Swedish Orphan Biovitrum Ltd
1 Fordham House Court, Fordham House Estate, Newmarket Road,
Cambridgeshire, CB7 5LL
Telephone: +44 (0)1638 722 380
Fax: +44 (0) 1638 723 167
WWW: http://www.sobi.com
Medical Information Direct Line: + 44 (0) 1638 722 380
Medical Information e-mail: sobi@professionalinformation.co.uk
Customer Care direct line: +44 (0) 1638 722 380
Medical Information Fax: + 44 (0) 1638 723 167

Summary of Product Characteristics last updated on the eMC: 03/07/2013

Kepivance 6.25 mg powder for solution for injection

1. Name of the medicinal product

Kepivance 6.25 mg powder for solution for injection

2. Qualitative and quantitative composition

Each vial contains 6.25 mg of palifermin.

Palifermin is a human keratinocyte growth factor (KGF), produced by recombinant DNA technology in *Escherichia coli*.

Once reconstituted, Kepivance contains 5 mg/ml of palifermin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection (powder for injection).

White lyophilised powder.

4. Clinical particulars

4.1 Therapeutic indications

Kepivance is indicated to decrease the incidence, duration and severity of oral mucositis in adult patients with haematological malignancies receiving myeloablative radiochemotherapy associated with a high incidence of severe mucositis and requiring autologous haematopoietic stem cell support.

4.2 Posology and method of administration

Kepivance treatment should be supervised by a physician experienced in the use of anti-cancer therapy.

Posology

Adults

The recommended dosage of Kepivance is 60 micrograms/kg/day, administered as an intravenous bolus injection for three consecutive days before and three consecutive days after myeloablative therapy for a total of six doses.

Pre- myeloablative therapy:

The first three doses should be administered prior to myeloablative therapy, with the third dose 24 to 48 hours before myeloablative therapy.

Post- myeloablative therapy:

The last three doses should be administered post myeloablative therapy; the first of these doses should be administered after, but on the same day of haematopoietic stem cell infusion and more than four days after the most recent Kepivance administration (see section 4.4).

Paediatric population

The safety and efficacy of Kepivance in children aged 0 to 18 years have not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Renal impairment

Dose adjustment in patients with renal impairment is not necessary (see section 5.2).

Hepatic impairment

Safety and efficacy has not been evaluated in patients with hepatic impairment (see section 5.2). Caution should be used when dosing patients with hepatic impairment.

Older people

Safety and efficacy has not been evaluated in older people. Currently available data are described in section 5.2 but no recommendation on dose adjustment can be made.

Method of administration

Intravenous use.

Kepivance should not be administered subcutaneously due to poor local tolerability.

Reconstituted Kepivance should not be left at room temperature for more than one hour, and should be protected from light. Prior to administration, visually inspect the solution for discolouration and particulate matter before administration, see section 6.6.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to *Escherichia coli*-derived proteins.

4.4 Special warnings and precautions for use

Use with chemotherapy

Kepivance should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of cytotoxic chemotherapy. In a clinical trial, administration of Kepivance within 24 hours of chemotherapy resulted in an increased severity and duration of oral mucositis.

Concomitant heparin use

If heparin is used to maintain an intravenous line, sodium chloride solution should be used to rinse the line prior to and after Kepivance administration (see section 6.2).

Visual acuity

KGF receptors are known to be expressed on the lens of the eye. Cataractogenic effects of palifermin cannot be excluded (see section 5.1). Long term effects are not yet known.

Long term safety

The long-term safety of Kepivance has not been fully evaluated with respect to overall survival, progression free survival and secondary malignancies.

Non-haematological malignancies

Kepivance is a growth factor that stimulates the proliferation of KGF receptor expressing epithelial cells. The safety and efficacy of Kepivance has not been established in patients with KGF receptor expressing non-haematological malignancies. Palifermin should therefore not be given to patients with known or suspected non-haematological malignancies.

High dose melphalan conditioning regimen

In a postmarketing clinical trial investigating multiple myeloma patients receiving melphalan 200 mg/m^2 as conditioning regimen, palifermin administration with four days between the last pre dose and the first post dose did not show a therapeutic benefit in the frequency or duration of severe oral mucositis compared to placebo. Palifermin should therefore not be used in association with myeloablative chemotherapy-only conditioning.

4.5 Interaction with other medicinal products and other forms of interaction

As a protein therapeutic, the risk for Kepivance to interact with other medicinal products is low.

In-vitro and *in-vivo* data suggest that palifermin binds to unfractionated as well as low molecular weight heparins. In two studies in healthy volunteers, co-administration of Kepivance and heparin resulted in approximately 5 times higher systemic exposure to palifermin, due to a lower volume of distribution. The pharmacodynamic effect of palifermin, as measured by the change in Ki67 expression, tended to be lower when administered with heparin but the clinical relevance of this finding is unclear. However, the administration of palifermin did not affect heparin´s anticoagulant effect in the experimental conditions (single dose, subtherapeutic dose regimen). Due to limited data in patients, heparins should be used with care in patients receiving palifermin and appropriate blood coagulation tests should be carried out to monitor their treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Kepivance in pregnant women. Studies in animals have shown reproductive and developmental toxicity (see section 5.3). The potential risk to the human embryo or foetus is unknown. Kepivance should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether Kepivance is excreted in human milk, therefore Kepivance should not be administered to women who are breast-feeding.

Fertility

In studies in rats, no adverse effects on reproductivity/fertility parameters were observed at doses of up to 100 micrograms/kg/day. Systemic toxicity (clinical signs and/or changes in body weight) and adverse effects on male and female fertility parameters were seen at doses ≥ 300 micrograms/kg/day (5-fold higher than the recommended human dose).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Safety data are based on patients with haematological malignancies enrolled in randomised, placebo-controlled clinical studies, including one pharmacokinetic study, and post marketing experience.

The most commonly reported adverse drug reactions (reported in > 1/10 patients) are reactions consistent with the pharmacologic action of Kepivance on skin and oral epithelium, e.g. oedema, including peripheral oedema, and hypertrophia of oral structures. These reactions were primarily mild to moderate in severity and were reversible. Median time to onset was approximately 6 days following the first of 3 consecutive daily doses of Kepivance, with a median duration of approximately 5 days. Pain and arthralgia are other common adverse reactions, consistent with Kepivance treated patients having received less opioid analgesia than placebo-treated patients (see Table 2). Hypersensitivity, including Anaphylactic reactions, has also

been associated with palifermin.

Table 1. Adverse reactions from clinical trials and spontaneous reporting

The frequency listed below is defined using the following convention: very common (> 1/10), common (≥ 1/100 to < 1/10), not known (frequency cannot be estimated from available data).

System organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Not known:	Anaphylactic reaction/Hypersensitivity
Nervous system disorders	Very common:	Dysgeusia
	Common:	Paraesthesia oral
Gastrointestinal disorders	Very common:	Oral mucosal hypertrophy / Hypertrophy of tongue papillae,Oral mucosal discolouration / Tongue discolouration,

	Not known:	Tongue disorder (e.g. redness, bumps), Tongue oedema
Skin and subcutaneous tissue disorders	Very common:	Rash, pruritus and erythema
	Common:	Skin hyperpigmentation
	Not known:	Palmar-plantar erythrodysaesthesia syndrome (dysaesthesia, erythema, oedema on the palms and soles)
Musculoskeletal and connective tissue disorders	Very common:	Arthralgia
Reproductive system and breast disorders	Not known	Vaginal oedema and vulvovaginal erythema
General disorders and administration site conditions	Very common:	Oedema, oedema peripheral, pain and pyrexia
	Common:	Lip swelling, eyelid oedema
	Not known:	Face oedema, oedema mouth
Investigations	Very common:	Blood amylase increased and Lipase Increased[1]

[1] Kepivance may cause increased lipase and amylase levels in some patients with or without symptoms of abdominal pain or backache. No overt cases of pancreatitis have been reported in this patient population. Fractionation of increased levels of amylase revealed the increase to be predominantly salivary in origin.

Haematopoietic recovery following PBPC infusion was similar between patients who received Kepivance or placebo, and

there were no observed differences in disease progression or survival.

Dose limiting toxicities were observed in 36% (5 of 14) patients receiving 6 doses of 80 micrograms/kg/day administered intravenously over 2 weeks (3 doses preceding and three doses following myeloablative therapy). These events were consistent with those observed at the recommended dose but were generally more severe.

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 Appendix V.

4.9 Overdose

There is no experience with Kepivance doses greater than 80 micrograms/kg/day administered intravenously in patients over 2 weeks (3 doses preceding and 3 doses following myeloablative therapy).

For information on dose limiting toxicities see section 4.8.

A single dose of 250 micrograms/kg has been administered intravenously to 8 healthy volunteers without severe or serious adverse effects.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment, ATC code: V03A F08.

Palifermin is a 140 amino acid protein with a molecular weight of 16.3 kilodaltons. It differs from endogenous human KGF in

Palifermin is a 140 amino acid protein with a molecular weight of 15.5 kilodaltons. It differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability.

Mechanism of action

KGF is a protein that targets epithelial cells by binding to specific cell-surface receptors thereby stimulating proliferation, differentiation, and upregulation of cytoprotective mechanisms (e.g., induction of antioxidant enzymes). Endogenous KGF is an epithelial cell specific growth factor which is produced by mesenchymal cells and is naturally upregulated in response to epithelial tissue injury.

Pharmacodynamic effects

Epithelial cell proliferation was assessed by Ki67 immunohistochemical staining in healthy subjects. A 3-fold or greater increase in Ki67 staining was observed in buccal biopsies from 3 of 6 healthy subjects given palifermin at 40 micrograms/kg/day intravenously for 3 days, when measured 24 hours after the third dose. Dose-dependent epithelial cell proliferation was observed 48 hours post-dosing in healthy subjects given single intravenous doses of 120 to 250 micrograms/kg.

Clinical efficacy and safety

The palifermin clinical program in the setting of myelotoxic therapy requiring haematopoietic stem cell (HSC) support included 650 patients with haematologic malignancies enrolled in 3 randomised, placebo-controlled clinical studies and a pharmacokinetic study.

Efficacy and safety of palifermin were established in a randomised, double-blind, placebo-controlled study in which patients received high-dose cytotoxic therapy consisting of fractionated total-body irradiation (12 Gy total dose), high-dose etoposide (60 mg/kg), and high-dose cyclophosphamide (100 mg/kg) followed by PBPC support for the treatment of haematological malignancies ((Non-Hodgkin's Lymphoma (NHL), Hodgkin's disease, Acute Myeloid Leukaemia (AML), Acute Lymphocytic Leukaemia (ALL), Chronic Myeloid Leukaemia (CML), Chronic Lymphocytic Leukaemia (CLL), or multiple myeloma). In this study, 212 patients were randomised and received either palifermin or placebo. Palifermin was administered as a daily intravenous injection of 60 micrograms/kg for 3 consecutive days prior to initiation of cytotoxic therapy and for 3 consecutive days following infusion of peripheral blood progenitor cells.

The main efficacy endpoint of the study was the number of days during which patients experienced severe oral mucositis (grade 3/4 on the World Health Organisation (WHO) scale). Other endpoints included the incidence, duration and severity of oral mucositis and the requirement for opioid analgesia. There was no evidence of a delay in time to haematopoietic recovery in patients who received palifermin as compared to patients who received placebo. The efficacy results are presented in Table 2.

Table 2. Oral mucositis and related clinical sequelae - HSC transplant study

	Placebo **n = 106**	**Palifermin** **(60 micrograms/kg/day)** **n = 106**	**p-value***
Median (25^{th}, 75^{th} percentile) days of WHO Grade 3/4 oral mucositis**	9 (6, 13)	3 (0, 6)	< 0.001
Patient incidence of WHO Grade 3/4 oral mucositis	98%	63%	< 0.001
Median (25^{th}, 75^{th} percentile) days of WHO Grade 3/4 oral mucositis in affected patients	9 (6, 13) (n = 104)	6 (3, 8) (n = 67)	
Patient incidence of WHO Grade 4 oral mucositis	62%	20%	< 0.001
Median (25^{th}, 75^{th} percentile) days of WHO Grade 2/3/4 oral mucositis	14 (11, 19)	8 (4, 12)	< 0.001
Opioid Analgesia for oral mucositis: Median (25^{th}, 75^{th} percentile) Days	11 (8, 14)	7 (1, 10)	< 0.001

Median (25^{th}, 75^{th} percentile) Cumulative Dose (morphine mg equivalents)	535 (269, 1429)	212 (3, 558)	< 0.001
Patient Incidence of Total Parenteral Nutrition (TPN)	55%	31%	< 0.001
Patient Incidence of Febrile Neutropenia	92%	75%	< 0.001

* Using Cochran-Mantel-Haenszel (CMH) test stratified for study centre.

** WHO Oral Mucositis Scale: Grade 1 = soreness/erythema; Grade 2 = erythema, ulcers, can eat solids; Grade 3 = ulcers, requires liquid diet only; Grade 4 = alimentation not possible

In this Phase 3 clinical study, palifermin treated patients demonstrated significant benefits in patient-reported outcomes of mouth and throat soreness and its impact on swallowing, drinking, eating and talking. These patient-reported outcomes were highly correlated to the clinician grading of oral mucositis using the WHO scale.

A randomised, placebo-controlled, double-blind study was conducted post-approval to evaluate the efficacy of palifermin given pre- or pre- and post- chemotherapy (CT). The study included three treatment arms and was designed to compare each of the palifermin arms (pre- and pre/post-) to placebo.

In this study (n = 281), patients with multiple myeloma received conditioning with melphalan (200 mg/m^2) prior to autologous haematopoietic stem cell transplantation.
The incidence of ulcerative oral mucositis was 57.9% in the placebo arm, 68.7% in the pre/post CT group and 51.4% in the pre-CT group. Neither of the two dosing regimens demonstrated statistically significant results versus placebo. The incidence of severe (grades 3 and 4) oral mucositis in the 3 groups was 36.8%, 38.3% and 23.9% for the placebo, pre/post CT and pre-CT groups respectively, with no statistical significance being demonstrated. Treatment-emergent adverse events with respect to infections were reported in 24.6%, 49.5% and 46.8% for the placebo, pre/post-CT and pre-CT groups respectively.

Cataractogenic effects of palifermin cannot be excluded following results of ophthalmologic examinations in a subset of patients (n = 66; 14 in the placebo group, 52 in the palifermin group) who were followed for 12 months after the acute phase of the above post-approval study. For the primary endpoint, which was incidence of cataract development or progression at 12 months (defined as an increase of ≥ 0.3 in the LOCS III score), a greater proportion of subjects experienced cataract development in the palifermin group compared with the placebo group (28.6 % in the placebo group vs 48.1% in the palifermin group). This difference was not statistically significant. Visual acuity was not affected at 6 or 12 months in either treatment group. There was an imbalance in age distribution with more elderly (> 65 years) patients in the palifermin group.

Paediatric population

A phase I dose escalation study was conducted in paediatric patients aged 1-16 years. A total of 27 paediatric patients with leukaemia were randomized to 40, 60 or 80 micrograms/kg/day of palifermin for 3 days pre- and post- hematopoietic stem cell transplantation (HSCT). The conditioning regimen consisted of total body irradiation (TBI), etoposide and cyclophosphamide. There was a lower incidence of severe oral mucositis in patients receiving 80 micrograms/kg/day but no effect on the incidence of acute graft-versus-host disease (GVHD). Although palifermin was safe at all doses tested the incidence of skin reactions increased with the dose.

5.2 Pharmacokinetic properties

The pharmacokinetics of palifermin were studied in healthy volunteers and patients with haematological malignancies. After single intravenous doses of 20 to 250 micrograms/kg (healthy volunteers) and 60 micrograms/kg (cancer patients), palifermin exhibited rapid extravascular distribution In patients with haematological malignancies mean V_{ss} was 5 l/kg and mean clearance about 1300 ml/hour/kg with an average terminal half-life of approximately 4.5 hours. Approximately dose-linear pharmacokinetics were observed in healthy volunteers after single dose administration up to 250 micrograms/kg. No accumulation of palifermin occurred after 3 consecutive daily doses of 20 and 40 micrograms/kg (healthy volunteers) or 60 micrograms/kg (adult patients) or 40 to 80 micrograms/kg (paediatric patients). Inter-subject variability is high with a CV% of about 50% for CL and 60% for V_{ss}.

No gender-related differences were observed in the pharmacokinetics of palifermin. Mild to moderate renal impairment (creatinine clearance 30-80 ml/min) did not influence palifermin pharmacokinetics. In patients with severe renal impairment (creatinine clearance < 30 ml/min), clearance was decreased by 22% (n = 5). In patients with end-stage renal disease (requiring dialysis) palifermin clearance was decreased by 10% (n = 6). The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed.

Older people

In a single dose study the clearance of palifermin was approximately 30% lower in 8 healthy subjects aged 66-73 years after a dose of 90 micrograms/kg than in younger subjects (≤ 65 years) after a dose of 180 micrograms/kg. Based on these limited data no recommendation on dose adjustment can be made.

Paediatric population

In a small multiple-dose study in paediatric patients (1 to 16 years old) receiving 40, 60 or 80 micrograms/kg/day for 3 days pre- and post- HSCT, there was no effect of age on the pharmacokinetics of palifermin although a large variability was observed in the estimated parameters. Systemic exposure did not appear to increase with the dose.

5.3 Preclinical safety data

Salient findings in toxicology studies in rat and monkey were generally attributable to the pharmacological activity of palifermin, specifically, proliferation of epithelial tissues.

In fertility/general reproductive toxicity studies in rats, palifermin treatment was associated with systemic toxicity (clinical signs and/or changes in body weight) and adverse effects on male and female reproductive/fertility parameters at doses greater than or equal to 300 micrograms/kg/day. No adverse effects on reproductive/fertility parameters were observed at doses of up to 100 micrograms/kg/day. These no observed adverse effect level (NOAEL) doses were associated with systemic exposures up to 2.5 times greater than anticipated clinical exposure.

In embryo/foetal development toxicity studies in rats and rabbits, palifermin treatment was associated with developmental

toxicity (increased post-implantation loss, reduced litter size, and/or reduced foetal weight) at doses of 500 and 150 micrograms/kg/day, respectively. Treatment with these doses was also associated with maternal effects (clinical signs and/or changes in body weight/food consumption), suggesting that palifermin was not selectively toxic to development in either species. No adverse developmental effects were observed in rats and rabbits at doses of up to 300 and 60 micrograms/kg/day, respectively. These NOAEL doses were associated with systemic exposures (based on AUC) up to 9.7 and 2.1 times, respectively, anticipated clinical exposure. Peri- and postnatal development has not been studied.

Palifermin is a growth factor that primarily stimulates epithelial cells through the KGF receptor. Haematologic malignancies do not express the KGF receptor. However, patients treated with chemotherapy and/or radiotherapy are at higher risk of developing secondary tumours some of which may express KGF receptors, and theoretically, be stimulated by KGF receptor ligands. In a study to assess potential carcinogenicity in transgenic rasH2 mice, no treatment related increases in the incidence of neoplastic lesions were observed.

6. Pharmaceutical particulars

6.1 List of excipients

L-histidine

Mannitol

Sucrose

Polysorbate 20

Diluted Hydrochloric acid

6.2 Incompatibilities

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

If heparin is used to maintain an intravenous line, sodium chloride solution should be used to rinse the line prior to and after Kepivance administration, since palifermin has been shown to bind to heparin *in vitro*.

6.3 Shelf life

6 years.

After reconstitution: 24 hours at 2 °C – 8 °C, protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

6.25 mg of powder in a vial (Type I glass) with a rubber stopper, an aluminium seal and a plastic flip-off cap.

Carton containing 6 vials.

6.6 Special precautions for disposal and other handling

Kepivance is a sterile but unpreserved product and is intended for single use only.

Kepivance should be reconstituted with 1.2 ml water for injections. The diluent should be injected slowly into the Kepivance vial. The contents should be swirled gently during dissolution. Do not shake or vigorously agitate the vial.

Generally, dissolution of Kepivance takes less than 5 minutes. Visually inspect the solution for discolouration and particulate matter before administration. Kepivance should not be administered if discolouration or particulates are observed.

Before injection, Kepivance may be allowed to reach room temperature for a maximum of 1 hour but should be protected from light. Kepivance left at room temperature for more than 1 hour should be discarded.

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

7. Marketing authorisation holder

Swedish Orphan Biovitrum AB (publ)

SE-112 76 Stockholm

Sweden

8. Marketing authorisation number(s)

EU/1/05/314/001

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 25 October 2005

Date of latest renewal: 23 September 2010

10. Date of revision of the text

05/2013

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu