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Summary of Product Characteristics
PLERISTEM

Rx **Plerixafor 20 mg/mL Solution for Injection**

1. Name of the medicinal product

Plerixafor 20 mg/mL Solution for Injection.

2. Qualitative and quantitative composition

Each mL contains Plerixafor 20 mg.

Each vial contains 24 mg Plerixafor in 1.2 ml solution

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for injection.

Clear, colourless to pale yellow solution, essentially free from visible particles filled in clear glass vial stoppered with gray rubber stopper and sealed with aluminium seal having parrot green colour PP disc.

4. Clinical particulars

4.1 Therapeutic indications

Adult patients

Plerixafor 20 mg/mL Solution for Injection 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)

Plerixafor 20 mg/mL Solution for Injection 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.

4.2 Posology and method of administration

Plerixafor 20 mg/mL Solution for Injection 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:

- 20 mg 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, a 1 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 20 mg/mL Solution for Injection 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 20 mg/mL Solution for Injection, 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 20 mg/mL Solution for Injection in children (1 to less than 18 years) were studied in an open label, multicenter, 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.

Method of administration

Plerixafor 20 mg/mL Solution for Injection 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 20 mg/mL Solution for Injection 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Tumour cell mobilisation in patients with lymphoma and multiple myeloma

When Plerixafor 20 mg/mL Solution for Injection 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. In case tumour cells are mobilised, the number of tumour cells mobilised is not increased upon Plerixafor 20 mg/mL Solution for Injection plus G-CSF compared to G-CSF alone.

Tumour cell mobilisation in leukaemia patients

Plerixafor 20 mg/mL Solution for Injection 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 Plerixafor 20 mg/mL Solution for Injection in conjunction with G-CSF increases circulating leukocytes as well as haematopoietic stem cell populations. White blood cell counts should be monitored during Plerixafor 20 mg/mL Solution for Injection therapy. Clinical judgment should be exercised when administering Plerixafor 20 mg/mL Solution for Injection 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 Plerixafor 20 mg/mL Solution for Injection. Platelet counts should be monitored in all patients receiving Plerixafor 20 mg/mL Solution for Injection and undergoing apheresis.

Allergic reactions

Plerixafor 20 mg/mL Solution for Injection has been uncommonly associated with potential systemic reactions related to subcutaneous injection such as urticaria, periorbital swelling, dyspnoea, or hypoxia. 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

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 Plerixafor 20 mg/mL Solution for Injection in conjunction with growth factor G-CSF. Individuals receiving Plerixafor 20 mg/mL Solution for Injection in conjunction with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity.

Sodium

Plerixafor 20 mg/mL Solution for Injection contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ,sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. 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 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.

4.6 Fertility, 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. Teratogenicity has been observed in animals. Plerixafor 20 mg/mL Solution for Injection should not be used during pregnancy unless the clinical condition of the woman requires treatment with plerixafor.

Breast-feeding

It is unknown whether plerixafor is excreted in human milk. A risk to the suckling child cannot be excluded. Breastfeeding should be discontinued during treatment with Plerixafor 20 mg/mL Solution for Injection.

Fertility

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

4.7 Effects on ability to drive and use machines

Plerixafor 20 mg/mL Solution for Injection 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.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions that occurred more frequently with Plerixafor 20 mg/mL Solution for Injection and G-CSF than placebo and G-CSF and were reported as related in ≥1% of the patients who received Plerixafor 20 mg/mL Solution for Injection, 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; common; uncommon; rare; very rare; not known (cannot be estimated from the available data).

Table 1. Adverse reactions occurring more frequently with Plerixafor 20 mg/mL Solution for Injection than placebo and considered related to Plerixafor 20 mg/mL Solution for Injection during mobilisation and apheresis

Blood and lymphatic system disorders	
Not known	Splenomegaly, splenic rupture (see section 4.4)**
Immune system disorders	
Uncommon	Allergic reaction* Anaphylactic reactions, including anaphylactic shock (see section 4.4)**
Psychiatric disorders	
Common	Insomnia
Uncommon	Abnormal dreams, nightmares

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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. Events included one or more of the following: urticaria, periorbital swelling, dyspnoea, or hypoxia. 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 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

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 20 mg/ mL Solution for Injection administration.

Hyperleukocytosis

White blood cell counts of 100 x 10⁹/L or greater were observed, on the day prior to or any day of apheresis, in 7% patients receiving Plerixafor 20 mg/mL Solution for Injection and in 1% patients receiving placebo. No complications or clinical symptoms of leukostasis were observed.

Vasovagal reactions

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 20 mg/mL Solution for Injection administration.

Gastrointestinal disorders

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. The incidence of paraesthesia was 20.6% and 21.2% in the plerixafor and placebo groups, respectively.

Elderly patients

No notable differences in the incidence of adverse reactions were observed in these elderly patients when compared with younger ones.

Paediatric population

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.

4.9 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunostimulants; ATC code: L03AX16

Mechanism of action

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

Peak mobilisation of CD34+ cells was observed from 6 to 9 hours after administration. In pharmacodynamic studies 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.

5.2 Pharmacokinetic properties

Absorption

Plerixafor is rapidly absorbed following subcutaneous injection, reaching peak concentrations in approximately 30-60 minutes (t_{max}). Following subcutaneous administration of a 0.24 mg/kg after receiving 4-days of G-CSF pre-treatment, the maximal plasma concentration (C_{max}) 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 metabolised 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). Plerixafor does not induce CYP1A2, CYP2B6, and CYP3A4 enzymes. These 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. Approximately 70% of the dose was excreted unchanged in urine during the first 24 hours following administration. The elimination half-life (t_{1/2}) in plasma is 3-5 hours. Plerixafor did not act as a substrate or inhibitor of P-glycoprotein.

Special populations

Renal impairment

Clearance was reduced with varying degrees of renal impairment and was positively correlated with creatinine clearance (CrCl). Mean values of AUC_{0-24h} of plerixafor in 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 normal renal function (5070 ng·hr/ml). Renal impairment had no effect on C_{max}.

Gender

No effect of gender on pharmacokinetics of plerixafor.

Elderly

No effect of age on pharmacokinetics of plerixafor.

Paediatric population

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 (AUC_{0-24h}) is lower in paediatric patients aged 2 to <6 years (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). According to population pharmacokinetic modelling, the plerixafor mean exposures (AUC_{0-24h}) 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. Mobilization of PB CD34+ count has been observed.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Chloride
Sodium hydroxide
Hydrochloric acid, Concentrated
Water for Injection

6.2 Incompatibilities

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

6.3 Shelf life

24 Months

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.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Clear tubular type-I glass vial of 4 mL volume, closed with a 13 mm gray chlorobutyl rubber stopper and sealed with a 13 mm aluminium seal having a parrot green coloured polypropylene disc. Pack size of 1 vial (1.2 mL) per box with one product information leaflet.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufactured by:

Eugia Pharma Specialities Limited,
Survey No. 550, 551 & 552, Kolthur Village,
Shamirpet Mandal, Medchal-Malkajgiri District,
Telangana 500101, India.

8. Product Registration Holder in Malaysia

Synerrv Sdn Bhd,
SO-29-2, Menara 1, KL ECO City,
Jalan Bangsar, KG Haji Abdullah Hukum,
59200 Kuala Lumpur Malaysia.

9. Date of revision of the text

August 2022