1.3.1.1 Professional Information for Medicines for Human Use (clean)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZAPLEXET Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZAPLEXET Solution for injection:

Each 1,2 mL vial contains 24,0 mg plerixafor (20 mg/mL)

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Subcutaneous injection

Clear, colourless to pale yellow solution, essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ZAPLEXET 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).

4.2. Posology and method of administration

Posology

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

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

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

The patient's actual body weight will be used to calculate the volume of ZAPLEXET 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, ZAPLEXET dose has been calculated based on actual body weight in patients upto 175 % of ideal body weight. ZAPLEXET 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 ZAPLEXET should be obtained within 1 week of the first dose of [PRODUCT NAME].

Recommended concomitant medications:

In pivotal clinical studies supporting the use of [PRODUCT NAME], 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 ZAPLEXET and on each morning prior to apheresis.

Special Populations

Patients with renal impairment:

Patients with moderate and severe renal insufficiency (creatinine clearance (CrCl) ≤ 50 mL/min) should have their dose of ZAPLEXET 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.

Elderly patients:

In the two placebo-controlled clinical studies of [PRODUCT NAME], 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 [PRODUCT NAME], 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.

Paediatric population:

The safety and efficacy of ZAPLEXET in paediatric patients has not been established in controlled clinical studies.

Method of administration

ZAPLEXET is administered as a subcutaneous injection.

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

4.3. Contraindications

Hypersensitivity to plerixafor or to any of the ingredients of ZAPLEXET (see section 6.1).

Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

Tumour cell mobilisation in leukaemia patients

In a compassionate use programme, ZAPLEXET 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, [PRODUCT NAMR] may cause mobilisation of leukaemic cells and subsequent contamination of the apheresis product. Therefore, ZAPLEXET is not recommended for haematopoietic stem cell mobilisation and harvest in patients with leukaemia.

Hematologic effects

Leukocytosis: Administration of ZAPLEXET in conjunction with G-CSF increases circulating leukocytes as well as HSC populations. White blood cell counts should be monitored during ZAPLEXET use. Clinical judgment should be exercised when administering ZAPLEXET 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 [PRODUCT NAME]. Platelet counts should be monitored in all patients who receive ZAPLEXET and then undergo apheresis.

Potential for tumour cell mobilisation in lymphoma and multiple myeloma patients

When ZAPLEXET 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 [PRODUCT NAME].

Systemic reactions

In ZAPLEXET oncology clinical studies, less than 1 % of patients experienced mild or moderate systemic reactions within approximately 30 minutes after ZAPLEXET 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 ZAPLEXET oncology and healthy volunteer clinical studies, less than 1 % of subjects experienced vasovagal reactions (orthostatic hypotension and/or syncope) following SC administration of ZAPLEXET doses ≤ 0,24 mg/kg. The majority of these events occurred within 1 hour of ZAPLEXET 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 ZAPLEXET on spleen size in patients has not been specifically evaluated in clinical studies. The possibility that ZAPLEXET 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 ZAPLEXET in conjunction with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity.

Useful laboratory tests for monitoring patients

White blood cell and platelet counts should be monitored during ZAPLEXET use and apheresis.

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

This medicinal product contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per effervescent tablet, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicines and other forms of interaction

Based on *In vitro*-studies done 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 ZAPLEXET 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

ZAPLEXET is contraindicated during pregnancy. (see section 4.3)

ZAPLEXET 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 [PRODUCT NAME].

If the patient becomes pregnant while taking [PRODUCT NAME], the patient should be informed of the potential hazard to the foetus.

Lactation

It is not known whether plerixafor is excreted in human milk. Patients should not breastfeed their baby whilst on treatment with [PRODUCT NAME]. (see section 4.3).

Fertility

The effects of ZAPLEXET on male and female fertility are not known (see section 5.3).

4.7. Effects on ability to drive and use machines

ZAPLEXET 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

a. *Tabulated list of adverse reactions*

Table 1

MedDRA System Organ Class	**Frequency**	**MedDRA preferred term**
Blood and lymphatic system disorders	Frequency unknown	Splenomegaly, splenic rupture
Immune system disorders	Less frequent	Allergic reaction Anaphylactic reactions, including anaphylactic
Psychiatric disorders	Frequent	Insomnia

	Less frequent	Abnormal dreams, nightmares, anticipatory anxiety, anxiety
Nervous system disorders	Frequent	Dizziness, headache
	Less frequent	Dysgeusia
Gastrointestinal disorders	Frequent	Diarrhoea, nausea
	Frequent	Vomiting, abdominal pain, stomach discomfort, dyspepsia, abdominal distention, constipation, flatulence, hypoaesthesia oral, dry mouth
	Less frequent	Abdominal discomfort, eructation, retching, stomatitis
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, erythema
	Less frequent	Cold sweat, ecchymosis, hypoaesthesia facial, night sweats, urticaria, urticaria localised
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, musculoskeletal pain
	Less frequent	Muscular weakness, musculoskeletal stiffness, neck pain
General disorders and administration site conditions	Frequent	Injection and infusion site reactions
	Frequent	Fatigue, malaise
	Less frequent	Asthenia, influenza like illness, irritability
Cardiac disorders	Less frequent	Extrasystoles

Ear and labyrinth disorders	Less frequent	Vertigo
Eye disorders	Less frequent	Eye swelling
Injury, poisoning and procedural complications	Less frequent	Procedural hypertension, procedural nausea
Investigations	Less frequent	Aspartate aminotransferase increased
Metabolism and nutrition disorders	Less frequent	Decreased appetite, hypocalcaemia, hyponatraemia, hypophosphataemia
Renal and urinary disorders	Less frequent	Pollakiuria
Respiratory, thoracic and mediastinal disorders	Less frequent	Sinus congestion
Vascular disorders	Less frequent	Flushing, hot flush, hypotension

The adverse reactions reported in patients with lymphoma and multiple myeloma who received ZAPLEXET in the conducted controlled Phase III studies and uncontrolled studies, including a Phase II study of ZAPLEXET 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.

c.Description of selected adverse reactions

Myocardial infarction

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

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 ZAPLEXET and in 1 % patients receiving placebo in the Phase III studies. No complications or clinical symptoms of leukostasis were observed.

Vasovagal reactions

Based on ZAPLEXET conducted 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 ZAPLEXET administration.

Gastrointestinal disorders

Based on ZAPLEXET conducted 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 ZAPLEXET and placebo groups, respectively.

Elderly patients

Based on the two placebo-controlled conducted clinical studies of [PRODUCT NAME], 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.

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 to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9. Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other immunostimulants; ATC code: L03AX16

Mechanism of 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 conducted placebo-controlled clinical studies in patients with lymphoma and multiple myeloma During that 24-hour period, the first dose of plerixafor 0,24 mg/kg or placebo was administered 10-11 hours prior to apheresis.

In pharmacodynamic studies conducted in healthy volunteers of plerixafor, peak mobilisation of CD34+ cells was observed from 6 to 9 hours after administration. In pharmacodynamic studies conducted 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~~ Based on a study conducted in healthy volunteers at single doses of 0,24 and 0,40 mg/kg, plerixafor had no effects on QT interval, heart rate, PR interval, QRS interval duration, or ECG morphology.

5.2. Pharmacokinetic properties

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 (t_{max}). 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 (C_{max}) and systemic exposure (AUC_{0-24}) 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 *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 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 ($t_{1/2}$) 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

Elderly

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

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 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.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 C_{max}.

Gender

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

Effects of food

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

Preclinical safety data

Carcinogenicity studies with plerixafor have not been conducted. Plerixafor was not genotoxic in an adequate battery of genotoxicity tests.

Plerixafor inhibited tumour growth in in vivo models of non-Hodgkin's lymphoma, glioblastoma, medulloblastoma, and acute lymphoblastic leukaemia when dosed intermittently. An increase of non-Hodgkin's lymphoma growth was noted after a continuous administration of plerixafor for 28 days. The potential risk associated with this effect is expected to be low for the intended short term duration of dosing plerixafor in humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

ZAPLEXET injection contains the following inactive ingredients:

Sodium chloride, Hydrochloric acid, concentrated (pH adjustment), Sodium hydroxide (pH adjustment), Water for injections.

6.2. Incompatibilities

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

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

ZAPLEXET is supplied in a single-use glass vial Tubular Type – I, 4 ml clear with 13 mm neck stoppered with grey rubber stopper and sealed with aluminium seal having parrot green colour PP disc. The vial will be further packed in pre-printed carton with a package leaflet.

ZAPLEXET will be packed as one vial.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

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

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

TBA

9. DATE OF FIRST AUTHORISATION

TBA

10. DATE OF REVISION OF TEXT