Gador
Devoted to People's Health

REVIXIL® 20
PLERIXAFOR 20 mg/ml

POM
Made in Argentina

Injectable Solution

Every milliliter of injectable solution contains:
Plerixafor ..... 20.000 mg
Excipients: sodium chloride, concentrated hydrochloric acid and water for injection q.s.f ..... 1.000 ml

THERAPEUTIC ACTION
Mobilizer of haematopoietic stem cells.

INDICATIONS
In patients with non-Hodgkin lymphoma and multiple myeloma, plerixafor is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize haematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation.

PHARMACOLOGICAL ACTION
Plerixafor acts by inhibiting the CXCR4 chemokine receptor, blocking binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α). This receptor and ligand play an important role in the circulation and storage of haematopoietic stem cells in the bone marrow compartment. CXCR4 can help bind stem cells to the marrow matrix, whether through the SDF-1α ligand or the induction of other adhesion molecules. Plerixafor induces leukocytosis and elevations in circulating haematopoietic stem cells. Mobilized CD34+ cells can be engrafted with repopulating capacity up to one year after initiating treatment with plerixafor.
Peak mobilization of CD34+ cells, demonstrated in pharmacodynamic studies with plerixafor, takes place from 6 to 9 hours after administration. This peak is observed from 10 to 14 hours when plerixafor is administered in combination with G-CSF.

PHARMACOKINETICS
Plerixafor exhibits linear kinetics in the dose range between 0.04 mg/kg and 0.24 mg/kg. Similar pharmacokinetics parameters were observed in studies in healthy subjects who received plerixafor and non-Hodgkin lymphoma and multiple myeloma patients who received plerixafor in combination with G-CSF. Posolgy adjusted per mg/kg causes an increase in the area under the curve vs. time (AUC_{0-24}) as body weight increases.
Following subcutaneous injection, peak plasma concentrations are reached in 30-60 minutes. Its apparent distribution takes place largely in the extravascular space, although not exclusively. It is bound to plasma proteins up to 58%. In vitro studies show that plerixafor is not metabolized and does not inhibit cytochrome P450 enzymes; therefore, it is unlikely to have P450-dependent drug interactions. Plerixafor is eliminated in urine. In healthy subjects with normal renal function, 70% is excreted as the original drug during the first 24 hours.
Plerixafor clearance is reduced in subjects with renal impairment and is positively correlated with the clearance of creatinine (CL_{CR}). In patients with moderate (CL_{CR} 31-50 mL/min) to severe (CL_{CR} < 31 mL/min) renal impairment, a significant increase in (AUC_{0-24}) was observed compared to patients with CL_{CR} > 50 mL/min. This supports a one-third dose reduction in patients with moderate to severe renal impairment. Renal impairment has no effect on C_{max}.
The effects of coadministration of plerixafor with other drugs that are eliminated by the kidneys or that affect renal function have not been evaluated.
No race, gender, or age differences have been observed in pharmacokinetic parameters.

POSOLOGY AND ADMINISTRATION
Each **REVIXIL®** vial should be inspected visually and should not be used if there is particulate matter or discoloration. Each vial is intended for single use only, and any unused solution should be discarded.
Treatment with **REVIXIL®** may be initiated after the patient has received G-CSF once daily for 4 days. Treatment can last up to 4 consecutive days, and the dose of **REVIXIL®** should be administered at least 11 hours prior to apheresis.
The recommended dose of **REVIXIL®** is 0.24 mg/kg body weight/day, administered by subcutaneous injection. Each vial delivers 1.2 mL of 20 mg/mL solution, therefore the volume to be administered should be calculated using the following formula:
0.012 x patient's body weight (kg) = volume to be administered (in mL)
Since the drug's AUC_{0-24} increases with increasing body weight, plerixafor dose should not exceed 40 mg/day.
Concomitant medications
Morning doses of G-CSF 10 µg/kg are administered for 4 days prior to the first evening dose of **REVIXIL®** and on each day before the apheresis.
Renal Impairment
In patients with moderate and severe renal impairment (CL_{CR} ≤ 50 mL/min), the dose should be reduced by one-third to 0.16 mg/kg. If CL_{CR} is ≤ 50 mL/min, the dose should not exceed 27 mg/day, as the mg/kg-based dosage results in increased plerixafor AUC_{0-24} with increasing body weight.
There is no information available to make posology recommendations for patients on haemodialysis.

CONTRAINDICATIONS
Known hypersensitivity to the active ingredient or to the components of **REVIXIL®**.

WARNINGS AND PRECAUTIONS
Tumor cell mobilization in leukemia patients
REVIXIL® may also cause mobilization of leukemic cells and subsequent contamination of the apheresis product. Therefore, **REVIXIL®** is not intended for haematopoietic stem cell mobilization and harvest in patients with leukemia.
Haematological effects
Leukocytosis. White blood cell counts should be monitored, as administration in conjunction with G-CSF increases circulating leukocytes as well as haematopoietic stem cell populations. Clinical assessment should be carried out when administering **REVIXIL®** to patients with neutrophil counts above 50,000 cells/mcL.
Thrombocytopenia. Thrombocytopenia has been observed in patients receiving **REVIXIL®**, therefore platelet counts should be monitored in these patients who subsequently undergo apheresis.
Potential for tumor cell mobilization
When **REVIXIL®** is used in combination with G-CSF, tumor cells may be released from the bone marrow and subsequently collected in apheresis. The effect of potential reinfusion of tumor cells has not been studied yet.
Splenic enlargement and potential for rupture
Higher spleen weights and extramedullary hematopoiesis were observed following prolonged (up to 4 weeks) plerixafor administration in rats at doses 4 times the recommended human dose. This effect of plerixafor has not been evaluated in clinical studies. Therefore, spleen integrity should be evaluated in patients receiving **REVIXIL®** in combination with G-CSF who report left upper abdominal pain or scapular or shoulder pain.
Drug interactions
Plerixafor is not a substrate, inhibitor or inducer of cytochrome P450 isozymes in *in vitro* studies. Therefore, *in vivo* drug interactions involving these enzymes are unlikely.
Carcinogenesis, mutagenesis, and impairment of fertility
Carcinogenicity studies with plerixafor have not been conducted.
No genotoxicity has been observed in Ames tests, in chromosome aberration tests in Chinese hamster ovary cells, or in *in vivo* rat bone marrow micronucleus tests.
Reproductive toxicity studies have not been conducted. No signs of toxicity were observed in male or female reproductive organs in 28-day repeated dose toxicity studies in rats.
Pregnancy
Pregnancy Category D.
Plerixafor has exhibited teratogenicity in rats. Embryofetal toxicity occurs at a dose approximately 10 times the recommended human dose. There are no adequate and controlled studies on the use of plerixafor in pregnant women.
REVIXIL® may cause fetal damage when administered to pregnant women. Therefore, women of childbearing potential should be advised to prevent pregnancy during treatment with **REVIXIL®**. **REVIXIL®** should be used during pregnancy only when the potential benefit to the mother outweighs the potential risk to the fetus.
Nursing Mothers
It is not yet 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 to **REVIXIL®** in nursing infants, the treating physician should decide whether to discontinue breastfeeding or to discontinue the drug.
Pediatrics
The safety and efficacy of plerixafor in the pediatric population have not been established yet.
Geriatrics
No differences in safety or effectiveness of the drug have been observed between the elderly and younger patients. No dose modifications are necessary in elderly patients with normal renal function. However, care should be taken in dose due to the potential decreased renal function in these patients. In this case, the dose should be adjusted when CL_{CR} ≤ 50 mL/min.

ADVERSE REACTIONS
Adverse reactions classified by system and frequency are listed below.
Common reactions are those with an incidence over 10%, *occasional* reactions have an incidence of 1-10%, and *rare* reactions have an incidence under 1%.
General: *Common:* Fatigue. *Occasional:* Discomfort, dry mouth.
Local: *Common:* Injection site reactions such as inflammation, erythema, induration, hematoma, irritation, hemorrhage, pruritus, pain, paresthesia, urticaria, swelling, and rash.
Gastrointestinal: *Common:* Nausea, vomiting, diarrhea. *Occasional:* Flatulence, abdominal pain, stomach discomfort, abdominal distention, constipation, dyspepsia.
Neurological: *Common:* Headache, dizziness. *Occasional:* Insomnia, oral hypoaesthesia.
Dermatological: *Common:* Erythema, hyperhidrosis. *Rare:* Urticaria, periorbital swelling.
Breathing: *Rare:* Dyspnea, hypoxia.
Cardiovascular: *Rare:* vasovagal reactions, orthostatic hypotension, syncope.
Musculoskeletal: *Common:* Arthralgia. *Occasional:* Musculoskeletal pain.

OVERDOSE
The frequency of vasovagal reactions, orthostatic hypotension and/or syncope, and gastrointestinal disorders may be higher at doses above the subcutaneous dose of 0.24 mg/kg.
"In case of an overdose, go to the nearest hospital or contact a poison control center:

FORMULATION
Package with 1vial containing 1.2 ml of injectable solution.

CONSERVATION AND STORAGE
Keeps in its original package at room temperature (15ºC - 30ºC).

"This medicine should only be used under medical prescription and surveillance and cannot be repeated without a new medical prescription."

"Keep all medicines out of the reach of children"

INFORMATION FOR PATIENTS

- Communication to the patient:
Inform the patient about the signs and symptoms of potential systemic reactions after injection, such as urticaria, dyspnea, hypoxia, and periorbital swelling.
REVIXIL® can cause gastrointestinal disorders: diarrhea, nausea, vomiting, abdominal pain, flatulence. Tell patients how to manage and prevent these events, and to report any serious post-injection events to their doctor.
Patients with childbearing potential should use effective contraceptive methods during treatment with **REVIXIL®**.
- Communication to the doctor:
During or immediately after **REVIXIL®** injection, vasovagal reactions such as orthostatic hypotension and syncope may occur. These should be reported immediately to the doctor.
Any event of pruritus, exanthema or reaction at the injection site should be reported to the doctor, since these signs can be treated with over-the-counter drugs.

Gador

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Recyclable Materials