.

Hematologic effects

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 is a known complication of apheresis and has been observed in patients receiving **Mozobil®**. Platelet counts should be monitored in all patients who receive **Mozobil®** and then undergo apheresis.

Potential for tumour cell mobilisation in lymphoma and multiple myeloma patients

When **Mozobil®** is used in conjunction with G-CSF for HSC mobilisation in patients with lymphoma or MM, tumour cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of potential reinfusion of tumour cells has not been well-studied. In clinical studies of patients with non-Hodgkin's lymphoma (NHL) and MM, mobilisation of tumour cells has not been observed with **Mozobil®**.

Systemic reactions

In **Mozobil®** oncology clinical studies, less than 1 % 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), dyspnoea (n = 1) or hypoxia (n = 1). Symptoms generally responded to treatments (e.g. antihistamines, corticosteroids, hydration or supplemental oxygen) or resolved spontaneously. Appropriate precautions should be taken because of the potential for these reactions.

Vasovagal reactions

Vasovagal reactions, orthostatic hypotension, and/or syncope can occur following SC injections. In **Mozobil®** oncology and healthy volunteer clinical studies, less than 1 % of subjects experienced vasovagal reactions (orthostatic hypotension and/or syncope) following SC administration of **Mozobil®** doses ≤ 0,24 mg/kg. The majority of these events occurred within 1 hour of **Mozobil®** administration. Appropriate precautions should be taken because of the potential for these reactions.

Potential effect on spleen size

Higher absolute and relative spleen weights associated with extramedullary haematopoiesis 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. The effect of **Mozobil®** on spleen size in patients has not been specifically evaluated in clinical studies. The possibility that **Mozobil®** in conjunction with the growth factor G-CSF can cause splenic enlargement cannot be excluded. Due to the rare occurrence of splenic rupture following G-CSF administration, 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.

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 (see **Pharmacokinetics**). In clinical studies of patients with NHL, the addition of rituximab to a mobilisation regimen of **Mozobil®** and G-CSF did not impact patient safety or CD34+ cell yield.

PREGNANCY AND LACTATION:

Safety and efficacy in pregnancy and lactation has not been established.

Pregnancy

Mozobil® may cause foetal harm when administered to a pregnant woman. Studies in animals have shown teratogenicity. There are no adequate and well-controlled studies in pregnant women using **Mozobil®**. If **Mozobil®** is used during pregnancy, or if the patient becomes pregnant while taking **Mozobil®**, the patient should be informed of the potential hazard to the foetus. Advise women of childbearing potential to use effective contraception during treatment.

Lactation

It is not known whether **Mozobil®** is excreted in human milk. You should not breastfeed your baby whilst on treatment with **Mozobil®**.

DOSAGE AND DIRECTIONS FOR USE:

The recommended dose of **Mozobil®** is 0,24 mg/kg body weight by subcutaneous injection.

Mozobil® should be administered 6 to 11 hours prior to initiation of apheresis following 4 days of treatment with G-CSF.

Mozobil® should be administered by a nurse, physician, or other healthcare professional.

Mozobil® has been commonly used for 2 to 4 consecutive days. It has been used for up to 7 consecutive days in a clinical setting.

The patient's actual body weight will be used 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 will be calculated from the following equation:

0,012 x patient's actual body weight (in kg) = dose 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.

The weight used to calculate the volume of **Mozobil®** should be obtained within 1 week of the first dose of **Mozobil®**.

Recommended concomitant medications

In pivotal clinical studies supporting the use of **Mozobil®**, all patients received daily morning doses of granulocyte-colony stimulating factor (G-CSF) 10 µg/kg for 4 days prior to the first dose of **Mozobil®** and on each morning prior to apheresis.

Patient with renal impairment

Patients with moderate and severe renal insufficiency (creatinine clearance (CrCl) ≤ 50 ml/min) should have their dose of **Mozobil®** reduced by one-third to 0,16 mg/kg. Similar systemic exposure is expected if the dose is reduced by one-third in patients with moderate and severe renal impairment compared with subjects with normal renal function. Clinical data with this dose adjustment in patients with renal impairment are limited.

The following (Cockroft-Gault) formula may be used to estimate CrCl:

Males:

Creatinine clearance (ml/min) = [weight (kg) x (140 - age in years)] / [72 x serum creatinine (mg/dl)]

Females:

Creatinine clearance (ml/min) = 0,85 x value calculated for males

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

Incompatibilities

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects

In the two Phase 3 studies in patients with NHL and MM (AMD3100-3101 and AMD3100-3102, respectively), 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 µg/kg for 4 days prior to the first dose of **Mozobil®** or placebo and on each morning prior to apheresis. Adverse events that occurred more frequently with **Mozobil®** than placebo and were reported as related in ≥ 1 % of the patients who received **Mozobil®** during HSC mobilisation and apheresis and prior to chemotherapy/ablative treatment in preparation for transplantation are shown in **Table 2**. From chemotherapy/ablative treatment in preparation of transplantation through 12 months post-transplantation, no notable differences in the incidence of adverse events were observed across treatment groups.

Table 2: Adverse events occurring more frequently with Mozobil® than placebo and considered related to Mozobil® during HSC mobilisation and apheresis

(Very common = ≥ 1/10; Common = ≥ 1/100 to < 1/10)

MedDRA System Organ Class	**MedDRA preferred term**	**Frequency**
Cardiac disorders	Extrasystoles	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Eye disorders	Eye swelling	Uncommon
Gastrointestinal disorders	Diarrhoea, nausea	Very common
	Flatulence, abdominal pain, vomiting, abdominal distension, dry mouth, stomach discomfort, constipation, dyspepsia, hypoaesthesia oral	Common
	Abdominal discomfort, eructation, retching, stomatitis	Uncommon
General disorders and administrative site conditions	Injection site reactions	Very common
	Fatigue, malaise	Common
	Asthenia, influenza like illness, irritability	Uncommon
Injury, poisoning and procedural complications	Procedural hypertension, procedural nausea	Uncommon
Investigations	Aspartate aminotransferase increased	Uncommon
Metabolism and nutrition disorders	Decreased appetite, hypocalcaemia, hyponatraemia, hypophosphataemia	Uncommon
Musculoskeletal, connective tissue and bone disorders	Arthralgia, musculoskeletal pain	Common
	Muscular weakness, musculoskeletal stiffness, neck pain	Uncommon
Nervous system disorders	Headache, dizziness	Common

	Dysgeusia	Uncommon
Psychiatric disorders	Insomnia	Common
	Anticipatory anxiety, anxiety, nightmare	Uncommon
Renal and urinary disorders	Pollakiuria	Uncommon
Respiratory, thoracic and mediastinal disorders	Sinus congestion	Uncommon
Skin and subcutaneous tissue disorders	Hyperhidrosis, erythema	Common
	Cold sweat, ecchymosis, hypoaesthesia facial, night sweats, urticaria, urticaria localised	Uncommon
Vascular disorders	Flushing, hot flush, hypotension	Uncommon

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

Myocardial infarction

In clinical studies, seven of 679 oncology patients experienced myocardial infarctions after HSC mobilisation with **Mozobil®** and G-CSF. All events occurred at least 14 days after last **Mozobil®** administration. Additionally, two female oncology patients in the compassionate use program experienced myocardial infarctions following HSC mobilisation with **Mozobil®** and G-CSF. One of these events occurred 4 days after last **Mozobil®** administration. Lack of temporal relationship in 8 of 9 patients coupled with risk profile of patients with myocardial infarction does not suggest **Mozobil®** confers an independent risk for myocardial infarction in patients who also receive G-CSF.

Gastrointestinal disorders

In **Mozobil®** clinical studies of oncology patients, there have been rare reports of severe gastrointestinal events, including diarrhoea, nausea, vomiting, and abdominal pain.

Paraesthesias

Paraesthesias are commonly observed in oncology patients undergoing autologous transplantation following multiple disease interventions. In the placebo-controlled Phase 3 studies, the incidence of paraesthesias was 20,6 % and 21,2 % in the **Mozobil®** and placebo groups, respectively.

SPECIAL PRECAUTIONS

Useful laboratory tests for monitoring patients

White blood cell and platelet counts should be monitored during **Mozobil®** use and apheresis.

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

Paediatric use

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

Geriatric use

In the two placebo-controlled clinical studies of **Mozobil®**, 24 % of patients were ≥ 65 years old. No notable differences in the incidence of adverse drug reactions were observed in elderly and younger patients.

Since the active ingredient of **Mozobil®**, 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 CrCl ≤ 50 ml/min is recommended (see **DOSAGE AND DIRECTIONS FOR USE**).

Renal impairment

Dosage adjustment in patients with CrCl ≤ 50 ml/min is recommended (see **DOSAGE AND DIRECTIONS FOR USE**).

Effects on ability to drive and handle heavy machinery

No studies on the ability to drive and use machines have been conducted with **Mozobil®**.

Drug/Food Interactions

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms

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.

Treatment

Treatment is symptomatic and supportive.

IDENTIFICATION:

Sterile, preservative-free, clear, colourless to pale yellow, pH neutral, isotonic solution.

PRESENTATION:

2,0 ml clear glass (Type I) vial, sealed with a rubber stopper and aluminium seal with a plastic flip-off cap.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

For single use only. Discard any unused portion.

From a microbiological point of view, once drawn into a syringe, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

44/32.2/0546

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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