MOZIFOR
(Plerixafor 20mg/mL Solution for Injection)
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NAME AND STRENGTH OF ACTIVE INGREDIENT
MOZIFOR (Plerixafor 20mg/mL Solution for Injection)

1 ml solution contains 20 mg plerixafor.
Each vial contains 24 mg plerixafor in 1.2 ml solution.

DOSAGE FORM
Solution for injection.

PRODUCT DESCRIPTION
Clear colorless to pale yellow solution free from visible particles.

PHARMACODYNAMICS
Pharmacotherapeutic group: Other immune stimulants
ATC code: L03AX16

Plerixafor is a bicyclam derivative, a selective reversible antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α), also known as CXCL12. Plerixafor-induced leukocytosis and elevations in circulating haematopoietic 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.

Pharmacodynamic effects
In pharmacodynamic studies in healthy volunteers of plerixafor alone, 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 administered at identical dose regimen to that in studies in patients, 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.

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 subcutaneous injection, reaching peak concentrations in approximately 30 - 60 minutes (tmax). Following subcutaneous administration of a 0.24 mg/kg dose to patients after receiving 4-days of G-CSF pre-treatment, the maximal plasma concentration (Cmax) and systemic exposure (AUC0-24) of plerixafor were 887 ± 217 ng/ml and 4337 ± 922 ng.hr/ml, respectively.

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.

Biotransformation
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 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 unchanged in urine during the first 24 hours following administration. The elimination half-life (t1/2) 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.

Special populations
Renal impairment
Following a single dose of 0.24 mg/kg plerixafor, clearance was reduced in subjects with varying degrees of renal impairment and was positively correlated with creatinine clearance (CrCl). Mean values of AUC0-24 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.hr/ml, respectively, which were higher than the exposure observed in healthy subjects with normal renal function (5070 ng.hr/ml). Renal impairment had no effect on Cmax.

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

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

Paediatric population
The pharmacokinetics of plerixafor were evaluated in 48 paediatric patients (1 to less than 18 years) with solid tumours at subcutaneous doses of 0.16, 0.24 and 0.32 mg/kg with standard mobilisation (G-CSF plus or minus chemotherapy). Based on population pharmacokinetic modeling and similar to adults, μg/kg-based dosage results in increase in plerixafor exposure with increasing body weight in paediatric patients. At the same weight-based dosing regimen of 240 μg/kg, the plerixafor mean exposure (AUC0-24h) is lower in paediatric patients aged 2 to < 6 ears (1410 ng.h/mL), 6 to < 12 years (2318 ng.h/mL), and 12 to < 18 years (2981 ng.h/mL) than in adults (4337 ng.h/mL). Based on population pharmacokinetic modeling, the plerixafor mean exposures (AUC0-24h) in paediatric patients aged 2 to < 6 years (1905 ng.h/mL), 6 to < 12 years (3063 ng.h/mL), and 12 to < 18 years (4015 ng.h/mL), at the dose of 320 μg/kg are closer to the exposure in adults receiving 240 μg/kg. However, mobilization of PB CD34+ count was observed in stage 2 of the trial.

INDICATION
Adult patients
Mozifor is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma or multiple myeloma whose cells mobilise poorly.

Paediatric patients (1 to less than 18 years)
Mozifor is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells.

RECOMMENDED DOSE
Mozifor therapy should be initiated and supervised by a physician experienced in oncology and/or haematology. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Age over 60 and/ or prior myelosuppressive chemotherapy and/or extensive prior chemotherapy and/or a peak circulating stem cell count of less than 20 stem cells/microliter, have been identified as predictors of poor mobilisation.

Posology
Adult
The recommended daily dose of plerixafor by subcutaneous injection (SC) is:

- 20mg fixed dose or 0.24 mg/kg of body weight for patients weighing ≤ 83 kg.
- 0.24 mg/kg of body weight for patients weighing > 83 kg.

Paediatric (1 to less than 18 years)
The recommended daily dose of plerixafor by subcutaneous injection (SC) is:

- 0.24 mg/kg of body weight.

Each vial of plerixafor is filled to deliver 1.2 ml of 20 mg/ml plerixafor aqueous solution for injection containing 24 mg of plerixafor.

Plerixafor has to be drawn up into a syringe size type which should be selected according to the weight of the patient.

For low weight patients, up to 45 kg of body weight, 1 ml syringes for use in infant patients can be used. This type of syringe has major graduations for 0.1 ml and minor graduations for 0.01 ml and therefore is suitable to administer plerixafor, at a dose of 240 μg/kg, to paediatric patients of at least 9 kg body weight. For patients of more than 45 kg, a1 ml or 2 ml syringe with graduations that allow a volume to 0.1 ml to be measured can be used.

It should be administered by subcutaneous injection 6 to 11 hours prior to initiation of each apheresis following 4 day pre-treatment with G-CSF. In clinical trials, plerixafor has been commonly used for 2 to 4 (and up to 7) consecutive days.

The weight used to calculate the dose of plerixafor should be obtained within 1 week before the first dose of plerixafor. In clinical studies, the dose of plerixafor has been calculated based on body weight in patients up to 175% of ideal body weight. Plerixafor dose and treatment of patients weighing more than 175% of ideal body weight have not been investigated. Ideal body weight can be determined using the following equations:
male (kg): 50 + 2.3 x ((Height (cm) x 0.394) – 60);
female (kg): 45.5 + 2.3 x ((Height (cm) x 0.394) – 60).

Based on increasing exposure with increasing body weight, the plerixafor dose should not exceed 40 mg/day.

Recommended concomitant medicinal products
In pivotal clinical studies supporting the use of plerixafor, all patients received daily morning doses of 10 μg/kg G-CSF for 4 consecutive days prior to the first dose of plerixafor and on each morning prior to apheresis.

Special populations
Renal impairment
Patients with creatinine clearance 20 - 50 ml/min should have their dose of plerixafor reduced by one-third to 0.16 mg/kg/day. Clinical data with this dose adjustment are limited. There is insufficient clinical experience to make alternative posology recommendations for patients with a creatinine clearance < 20 ml/min, as well as to make posology recommendations for patients on haemodialysis.

Based on increasing exposure with increasing body weight the dose should not exceed 27 mg/day if the creatinine clearance is lower than 50 ml/min.

Paediatric population
The safety and efficacy of plerixafor in children (1 to less than 18 years) were studied in an open label, multicentre, controlled study.

Elderly patients (> 65 years old)
No dose modifications are necessary in elderly patients with normal renal function. Dose adjustment in elderly patients with creatinine clearance ≤ 50 ml/min is recommended (see Renal impairment above). In general, care should be taken in dose selection for elderly patients due to the greater frequency of decreased renal function with advanced age.

MODE OF ADMINISTRATION
Subcutaneous injection

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients listed in section list of excipients.

WARNINGS AND PRECAUTIONS
Tumour cell mobilisation in patients with lymphoma and multiple myeloma
When Mozifor is used in conjunction with G-CSF for haematopoietic stem cell mobilisation in patients with lymphoma or multiple myeloma, tumour cells may be released from the marrow and subsequently collected in the leukapheresis product. Results showed that, in case tumour cells are mobilised, the number of tumour cells mobilised is not increased upon Mozifor plus GCSF compared to G-CSF alone.

Tumour cell mobilisation in leukaemia patients
In a compassionate use programme, Mozifor and G-CSF have been administered to patients with acute myelogenous leukaemia and plasma cell leukaemia. In some instances, these patients experienced an increase in the number of circulating leukaemia cells. For the purpose of haematopoietic stem cell mobilisation, plerixafor may cause mobilisation of leukaemic cells and subsequent contamination of the apheresis product. Therefore, plerixafor is not recommended for haematopoietic stem cell mobilisation and harvest in patients with leukaemia.

Haematological effects
Hyperleukocytosis
Administration of Mozifor in conjunction with G-CSF increases circulating leukocytes as well as haematopoietic stem cell populations. White blood cell counts should be monitored during Mozifor therapy. Clinical judgment should be exercised when administering Mozifor to patients with peripheral blood neutrophil counts above 50 x 109/L.

Thrombocytopenia
Thrombocytopenia is a known complication of apheresis and has been observed in patients receiving Mozifor. Platelet counts should be monitored in all patients receiving Mozifor and undergoing apheresis.

Allergic reactions
Mozifor has been uncommonly associated with potential systemic reactions related to subcutaneous injection such as urticaria, periorbital swelling, dyspnoea, or hypoxia (see section Undesirable effects). Symptoms 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.

Vasovagal reactions
Vasovagal reactions, orthostatic hypotension, and/or syncope can occur following subcutaneous injections. Appropriate precautions should be taken because of the potential for these reactions.

Effect on the spleen
In preclinical studies, higher absolute and relative spleen weights associated with extramedullary haematopoiesis 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. The effect of plerixafor 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 Mozifor in conjunction with growth factor G-CSF. Individuals receiving Mozifor in conjunction with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity.

Size: 200 x 307 mm
Color: Black

Sodium
Mozifor contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

INTERACTION OF OTHER MEDICAMENTS
No interaction studies have been performed. In vitro tests showed that plerixafor was not metabolised by P450 CYP enzymes, did not inhibit or induce P450 CYP enzymes. Plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an in vitro study.

In clinical studies of patients with non-Hodgkin's lymphoma, the addition of rituximab to a mobilisation regimen of plerixafor and G-CSF did not impact patient safety or CD34+ cell yield.

PREGNANCY AND LACTATION
Women of childbearing potential
Women of childbearing potential have to use effective contraception during treatment.

Pregnancy
There are no adequate data on the use of plerixafor in pregnant women. Based on the pharmacodynamic mechanism of action, plerixafor is suggested to cause congenital malformations when administered during pregnancy. Studies in animals have shown teratogenicity. Mozifor should not be used during pregnancy unless the clinical condition of the woman requires treatment with plerixafor.

Breastfeeding
It is not known whether plerixafor is xcreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Mozifor.

Fertility
The effects of plerixafor on male and female fertility are not known.

SIDE EFFECTS
Summary of the safety profile
Safety data for Plerixafor in conjunction with G-CSF in oncology patients with lymphoma and multiple myeloma were obtained from 2 placebo-controlled Phase III studies (301 patients) and 10 uncontrolled Phase II studies (242 patients). Patients were primarily treated with daily doses of 0.24 mg/kg plerixafor by subcutaneous injection. The exposure to plerixafor in these studies ranged from 1 to 7 consecutive days (median = 2 days).

In the two Phase III studies in non-Hodgkin's lymphoma and multiple myeloma patients (AMD3100-3101 and AMD3100-3102, respectively), a total of 301 patients were treated in the Plerixafor 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 plerixafor or placebo and on each morning prior to apheresis. Adverse reactions that occurred more frequently with Plerixafor and G-CSF than placebo and G-CSF and were reported as related in ≥1% of the patients who received Plerixafor, during haematopoietic stem cell mobilisation and apheresis and prior to chemotherapy/ablative treatment in preparation for transplantation are shown in Table 1.
From chemotherapy/ablative treatment in preparation of transplantation through 12 months post-transplantation, no significant differences in the incidence of adverse reactions were observed across treatment groups.

Tabulated list of adverse reactions
Adverse reactions are listed by System Organ Class and frequency. Frequencies are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1. Adverse reactions occurring more frequently with Plerixafor than placebo and considered related to Plerixafor during mobilisation and apheresis in phase III studies

Blood and lymphatic system disorders	
Not known	Splenomegaly, splenic rupture**
Immune system disorders	
Uncommon	Allergic reaction* Anaphylactic reactions, including anaphylactic shock**
Psychiatric disorders	
Common	Insomnia
Uncommon	Abnormal dreams, nightmares
Nervous system disorders	
Common	Dizziness, headache
Gastrointestinal disorders	
Very common	Diarrhoea, nausea
Common	Vomiting, abdominal pain, stomach discomfort, dyspepsia, abdominal distention, constipation, flatulence, hypoaesthesia oral, dry mouth
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis, erythema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, musculoskeletal pain
General disorders and administration site conditions	
Very common	Injection and infusion site reactions
Common	Fatigue, malaise

* The frequency of allergic reactions presented is based on adverse reactions that occurred in the oncology studies (679 patients). Events included one or more of the following: urticaria (n = 2), periorbital swelling (n = 2), dyspnoea (n = 1) or hypoxia (n = 1). These events were generally mild or moderate and occurred within approximately 30 min after Plerixafor administration.

** From post-marketing experience
The adverse reactions reported in patients with lymphoma and multiple myeloma who received Plerixafor in the controlled Phase III studies and uncontrolled studies, including a Phase II study of Plerixafor as monotherapy for haematopoietic stem cell mobilisation, are similar. No significant differences in the incidence of adverse reactions were observed for oncology patients by disease, age, or gender.

Description of selected adverse reactions
Myocardial infarction
In clinical studies, 7 of 679 oncology patients experienced myocardial infarctions after haematopoietic stem cell mobilisation with plerixafor and G-CSF. All events occurred at least 14 days after last Plerixafor administration. Additionally, two female oncology patients in the compassionate use programme experienced myocardial infarction following haematopoietic stem cell mobilisation with plerixafor and G-CSF. One of these events occurred 4 days after last Plerixafor administration. Lack of temporal relationship in 8 of 9 patients coupled with the risk profile of patients with myocardial infarction does not suggest Plerixafor confers an independent risk for myocardial infarction in patients who also receive G-CSF.

Hyperleukocytosis
White blood cell counts of 100 x 10^9/L or greater were observed, on the day prior to or any day of apheresis, in 7% patients receiving Plerixafor and in 1% patients receiving placebo in the Phase III studies. No complications or clinical symptoms of leukostasis were observed.

Vasovagal reactions
In Plerixafor 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 Plerixafor administration.

Gastrointestinal disorders
In Plerixafor clinical studies of oncology patients, there have been rare reports of severe gastrointestinal events, including diarrhoea, nausea, vomiting, and abdominal pain.

Paraesthesia
Paraesthesia is commonly observed in oncology patients undergoing autologous transplantation following multiple disease interventions. In the placebo-controlled Phase III studies, the incidence of paraesthesia was 20.6% and 21.2% in the plerixafor and placebo groups, respectively.

Elderly patients
In the two placebo-controlled clinical studies of plerixafor, 24% of patients were ≥ 65 years old. No notable differences in the incidence of adverse reactions were observed in these elderly patients when compared with younger ones.

Paediatric population
Thirty patients were treated with 0.24 mg/kg of plerixafor in an open label, multicenter, controlled study (DFI 12860). The safety profile in this paediatric study was consistent with what has been observed in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

SYMPTOMS AND TREATMENT OF OVERDOSE
No case of overdose has been reported. Based on limited data at doses above the recommended dose and up to 0.48 mg/kg the frequency of gastrointestinal disorders, vasovagal reactions, orthostatic hypotension, and/or syncope may be higher.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Plerixafor may influence the ability to drive and use machines. Some patients have experienced dizziness, fatigue or vasovagal reactions; therefore caution is advised when driving or operating machines.

INSTRUCTION FOR USE
Plerixafor is for subcutaneous injection. Each vial is intended for single use only.
Vials should be inspected visually prior to administration and not used if there is particulate matter or discolouration. Since Plerixafor is supplied as a sterile, preservative-free formulation, aseptic technique should be followed when transferring the contents of the vial to a suitable syringe for subcutaneous administration.

PACKAGING AVAILABLE:
MOZIFOR: 1 vial (20mg/ml) x1.2ml

LIST OF EXCIPIENTS:
Sodium Chloride
Sodium Hydroxide
Hydrochloric Acid
Water for Injection

INCOMPATIBILITIES
In the absence of compatibility studies, Mozifor must not be mixed with other medicinal products.

STORAGE CONDITION
Store below 30°C

After opening
From a microbiological point of view 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.

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HETERO LABS LIMITED, Unit-VI,
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DATE OF REVISION
17 January 2025

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