SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Plerixafor Seacross 20 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 20 mg plerixafor.

Each vial contains 24 mg plerixafor in 1.2 ml solution.

Excipients with known effect

Each ml contains approximately 5 mg (0.2 mmol) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution, with a pH of 6.0 - 7.5 and an osmolality of 270 - 310 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult patients

Plerixafor Seacross 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 (see section 4.2).

Paediatric patients (1 to less than 18 years)

Plerixafor Seacross 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 (see section 4.2).

4.2 Posology and method of administration

Plerixafor Seacross 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 $\leq$ 83 kg (see section 5.2).
- 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 (see section 5.1).

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 Seacross 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 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 (see section 5.2). 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, multicenter, controlled study (see section 4.8, 5.1, and 5.2).

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 Seacross 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 Seacross 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 (see section 6.3).

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 Seacross 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 Plerixafor Seacross plus G-CSF compared to G-CSF alone.

Tumour cell mobilisation in leukaemia patients

In a compassionate use programme, plerixafor 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 Seacross in conjunction with G-CSF increases circulating leukocytes as well as haematopoietic stem cell populations. White blood cell counts should be monitored during plerixafor therapy. Clinical judgment should be exercised when administering plerixafor to patients with peripheral blood neutrophil counts above 50×10^9/L.

Thrombocytopenia

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

Allergic reactions

Plerixafor has been uncommonly associated with potential systemic reactions related to subcutaneous injection such as urticaria, periorbital swelling, dyspnoea, or hypoxia (see section 4.8). 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 (see section 4.8). 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 plerixafor in conjunction with growth factor G-CSF. Individuals receiving plerixafor 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 Seacross 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. *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.

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. Studies in animals have shown teratogenicity (see section 5.3). Plerixafor 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. Breast-feeding should be discontinued during treatment with plerixafor.

Fertility

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

4.7 Effects on ability to drive and use machines

Plerixafor Seacross 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

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 (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
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) (see section 5.1).

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 listed in Yellow Card Scheme – Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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.

In order to compare the pharmacokinetics and pharmacodynamics of plerixafor following 0.24 mg/kg based and fixed (20 mg) doses, a trial was conducted in adult patients with NHL (N=61) who were treated with 0.24 mg/kg or 20 mg of plerixafor. The trial was conducted in patients weighing 70 kg or less (median: 63.7 kg, min: 34.2 kg, max: 70 kg). The fixed 20 mg dose showed 1.43-fold higher exposure ($AUC_{0\text{-}10h}$) than the 0.24 mg/kg dose (Table 2). The fixed 20 mg dose also showed numerically higher response rate (5.2% [60.0% vs 54.8%] based on the local lab data and 11.7% [63.3% vs 51.6%] based on the central lab data) in attaining the target of $\geq 5 \times 10^6$ CD34+ cells/kg than the mg/kg-based dose. The median time to reach $\geq 5 \times 10^6$ CD34+ cells/kg was 3 days for both treatment groups, and the safety profile between the groups was similar. Body weight of 83 kg was selected as the cut-off point to transition patients from fixed to weight based dosing (83 kg x 0.24 mg = 19.92 mg/kg).

Table 2. Systemic Exposure ($AUC_{0\text{-}10h}$) comparisons of fixed and weight based regimens

Regimen	**Geometric Mean AUC**
Fixed 20 mg (n=30)	3991.2
0.24 mg/kg (n=31)	2792.7
Ratio (90% CI)	1.43 (1.32, 1.54)

Clinical efficacy and safety

In two Phase III randomised-controlled studies patients with non-Hodgkin's lymphoma or multiple myeloma received plerixafor 0.24 mg/kg or placebo on each evening prior to apheresis. 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. Optimal (5 or 6 x 10^6 cells/kg) and minimal (2 x 10^6 cells/kg) numbers of CD34+ cells/kg within a given number of days, as well as the primary composite endpoints which incorporated successful engraftment are presented in Tables 3 and 5; the proportion of patients reaching optimal numbers of CD34+ cells/kg by apheresis day are presented in Tables 4 and 6.

Table 3. Study AMD3100-3101 efficacy results - CD34+ cell mobilisation in non-Hodgkin's lymphoma patients

Efficacy endpoint[b]	Plerixafor and G-CSF (n = 150)	Placebo and G-CSF (n = 148)	p-value[a]
Patients achieving $\geq 5 \times 10^6$ cells/kg in ≤ 4 apheresis days and successful engraftment	86 (57.3%)	28 (18.9%)	< 0.001
Patients achieving $\geq 2 \times 10^6$ cells/kg in ≤ 4 apheresis days and successful engraftment	126 (84.0%)	64 (43.2%)	< 0.001

[a] p-value calculated using Pearson's Chi-Squared test

[b] Statistically significantly more patients achieved $\geq 5 \times 10^6$ cells/kg in ≤ 4 apheresis days with plerixafor and G-CSF (n=89; 59.3%) than with placebo and G-CSF (n=29; 19.6%), $p < 0.001$; statistically significantly more patients achieved $\geq 2 \times 10^6$ cells/kg in ≤ 4 apheresis days with plerixafor and G-CSF (n=130; 86.7%) than with placebo and G-CSF (n=70; 47.3%), $p < 0.001$.

Table 4. Study AMD3100-3101 – Proportion of patients who achieved $\geq 5 \times 10^6$ CD34+ cells/kg by apheresis day in non-Hodgkin's lymphoma patients

Days	Proportion[a] in Plerixafor and G-CSF (n=147[b])	Proportion[a] in Placebo and G-CSF (n=142[b])
1	27.9%	4.2%
2	49.1%	14.2%
3	57.7%	21.6%
4	65.6%	24.2%

[a] Percents determined by Kaplan Meier method

[b] n includes all patients who received at least one day of apheresis

Table 5. Study AMD3100-3102 efficacy results – CD34+ cell mobilisation in multiple myeloma patients

Efficacy endpoint[b] [a] p	Plerixafor and G-CSF (n = 148)	Placebo and G-CSF (n = 154)	p-value[a]
Patients achieving $\geq 6 \times 10^6$ cells/kg in ≤ 2 apheresis days and successful engraftment	104 (70.3%)	53 (34.4%)	< 0.001

[a] p-value calculated using Cochran-Mantel-Haenszel statistic blocked by baseline platelet count

[b] Statistically significantly more patients achieved $\geq 6 \times 10^6$ cells/kg in ≤ 2 apheresis days with plerixafor and G-CSF (n=106; 71.6%) than with placebo and G-CSF (n=53; 34.4%), $p < 0.001$; statistically significantly more patients achieved $\geq 6 \times 10^6$ cells/kg in ≤ 4 apheresis days with plerixafor and G-CSF (n=112; 75.7%) than with placebo and G-CSF (n=79; 51.3%), $p < 0.001$; statistically significantly more patients achieved $\geq 2 \times 10^6$ cells/kg in ≤ 4 apheresis days with plerixafor and G-CSF (n=141; 95.3%) than with placebo and G-CSF (n=136; 88.3%), p=0.031.

Table 6. Study AMD3100-3102 – Proportion of patients who achieved $\geq 6 \times 10^6$ CD34+ cells/kg by apheresis day in multiple myeloma patients

Days	Proportion[a] in Plerixafor and G-CSF (n=144[b])	Proportion[a] in Placebo and G-CSF (n=150[b])
1	54.2%	17.3%
2	77.9%	35.3%
3	86.8%	48.9%
4	86.8%	55.9%

[a] Percents determined by Kaplan Meier method
[b] n includes all patients who received at least one day of apheresis

Rescue patients

In study AMD3100-3101, 62 patients (10 in the plerixafor + G-CSF group and 52 in the placebo + G- CSF group), who could not mobilise sufficient numbers of CD34+ cells and thus could not proceed to transplantation, entered into an open-label Rescue procedure with plerixafor and G-CSF. Of these patients, 55 % (34 out of 62) mobilised $\geq 2 \times 10^6$/kg CD34+ cells and had successful engraftment. In study AMD3100-3102, 7 patients (all from the placebo + G-CSF group) entered the Rescue procedure. Of these patients, 100% (7 out of 7) mobilised $\geq 2 \times 10^6$/kg CD34+ cells and had successful engraftment.

The dose of haematopoietic stem cells used for each transplant was determined by the investigator and all haematopoietic stem cells that were collected were not necessarily transplanted. For transplanted patients in the Phase III studies, median time to neutrophil engraftment (10-11 days), median time to platelet engraftment (18-20 days) and graft durability up to 12 months post-transplantation were similar across the plerixafor and placebo groups.

Mobilisation and engraftment data from supportive Phase II studies (plerixafor 0.24 mg/kg dosed on the evening or morning prior to apheresis) in patients with non-Hodgkin's lymphoma, Hodgkin's disease, or multiple myeloma were similar to those data for the Phase III studies.

In the placebo-controlled studies, fold increase in peripheral blood CD34+ cell count (cells/μl) over the 24-hour period from the day prior to the first apheresis to just before the first apheresis was evaluated (Table 7). 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 7. 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	6.1 (5.4)	1.4	1.9 (1.5)
AMD3100-3102	4.8	6.4 (6.8)	1.7	2.4 (7.3)

Paediatric population

The efficacy and safety of plerixafor were evaluated in an open label, multi-center, controlled study in paediatric patients with solid tumors (including neuroblastoma, sarcoma, Ewing sarcoma) or lymphoma who were eligible for autologous hematopoietic stem cell transplantation (DFI12860). Patients with leukemia, persistent high percentage marrow involvement prior to mobilization, or previous stem cell transplantation were excluded.

Forty-five paediatric patients (1 to less than 18 years) were randomised, 2:1, using 0.24 mg/kg of plerixafor plus standard mobilisation (G-CSF plus or minus chemotherapy) versus control (standard mobilisation alone). Median age was 5.3 years (min: max 1:18) in the plerixafor arm versus 4.7 years (min:max 1:17) in the control arm.

Only one patient aged less than 2 years old was randomized to the plerixafor treatment arm. There was an imbalance between treatment arms in peripheral blood CD34+ counts on the day prior to first apheresis (i.e. prior to administration of plerixafor), with less circulating PB CD34+ in the plerixafor arm. The median PB CD34+ cell counts at baseline were 15 cells/μl in the plerixafor arm versus 35 cells/μl in control arm. The primary analysis showed that 80% of patients in the plerixafor arm experienced at least a doubling of the PB CD34+ count, observed from the morning of the day preceding the first planned apheresis to the morning prior to apheresis, versus, 28.6 % of patients in the control arm (p=0.0019). The median increase in PB CD34+ cell counts from baseline to the day of apheresis was by 3.2 fold in the plerixafor arm versus by 1.4 fold in the control arm.

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 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 ($t_{1/2}$) 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

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.

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 (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). Based on population pharmacokinetic modeling, 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. However, mobilization of PB CD34+ count was observed in stage 2 of the trial.

5.3 Preclinical safety data

The results from single dose subcutaneous studies in rats and mice showed plerixafor can induce transient but severe neuromuscular effects (uncoordinated movement), sedative-like effects (hypoactivity), dyspnoea, ventral or lateral recumbency, and/or muscle spasms. Additional effects of plerixafor consistently noted in repeated dose animal studies included increased levels of circulating white blood cells and increased urinary excretion of calcium and magnesium in rats and dogs, slightly higher spleen weights in rats, and diarrhoea and tachycardia in dogs. Histopathology findings of extramedullary haematopoiesis were observed in the liver and spleen of rats and/or dogs. One or more of these findings were usually observed at systemic exposures in the same order of magnitude or slightly higher than the human clinical exposure.

The results of the dose range-finding study in juvenile miniature pigs and the range-finding and definitive studies in juvenile rats were similar to those observed in adult mice, rats, and dogs. Exposure margins in the juvenile rat study at the maximum tolerated dose (MTD) were ≥18 fold when compared with the highest clinical paediatric dose in children up to 18 years of age.

An *in vitro* general receptor activity screen showed that plerixafor, at a concentration (5 µg/ml) several fold higher than the maximum human systemic level, has moderate or strong binding affinity for a number of different receptors predominantly located on pre-synaptic nerve endings in the central nervous system (CNS) and/or the peripheral nervous system (PNS) (N-type calcium channel, potassium channel SK_{CA}, histamine H_3, acetylcholine muscarinic M_1 and M_2, adrenergic $\alpha1_B$ and $\alpha2_C$, neuropeptide Y/Y_1 and glutamate NMDA polyamine receptors). The clinical relevance of these findings is not known.

Safety pharmacology studies with intravenously administered plerixafor in rats showed respiratory and cardiac depressant effects at systemic exposure slightly above the human clinical exposure, whilst subcutaneous administration elicited respiratory and cardiovascular effects only at higher systemic levels.

SDF-1α and CXCR4 play major roles in embryo-foetal development. Plerixafor has been shown to cause increased resorptions, decreased foetal weights, retarded skeletal development and increased foetal abnormalities in rats and rabbits. Data from animal models also suggest modulation of foetal haematopoiesis, vascularisation, and cerebellar development by SDF-1α and CXCR4. Systemic exposure at No Observed Adverse Effect Level for teratogenic effects in rats and rabbits was of the same magnitude or lower as found at therapeutic doses in patients. This teratogenic potential is likely due to its pharmacodynamic mechanism of action.

In rat distribution studies concentrations of radiolabelled plerixafor was detected in reproductive organs (testes, ovaria, uterus) two weeks after single or 7 daily repeated doses in males and after 7 daily repeated doses in females. The elimination rate from tissues was slow.

The potential effects of plerixafor on male fertility and postnatal development have not been evaluated in non-clinical studies.

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

Sodium chloride

Hydrochloric acid (pH adjustment)

Sodium hydroxide (pH adjustment)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

5 years

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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear type I glass 2 ml vial with a chlorobutyl rubber stopper and aluminium seal with a plastic flip-off cap. Each vial contains 1.2 ml solution.

Pack size of 1 vial.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Seacross Pharmaceuticals Limited

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London EC1A 2AY

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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