PRODUCT MONOGRAPH

PrKEPIVANCE®

(palifermin)

Sterile, Lyophilized Powder for Reconstitution

(6.25 mg/vial)

Intravenous Use Only

Keratinocyte Growth Factor

Swedish Orphan Biovitrum AB (publ)
SE-112 76
Stockholm, Sweden

Imported by:
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Dundas, Ontario
L9H 7P3

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:

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PrKEPIVANCE®

(palifermin)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous use only	Sterile, Lyophilized Powder for Reconstitution / 6.25 mg/vial	Not Applicable *For a complete listing, see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Kepivance® (palifermin) is a human keratinocyte growth factor (KGF), produced by recombinant DNA technology in *Escherichia coli* (*E. coli*). Palifermin (rHuKGF) is a water-soluble, 140 amino acid protein with a molecular weight of 16.3 kilodaltons. It differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability. Kepivance® has demonstrated mitogenic activity commensurate with native KGF.[1]

Keratinocyte growth factor is a protein that targets epithelial cells by binding to specific cell-surface receptors, thereby stimulating proliferation, differentiation, and upregulation of cytoprotective mechanisms (eg. induction of antioxidant enzymes).[2,3] Endogenous KGF is an epithelial cell-specific growth factor that is produced by mesenchymal cells and is naturally upregulated in response to epithelial tissue injury.[3]

The KGF receptor, one of four receptors in the fibroblast growth factor family, has been reported to be present on epithelial cells in many tissues examined including the tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, skin (hair follicles and sebaceous gland), and the lens of the eye.

INDICATIONS AND CLINICAL USE

Kepivance® (palifermin) is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy and requiring hematopoietic stem cell support.

Geriatrics: Clinical studies of Kepivance® did not include sufficient numbers of subjects age 65 years and over to determine whether they respond differently from younger subjects.

Pediatrics: Kepivance® should not be used in children under 18 years of age (see **WARNINGS AND PRECAUTIONS**)

CONTRAINDICATIONS

Kepivance® is contraindicated in patients with known hypersensitivity to *Escherichia coli (E. coli)*-derived proteins, palifermin, or any other component of the product.

WARNINGS AND PRECAUTIONS

General

Kepivance® (palifermin) should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy (see **DOSAGE AND ADMINISTRATION). In a clinical trial, administration of Kepivance® within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.**

The safety and efficacy of Kepivance® have not been established in patients with nonhematologic malignancies.

Kepivance® treatment should be supervised by a physician experienced in the use of anticancer therapies.

Sensitivity Reactions

No fatal or severe anaphylactic reactions occurred in connection with the administration of Kepivance® to patients with hematologic malignancies receiving myelotoxic therapy in 3 randomized placebo-controlled clinical studies and one pharmacokinetic study. One patient out of 409 (0.2%) experienced life-threatening respiratory distress 20 days after exposure to Kepivance®.

Nevertheless, as a precaution, resuscitation equipment should be available when Kepivance® is administered.

In the same clinical studies, mild or moderate allergic reactions were reported in 130/409 (32%) and 56/241 (23%) of Kepivance®- and placebo-treated patients, respectively.

Carcinogenesis and Mutagenesis

The carcinogenic potential of Kepivance® in humans is not known. Because the KGF receptor is expressed on epithelial cells, there is a theoretical risk that palifermin could stimulate the proliferation of epithelial-derived tumour cells (see **TOXICOLOGY, Mutagenicity and Carcinogenicity Studies**).

Potential for Stimulation of Tumor Growth

The safety and efficacy of Kepivance® have not been established in patients with non-hematologic malignancies. The effects of Kepivance® on stimulation of KGF receptor-expressing, non-hematopoetic tumors in patients are not known. Kepivance® has been

shown to enhance the growth of human epithelial tumor cell lines *in vitro* and to increase the rate of tumor cell line growth in a human carcinoma xenograft model.

Ophthalmologic

KGF receptors are known to be expressed on the lens of the eye, thus a cataractogenic effect of Kepivance® cannot be excluded. Long-term effects are not yet known (see **CLINICAL TRIALS, Cataract Safety Report (Study 20050219)**)

Sexual Function/Reproduction

When Kepivance® was administered IV daily to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at doses up to 100 µg/kg/day. Systemic toxicity (clinical signs of toxicity and/or body weight effects), decreased epididymal sperm counts, and increased postimplantation loss were observed at doses ≥ 300 µg/kg/day (5-fold higher than the recommended human dose). Increased preimplantation loss and a decreased fertility index were observed at a Kepivance® dose of 1,000 µg/kg/day.

High Dose Melphalan Conditioning Regimen

In a postmarketing clinical trial investigating myeloma patients who received melphalan 200 mg/m^2 as a conditioning regimen, the safety profile of Kepivance® was as expected, with adverse effects primarily related to its pharmacological activity.
As Kepivance® did not provide any statistically significant difference in the maximum severity of oral mucositis as compared to placebo (p=0.188 for pre/post CT versus placebo and p=0.468 for the pre-CT group versus placebo), the use of Kepivance® in this setting is not recommended (see **CLINICAL TRIALS**, **Postmarketing Study of High Dose Melphalan Conditioning Regimen** (**Acute Phase Report of Study 20050219**)).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Kepivance® should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Women: It is not known whether Kepivance® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Kepivance®is administered to a nursing woman.

Pediatrics: The safety and effectiveness of Kepivance® in pediatric patients have not been established (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Effect of Age**).

Geriatrics: Of 409 patients with hematologic malignancies who received Kepivance® in clinical studies, 9 (2%) were ≥ age 65. No overall differences in safety were observed between these patients and patients < age 65; however, due to the small number of elderly patients, small but clinically relevant differences cannot be excluded. (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Effect of Age**)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Please refer to **WARNINGS AND PRECAUTIONS: Carcinogenesis and Mutagenesis** and **TOXICOLOGY** sections regarding the potential for tumour stimulatory effects in KGF receptor-expressing tumours.

Safety data are based upon clinical studies in which patients with hematologic malignancies received Kepivance® either before, or before and after myelotoxic chemotherapy, with or without total body irradiation (TBI), and peripheral blood progenitor cell (PBPC) support. The most common adverse reactions attributed to Kepivance® were skin toxicities, oral toxicities, pain, arthralgias, and dysesthesia. These events were primarily mild to moderate in severity and were reversible. The most common serious adverse reaction attributed to Kepivance® was skin rash, which was reported in less than 1% of patients treated with Kepivance® . The most frequently reported serious adverse events in Kepivance® and placebo-treated patients were fever, gastrointestinal events, and respiratory events.

There have been no new major post-marketing findings necessitating a change in the established overall safety information for Kepivance®. (See **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**)

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Safety data are based upon 650 patients with hematologic malignancies (non-Hodgkin's lymphoma [NHL], Hodgkin's disease, acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], chronic myeloid leukemia [CML], chronic lymphocytic leukemia [CLL], or multiple myeloma) enrolled in 3 randomized, placebo-controlled clinical studies and a pharmacokinetic study. Patients received Kepivance® either before, or before and after myelotoxic chemotherapy, with or without total body irradiation (TBI), and peripheral blood progenitor cell (PBPC) support.

Most adverse events were attributable to the underlying malignancy, cytotoxic chemotherapy, or TBI and occurred at similar rates in patients who received Kepivance® (n = 409) or placebo (n = 241). Those that occurred with at least a 5% higher incidence in Kepivance®-treated patients are listed in Table 1.

The most common adverse reactions attributed to Kepivance® were skin toxicities (rash, pruritus, erythema, edema), oral toxicities (mouth/tongue thickness or discolouration, and taste disorders), pain, arthralgias, and dysesthesia. These events were primarily mild to moderate in severity and were reversible. Median time to onset of cutaneous toxicity was approximately 6 days following the first of 3 consecutive daily doses of Kepivance® , with a median duration of approximately 5 days.

The most common serious adverse reaction attributed to Kepivance® was skin rash, which was reported in 3 of 409 patients (0.7%)treated with Kepivance®. Grade 3 skin rashes occurred in 14 patients, 9 of 409 (3%) receiving Kepivance® and 5 of 241 (2%) receiving placebo. In seven patients (5 Kepivance®, 2 placebo), the study drug was discontinued due to skin rash. Other serious adverse reactions occurred at a similar rate in patients who received Kepivance® (21%) or placebo (22%). The most frequently reported serious adverse events in Kepivance® and placebo-treated patients were fever, gastrointestinal events, and respiratory events.

Table 1. Clinical Trial Adverse Events Occurring With ≥ 5% Higher Incidence in Kepivance® vs Placebo

BODY SYSTEM Adverse Event	Placebo (n = 241)	KEPIVANCE® (n = 409)
BODY AS A WHOLE		
Edema	21%	28%
Pain	11%	16%
Fever	39%	34%
GASTROINTESTINAL		
Mouth/Tongue Thickness or Discolouration	8%	17%
MUSCULOSKELETAL		
Arthralgia	5%	10%
SKIN AND APPENDAGES		
Rash	50%	62%
Pruritus	24%	35%
Erythema	22%	32%
SPECIAL SENSES		
Taste altered	8%	16%
CNS/PNS		
Dysesthesia - Hyperesthesia/hypoesthesia/ Paresthesia	7%	12%

The following table (Table 2) provides additional information on adverse reactions reported in placebo-controlled studies. The safety data are based upon 637 patients enrolled in the 3 randomized, placebo-controlled clinical studies.

Table 2. Most Frequently* Reported Adverse Reactions in Randomized, Placebo-Controlled Clinical Trials

BODY SYSTEM Preferred Term (WHOART)	Placebo (N=241) N (%)	Kepivance® (N=396) N (%)
Number of Subjects Reporting ADRs	64 (27)	202 (51)
BODY AS A WHOLE	10 (4)	54 (14)
Edema Peripheral	2(1)	23(6)
Edema Face	4(2)	17(4)
Edema	1(0)	11(3)

BODY SYSTEM Preferred Term (WHOART)	Placebo (N=241) N (%)	Kepivance® (N=396) N (%)
Edema Circumoral	2(1)	11(3)
Pain	(0)	8(2)
Edema Genital	0(0)	4(1)
Warm Sensation	1(0)	4(1)
CNS/PNS	2(1)	31(8)
Paresthesia	2(1)	16(4)
Hypoesthesia	0(0)	14(4)
Hyperesthesia	0(0)	4(1)
GASTROINTESTINAL	14(6)	76(19)
Lesion Oral	4(2)	31(8)
Tongue Disorder	4(2)	22(6)
Tongue Discolouration	0(0)	10(3)
Pain Oral	0(0)	9(2)
Dry Mouth	1(0)	7(2)
Pain Abdominal	1(0)	6(2)
Saliva Increased	3(1)	6(2)
Edema Tongue	1(0)	5(1)
Nausea	2(1)	5(1)
MUSCULO-SKELETAL	1(0)	10(3)
Pain Limb	1(0)	10(3)
RESPIRATORY	2(1)	4(1)
Throat Tightness	2(1)	4(1)
SKIN AND APPENDAGES	46(19)	156(39)
Erythema	9(4)	72(18)
Rash	15(6)	68(17)
Flushing	9(4)	33(8)
Pruritus	11(5)	25(6)
Rash Maculo-Papular	9(4)	14(4)
Rash Erythematous	1(0)	12(3)
Skin Exfoliation	5(2)	10(3)
Skin Dry	3(1)	6(2)
Skin Hyperpigmentation	1(0)	4(1)
SPECIAL SENSES	1(0)	13(3)
Taste Perversion	1(0)	9(2)
Taste Loss	1(0)	4(1)

* Most frequently reported reactions were considered to be those reactions reported in ≥ 1% of the patients in the Kepivance® group.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
The following adverse reactions were reported at an incidence of <1% (occurring in more than 1 patient, with higher frequency than placebo). The safety data are based upon 637 patients enrolled in the 3 randomized, placebo-controlled clinical studies:
Body As A Whole: fever;
Gastrointestinal: hemorrhoids, sialoadenitis, vomiting;
Metabolic/Nutrition: hypokalemia;
Musculo-Skeletal: myalgia;
Reproductive (female): pain genital;
Respiratory: epistaxis;
Skin and Appendages: hypertrichosis, pruritus genital, skin discolouration;
Vision Disorders: vision abnormal.

Proteinuria
In a placebo-controlled study conducted in 145 patients with metastatic colorectal cancer receiving multi-cycle chemotherapy (5-FU/Leucovorin), serial urine specimens were collected for 27 placebo-treated and 54 Kepivance®-treated patients. Among the 54 Kepivance®-treated patients, nine patients with a baseline urinalysis negative for protein subsequently developed 2+ or greater proteinuria after treatment with Kepivance®. Among the 27 placebo-treated patients evaluated, none developed 2+ or greater proteinuria. Because of the study design, the number of cycles with urine analysis data collected was higher in the Kepivance®-treated patients. In addition, for the 9 patients with proteinuria, underlying medical conditions known to be associated with proteinuria were present at baseline. A causal relationship between Kepivance® and proteinuria has not been established. For patients with existing conditions associated with proteinuria, e.g. diabetes and/or hypertension, proteinuria monitoring may be considered.

Hematopoietic recovery following PBPC transplant was similar between patients who received Kepivance® or placebo, and there were no observed differences in disease progression or survival.

Abnormal Hematologic and Clinical Chemistry Findings
Reversible elevations in serum lipase and amylase, which did not require treatment interventions, were observed. The incidences of these changes, presented for Kepivance® relative to placebo, were: lipase (28% vs 23%) and amylase (62% vs 54%). Grade 3 or 4 increases were observed for serum lipase in 11% and 5% and for serum amylase in 38% and 31% of patients who received Kepivance® and placebo, respectively (see Table 3). In general, peak increases were observed during the period of cytotoxic therapy and returned to baseline by the day of PBPC infusion. Fractionation of amylase revealed it to be predominantly salivary in origin. No patients who received Kepivance® experienced acute pancreatitis.

Table 3. Abnormal Hematologic and Clinical Chemistry Findings in the Clinical Trials

Abnormal Laboratory Values	Placebo (n = 241)	Kepivance® (n = 409)
Elevated serum lipase (Grade 3/4)	23% (5%)	28% (11%)
Elevated serum amylase (Grade 3/4)	54% (31%)	62% (38%)

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Twelve out of the 645 (2%) Kepivance®-treated patients and 5 out of the 319 (2%) placebo-treated patients tested positive for antibodies to palifermin.. None of the samples had evidence of neutralizing activity in a cell-based assay.

The incidence of antibody positivity is highly dependent on the specific assay and its sensitivity. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to palifermin with the incidence of antibodies to other products may be misleading.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported during post-marketing clinical use of Kepivance®: anaphylactic / allergic reactions, Palmar-Plantar Erythrodysaesthesia Syndrome (PPES) (dysesthesia, erythema, edema on the palms and soles); tongue disorder (e.g., redness, bumps and edema); face edema and mouth edema; vaginal edema and erythema; hyperpigmentation of the skin.

DRUG INTERACTIONS

Drug-Drug Interactions

No formal drug-drug interactions studies have been conducted for Kepivance® in patients with hematologic malignancies, but two drug-drug interaction studies have been performed in healthy volunteers.*In vitro* data had suggested that palifermin interacts with unfractionated as well as low molecular weight heparins.

In one study in healthy volunteers, the effect of a continuous i.v. infusion of unfractionated heparin on the pharmacokinetics and pharmacodynamics of palifermin (Ki67 staining of buccal biopsy tissue) was evaluated in 15 subjects receiving 40 µg/kg/day for 3 consecutive days. In 2 two control groups, 16 subjects received 3 daily doses of 40 µg/kg/day of palifermin only and 8 subjects received no treatment, respectively.

When co-administered with heparin, palifermin serum concentrations were approximately 5 times higher, likely due to a lower volume of distribution, and the terminal phase declined more rapidly. Day 1 values were comparable to those seen at day 3. The changes in pharmacokinetics did not alter palifermin pharmacodynamics. The pharmacodynamic effect of multiple doses of palifermin, as measured by Ki67 expression,was comparable between the palifermin-heparin and palifermin alone groups.

In another study, 30 healthy male subjects were assigned to one of three treatment groups receiving either therapeutic levels of heparin with a single dose of 60 µg/kg palifermin, a single dose of 60 µg/kg palifermin alone or unfractionated heparin alone. There was a 5-fold increase in overall exposure to palifermin when co-administered with heparin, as compared to palifermin alone. However, there was no indication that palifermin had any effect on the pharmacodynamics (aPTT) of heparin.

If heparin is used to maintain an IV line, saline should be used to rinse the line prior to and after Kepivance® administration (see **DOSAGE AND ADMINISTRATION**). Kepivance® should not be administered through an IV line containing heparin.

Myelotoxic Chemotherapeutic Agents
Kepivance® should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy (see DOSAGE AND ADMINISTRATION). In a clinical trial, administration of Kepivance® within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Kepivance® should only be administered by IV bolus injection. If heparin is used to maintain an IV line, saline should be used to rinse the line prior to and after Kepivance® administration, since Kepivance® has been shown to bind to heparin *in vitro*.

No dose adjustment is recommended for patients with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions**).

Recommended Dose and Dosage Adjustment
The recommended dosage of Kepivance® is 60 µg/kg/day, administered as an IV bolus injection for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses (see **Administration**-*Reconstitution*).

Pre-myelotoxic therapy
The first 3 doses of Kepivance® should be administered prior to myelotoxic therapy, with the third dose 24 to 48 hours before myelotoxic therapy (see **WARNINGS AND PRECAUTIONS**).

Post-myelotoxic therapy
The last 3 doses should be administered after myelotoxic therapy; the first of these doses should be administered after, but on the same day of hematopoietic stem cell infusion and more than 4 days after the most recent Kepivance® administration.

Administration

Reconstitution
Kepivance® should be reconstituted aseptically with 1.2 mL of Sterile Water for Injection, USP (not supplied) to yield a solution containing 6.25 mg of palifermin (5 mg/mL). The

diluent should be injected slowly into the single-use Kepivance® vial. The contents should be swirled gently during dissolution. Do not shake or vigorously agitate the vial.

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

The contents of one single-use vial of Kepivance® solution should not be mixed with, or transferred into, the contents of another vial of Kepivance®. No other medications should be added to solutions containing palifermin and do not reconstitute Kepivance® with other diluents. Do not filter the reconstituted solution during preparation or administration.

Do not use Kepivance®beyond the date stamped on the vial label.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The maximum amount of Kepivance®) that can be safely administered in a single dose has not been determined. A dose of 250 µg/kg has been administered IV to 8 healthy volunteers without serious adverse effects. Kepivance®-related skin and oral reactions were more frequent at higher doses.

In single-dose toxicity studies conducted in rats and monkeys, no mortality or clinical signs of overt toxicity were observed at palifermin doses up to 30,000 µg/kg (IV or SC) or 50,000 µg/kg (IV), respectively.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Kepivance® (palifermin) is a human keratinocyte growth factor (KGF), produced by recombinant DNA technology in *Escherichia coli* (*E. coli*). Palifermin (rHuKGF) is a water-soluble, 140 amino acid protein with a molecular weight of 16.3 kilodaltons. It differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability. Palifermin has demonstrated mitogenic activity commensurate with native KGF.[1]

Keratinocyte growth factor is a protein that targets epithelial cells by binding to specific cell-surface receptors, thereby stimulating proliferation, differentiation, and upregulation of cytoprotective mechanisms (eg. induction of antioxidant enzymes).[2,3] Endogenous KGF is an epithelial cell-specific growth factor that is produced by mesenchymal cells and is naturally upregulated in response to epithelial tissue injury.[3]

Pharmacodynamics

Epithelial cell proliferative effects of palifermin given as 3 consecutive daily doses of 0.2 to 40 µg/kg/day and as single doses of 0.2 to 250 µg/kg were studied in healthy subjects as a marker of biologic activity. Evidence of increased epithelial cell proliferation (defined as 3-fold increases in staining for Ki67, a protein found in the nucleus of cycling cells)

was observed in buccal biopsies from healthy subjects given Kepivance® at 40 µg/kg/day IV for 3 days, when measured 24 hours after the third dose. For healthy subjects given single IV doses of 120 to 250 µg/kg, evidence of dose-dependent epithelial cell proliferation was observed, with an apparent plateau occurring above 160 µg/kg; proliferation was measured at baseline and at 48 and 72 hours postdose, was highest at 48 hours, and remained elevated compared to baseline at 72 hours postdose.

Pharmacokinetics

The pharmacokinetics (PK) of palifermin were studied in healthy subjects and patients with hematologic malignancies. After single IV doses of 20 to 250 µg/kg (healthy subjects) and 60 µg/kg (cancer patients), palifermin concentrations declined rapidly (over 95% decrease) in the first 30 minutes post-dose. A slight increase or plateau in concentration occurred at approximately 1 to 4 hours, followed by a terminal decline phase. palifermin exhibited linear pharmacokinetics with extravascular distribution. On average, total body clearance (CL) appeared to be 2- to 4-fold higher, and volume of distribution at steady state (Vss) to be 2-fold higher in cancer patients compared with healthy subjects after a 60 µg/kg single dose of Kepivance®. In patients with hematological malignancies, mean Vss was 5 L/kg and mean clearance about 1300 mL/hour/kg. The elimination half-life was similar between healthy subjects and cancer patients (average 4.5 hours with a range of 3.3 to 5.7 hours). No accumulation of palifermin occurred after 3 consecutive daily doses of 20 and 40 µg/kg (healthy subjects) or 60 µg/kg (adult patients) or 40 to 80 µg/kg (pediatric patients). Inter-subject variability is high with a CV% of about 50% for CL and 60% for Vss.

Special Populations and Conditions

Effect of Age

Pediatrics: In a Phase I dose escalation study, 27 leukemia patients, aged 1 – 16 years, were randomized to receive 40, 60 or 80 µg/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 µg /kg/day, but no effect on the incidence of acute graft-versus-host disease (GVHD). Although palifermin was safe at all doses tested, this study included only a limited number of patients and therefore the use of Kepivance in pediatric patients cannot be recommended.

Geriatrics: A single dose IV pharmacokinetic study of palifermin (90 or 180 mcg/kg) was conducted in 3 groups of healthy volunteers, aged 18 - 80 years: Group 1 (18-45 years, n=9), Group 2 (46 - 65years, n=12) and Group 3 (66 - 80 years, n=8). The mean clearance of palifermin in the oldest group was 571 mL/hr/kg versus 1070 mL/hr/kg in the youngest age group or approximately 50% lower. Data indicate that palifermin pharmacokinetics may be different in the geriatric patient population, however no definite conclusions can be drawn as different age groups received different doses.

Gender:

No gender-related differences have been observed in the pharmacokinetics of palifermin.

Hepatic insufficiency:
The pharmacokinetic profile in patients with hepatic impairment has not been assessed.

Renal insufficiency:
Results from a PK study in 24 subjects with varying degrees of renal impairment demonstrated that renal impairment has little or no influence on Kepivance® pharmacokinetics. No dose adjustment is recommended for patients with renal impairment.

STORAGE AND STABILITY

Kepivance® should be stored refrigerated at 2° to 8°C (36° to 46°F); vials should be kept in their carton to protect them from exposure to light until time of use.

Reconstituted Solution
The reconstituted solution of Kepivance® contains no preservative and is intended for single use only; therefore, it should be administered immediately (within 3 hours). However, when reconstituted by a health care professional under aseptic conditions, Kepivance® may be stored refrigerated in the carton at 2° to 8° C (36° to 46° F) for up to 24 hours. Before injection, Kepivance® may be allowed to reach room temperature for a maximum of 1 hour, but should be protected from exposure to light. Do not freeze reconstituted solution.

Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

Kepivance® vials should not be shaken.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Kepivance® is a sterile, white, preservative-free, lyophilized powder for IV injection after reconstitution with 1.2 mL of Sterile Water for Injection. Reconstitution yields a clear, colourless solution of palifermin (5 mg/mL) with a pH of 6.5. Each single-use vial of Kepivance® contains 6.25 mg palifermin, 50 mg mannitol, 25 mg sucrose, 1.94 mg L-histidine, and 0.13 mg polysorbate 20.

Availability of Dosage Forms
Kepivance® is supplied as a sterile, white, preservative-free, lyophilized powder containing 6.25 mg of palifermin in a single-dose vial. Kepivance® should only be reconstituted with 1.2 mL of Sterile Water for Injection, USP (not supplied).

Kepivance® is provided in a dispensing pack containing 6 vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: palifermin

Chemical name: recombinant human keratinocyte growth factor

Molecular formula and molecular mass: Palifermin has a molecular weight of 16.3 kilodaltons.

Structural formula: Palifermin is a human keratinocyte growth factor (KGF), produced by recombinant DNA technology in *Escherichia coli* (*E. coli*). Palifermin (rHuKGF) is a water-soluble, 140 amino acid, nonglycosylated protein. It differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability.

Product Characteristics

Kepivance® (palifermin) is a sterile, white, preservative-free, lyophilized powder for IV injection after reconstitution with 1.2 mL of Sterile Water for Injection. Reconstitution yields a clear, colourless solution of Kepivance® with a pH of 6.5.

CLINICAL TRIALS

Efficacy and Safety Studies

Study demographics and trial design

Table 4. Summary of patient demographics for clinical trials in hematologic malignancies

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number of subjects randomized to each treatment group)	Mean age in years	Gender
Study 1 (20000162)	Phase 3, randomized, double-blind, placebo-controlled	Palifermin IV injection of 60 µg/kg/day or placebo for 3 days prior to initiation of cytotoxic therapy and for 3 days following infusion of peripheral blood progenitor cells	212 (106 palifermin, 106 placebo)	46	81 women 131 men
Study 2 (980231)	Phase 2, randomized, multi-center, placebo-controlled study comparing varying schedules of palifermin	Palifermin IV injection of 60 µg/kg/day or placebo for 7 days, 1 of 3 treatment regimens: 1. Pre-post dosing of palifermin 2. Pre dosing of palifermin 3. Placebo	163 (57 palifermin pre-post, 55 palifermin pre, 51 placebo)	49	63 women 100 men
960189	Phase 1/2, randomized, double-blind, placebo-controlled, dose escalation	Palifermin IV injection at doses ranging from 5 to 80 µg/kg/day or placebo for 3 consecutive days	262 (53 palifermin pre-post, 124 palifermin pre, 85 placebo)	45	95 women 167 men

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number of subjects randomized to each treatment group)	Mean age in years	Gender
20010182 (Part A)	Phase 1, open label, PK study	Palifermin IV injection of 60 µg/kg/day for 3 consecutive days for 3 days prior to initiation of cytotoxic therapy and for 3 days following infusion of peripheral blood progenitor cells	13	52	6 women 7 men
960226	Long-term follow-up	Not applicable	650 Enrolled subjects in the treatment studies (960189, 980231, 20000162, and 20010182)	46	245 women 405 men

Study results

The Kepivance® clinical program in the setting of myelotoxic therapy requiring hematopoietic stem cell (HSC) support included 650 patients with hematologic malignancies (non-Hodgkin's lymphoma [NHL], Hodgkin's disease, acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], chronic myeloid leukemia [CML], chronic lymphocytic leukemia [CLL], or multiple myeloma) enrolled in 3 randomized, placebo-controlled clinical studies and one pharmacokinetic study.

Efficacy and safety of Kepivance® were established in a randomized, double-blind, placebo-controlled study (Study 1) in which patients received high-dose cytotoxic therapy consisting of fractionated total-body irradiation (TBI)(12 Gy total dose), high-dose etoposide (60 mg/kg), and high-dose cyclophosphamide (100 mg/kg) followed by peripheral blood progenitor cell (PBPC) support for the treatment of hematological malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma).6 In this study, 212 patients were randomized and received either Kepivance® or placebo. Kepivance® was administered as a daily IV injection of 60 µg/kg for 3 consecutive days prior to initiation of cytotoxic therapy and for 3 consecutive days following infusion of peripheral blood progenitor cells.

The primary endpoint of the study was the number of days during which patients experienced severe oral mucositis (grade 3/4 on the WHO [World Health Organization] scale)7 and key secondary endpoints included other measures of the incidence, duration, and severity of oral mucositis as well as clinical sequelae, such as mouth and throat soreness and the requirement for opioid analgesia.

Study 1 met its primary objective of demonstrating that, across all patients, Kepivance®-treated patients had a clinically and statistically significant reduction in the number of days during which they experienced severe oral mucositis, compared to placebo-treated patients (Table 5). In addition, use of Kepivance® was associated with clinically meaningful and statistically significant improvements in the following: incidence of severe oral mucositis; duration of ulcerative oral mucositis (WHO grade 2/3/4); requirement for parenteral or transdermal opioid analgesia for oral mucositis; requirement for total parenteral nutrition (TPN); and incidence of febrile neutropenia (absolute neutrophil count [ANC] < 0.5 x 109/L with a concurrent temperature ≥ 38.5°C) (Table 5).

Table 5. Oral Mucositis and Related Clinical Sequelae–Study 1

	Placebo n = 106	Kepivance® (60 µg/kg/day) n = 106	p - value*
Median (range) Days of WHO Grade 3/4 Oral Mucositis**	9 (0-27)	3 (0-22)	< 0.001
Patient Incidence of WHO Grade 3/4 Oral Mucositis	98%	63%	< 0.001
Median (range) Days of WHO Grade 3/4 Oral Mucositis in Patients who developed WHO Grade 3/4 Oral Mucositis	9 (1-27) (n = 104)	6 (1-22) (n = 67)	<0.001
Patient Incidence of WHO Grade 4 Oral Mucositis	62%	20%	< 0.001
Median (range) Days of WHO Grade 2/3/4 Oral Mucositis	14 (0-37)	8 (0-28)	< 0.001
Opioid Analgesia for Oral Mucositis:			
Median (range) Days	11 (0-32)	7 (0-28)	< 0.001
Median (range) Cumulative Dose (morphine mg equivalents)	535 (0-9418)	212 (0-9418)	< 0.001
Patient Incidence of TPN	55%	31%	< 0.001
Patient Incidence of Febrile Neutropenia	92%	75%	< 0.001

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

The profiles of mean WHO oral mucositis grades over time and incidence of graded oral mucositis, for patients who received placebo or Kepivance®, are shown in Figure 1 and 2, respectively.

Figure 1. Daily Mean (±95% CI) WHO Oral Mucositis Grade – Study 1

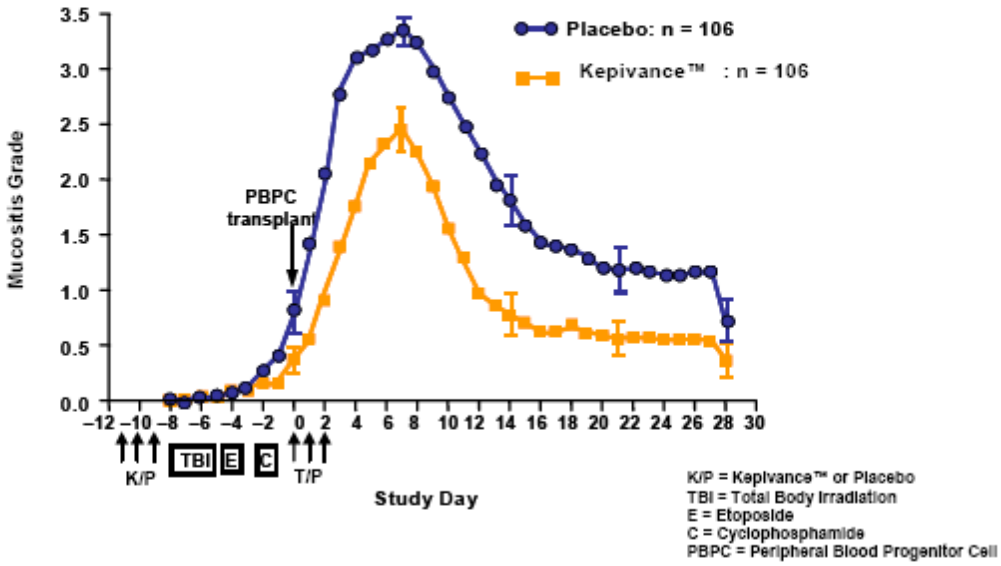
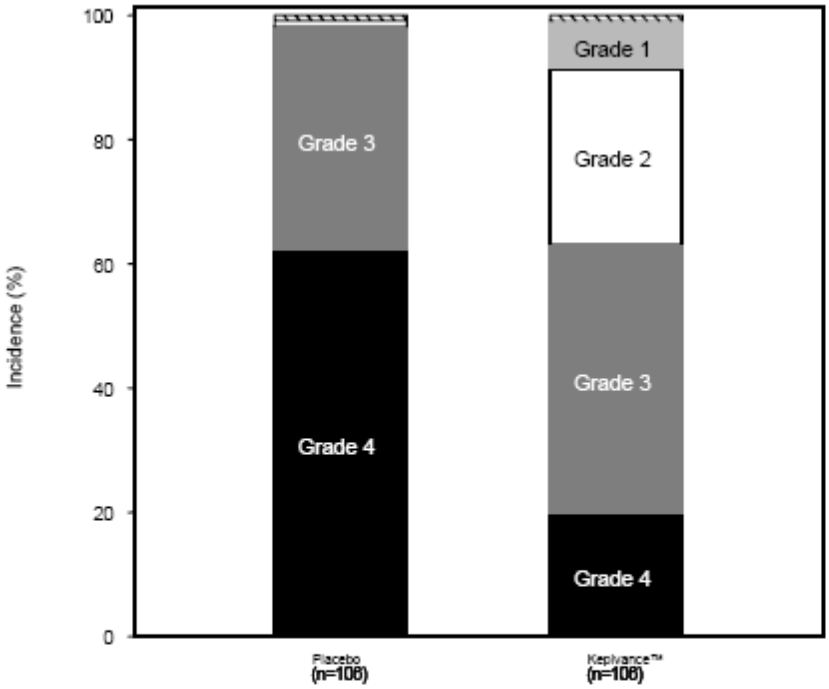


Figure 2. Incidence of Oral Mucositis by Maximum Grade –Study 1



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 Study 1, patients used a daily diary to record the amount of mouth and throat soreness. Compared with placebo-treated patients, Kepivance®-treated patients reported less mouth and throat soreness (see Table 6).

Table 6. Patient-Reported Outcomes–Study 1

	% Improvement–Kepivance® vs Placebo	p - value*
Mouth and Throat Soreness	38%	< 0.001
Ability to Swallow	38%	< 0.001
Ability to Eat	40%	< 0.001
Ability to Drink	38%	< 0.001
Ability to Talk	47%	< 0.001
Ability to Sleep	40%	< 0.001

* Using CMH test stratified for study center.

Study 2 was a randomized, multi-center, placebo-controlled study comparing varying schedules of Kepivance®. All patients received high-dose cytotoxic therapy consisting of fractionated TBI (12cGy total dose), high-dose etoposide (60 mg/kg), and high-dose cyclophosphamide (75-100 mg/kg) followed by PBPC support for the treatment of hematological malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma).

The results of Study 1 were supported by results observed in the subset of patients in Study 2 who received the same dose and schedule of Kepivance® as given in Study 1. Compared with placebo, there was a reduction in median days of WHO Grade 3/4 oral mucositis (4 vs. 6 days), lower incidence of WHO Grade 3/4 oral mucositis (67% vs. 80%) and lower incidence of WHO Grade 4 oral mucositis (26% vs. 50%) for Kepivance®.

One of the schedules tested in Study 2 randomized patients to receive Kepivance® for 3 consecutive days prior to initiation of cytotoxic therapy, a dose given on the last day of TBI prior to etoposide, and for 3 consecutive days following infusion of PBPC. This arm was prematurely closed by the Safety Committee after enrollment of 35 patients due to lack of efficacy and a trend towards increased severity and duration of oral mucositis as compared to placebo-treated patients. This finding was attributed to administration of Kepivance® within 24 hours of chemotherapy, resulting in an increased sensitivity of the rapidly dividing epithelial cells in the immediate post-chemotherapy period (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Postmarketing Study of High Dose Melphalan Conditioning Regimen
(**Acute Phase Report of Study 20050219**)

A post approval study, Study 20050219, was designed to determine the efficacy of Kepivance with a high dose melphalan preparative regimen. Patients with multiple myeloma were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial. The median age of enrolled patients was 57 years (range 32-69), and 55% were male. A total of 281 patients were randomized to 3 arms: Kepivance before melphalan on days -6, -5, -4 and after melphalan on days 0, 1, and 2 (pre-post) (n=115); Kepivance before melphalan on days -6, -5, -4 (pre) (n=109); or placebo (n=57). The conditioning regimen, melphalan (200 mg/m^2) was given on day -2 followed by autologous hematopoietic stem cell support. The primary outcome of the study was maximum severity (Grade 3 and 4) of WHO oral mucositis. The incidence of WHO Grade 3 and 4 oral mucositis in the Kepivance pre-post arm was 38%, compared to 37% in the placebo arm. There were no significant differences between either of the Kepivance regimens and the placebo arm in the incidence of severe oral mucositis.The safety profile of palifermin in this trial was as expected with AEs primarily related to its pharmacological activity, with the exception of infections which were more frequently reported in subjects receiveing palifermin.

Cataract Safety Report (Study 20050219)

A subset of subjects enrolled in the multiple myeloma study was included in an evaluation of the risk of cataract development in patients receiving Kepivance treatment. Ophthalmologic examinations were performed on 101 Multiple myeloma patients (of whom 66 were followed for 12 months) enrolled in a double-blind, randomized, placebo-controlled study of two different schedules of Kepivance for reduction in severity of oral mucositis: pre and post chemotherapy and pre chemotherapy only. The patients received high dose melphalan followed by autologous peripheral blood stem cell transplantation. For the primary cataract endpoint of incidence of cataract development or cataract progression at Month 12, there was a greater proportion of subjects that experienced cataract development in the Kepivance group: 48% (25/52) compared with the placebo group: 29% (4/14) (difference of 17 [95% CI: -11, 46]). There was an imbalance in age distribution with more elderly (> 65 years) patients in the Kepivance® group. Visual acuity was not affected at 6 or 12 months in either treatment group.

Long-term follow up (Study 960226)

In the hematology transplant setting, with a median follow-up of 51.9 months (range 0.2 to 164.8months) for the placebo group and 50.6months (range 0.8 to 167.5months) for the Kepivance® group, overall survival, disease progression, progression-free survival, and the incidences of second malignancies were similar between Kepivance® and placebo groups, and were in the range expected for this patient population. The overall proportion of patients with secondary malignancies was 21 patients (10.6%) in the placebo group and 43 patients (12.5%) in the Kepivance® group. Log-rank tests showed no statistically significant difference between the placebo and Kepivance® treatment groups for either survival (p=0.465) or progression-free survival (p=0.378).

DETAILED PHARMACOLOGY

The preclinical pharmacology of Kepivance® (palifermin) has been studied in mice, rats, and rhesus monkeys. In these studies, palifermin had trophic effects on epithelial cells in many tissues examined, including: tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, and skin (hair follicles and sebaceous gland).[2,3,4] Palifermin has been extensively studied in murine models of chemotherapy and radiation-induced gastrointestinal injury. In such models, palifermin administered before cytotoxic insult improved survival and reduced weight loss, both of which were attributed to maintenance and regeneration of the gastrointestinal mucosa by palifermin, enabling normal feeding, better nutrient and water absorption in the gut, and better protection against invasion by microorganisms through a more intact epithelial barrier.[2,3] Other studies have shown that palifermin enhances tolerance to radiation and thereby protects the normal mucosa of the digestive tract, lung, and salivary glands.[2,3,4,5]

Palifermin is a growth factor that primarily stimulates epithelial cells through the KGF receptor. KGF receptor has not been reported to be present on hematopoietic cell lines. Palifermin has been shown to enhance the growth of some human epithelial tumour cell lines *in vitro* at concentrations ≥ 10,000 ng/mL (> 15-fold higher than average therapeutic concentrations in humans), but did not affect the growth of cell lines derived from hematologic malignancies. In *in vitro* studies, palifermin did not inhibit the cytotoxic effects of radiation on epithelial tumour cell lines.[2] Three consecutive daily treatments of palifermin at doses up to 4,000 µg/kg (67-fold higher than the recommended human dose) repeated weekly for 4 to 6 weeks increased the growth rate of 1 of 7 human carcinoma (KGF-receptor expressing) xenografts in nude mice. In *in vivo* murine xenograft studies, palifermin did not inhibit the cytotoxic effects of radiation or chemotherapy on epithelial tumour cell lines.[2]

TOXICOLOGY

The preclinical toxicology studies of palifermin were conducted in multiple species.

Single-Dose Studies
In single-dose toxicity studies conducted in rats and monkeys, no mortality or clinical signs of overt toxicity were observed at doses up to 30,000 µg/kg (IV or SC) or 50,000 µg/kg (IV), respectively.

Reproduction and Developmental Toxicity
Increased postimplantation loss and decreased fetal body weights were observed when palifermin was administered to pregnant rabbits from days 6 to 18 of gestation at IV doses ≥ 150 µg/kg/day (2.5-fold higher than the recommended human dose). However, treatment with these doses was also associated with maternal toxicity (clinical signs and reductions in body weight gain/food consumption), suggesting that palifermin was not selectively toxic to rabbit development. No evidence of developmental toxicity was observed in rabbits at doses up to 60 µg/kg/day.

Increased postimplantation loss, decreased fetal body weight, and/or increased skeletal variations were observed when palifermin was administered to pregnant rats from days 6 to 17 or 19 of gestation at IV doses ≥ 500 µg/kg/day (> 8-fold higher than the

recommended human dose). Treatment with these doses was also frequently associated with maternal toxicity (clinical signs and body weight effects), suggesting that palifermin was not selectively toxic to rat development. No evidence of developmental toxicity was observed in rats at doses up to 300 µg/kg/day.

When palifermin was administered IV daily to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at doses up to 100 µg/kg/day. Systemic toxicity (clinical signs of toxicity and/or body weight effects), decreased epididymal sperm counts, and increased postimplantation loss were observed at doses ≥ 300 µg/kg/day (5-fold higher than the recommended human dose). Increased preimplantation loss and a decreased fertility index were observed at a palifermin dose of 1,000 µg/kg/day.

When palifermin was administered at IV doses up to 1,000 µg/kg in pregnant rats and up to 500 µg/kg in pregnant rabbits during gestation, palifermin levels in fetal serum and amniotic fluid were at or below the assay limit of quantification (0.25 ng/mL), suggesting negligible transplacental transfer.

Mutagenicity and Carcinogenicity Studies

The mutagenic properties of palifermin have been evaluated both *in vitro* (bacterial and mammalian genotoxicity assays and a chromosome aberration assay) and *in vivo* (mouse bone marrow micronucleus assay). Palifermin was not found to be mutagenic in any of these assays.

The carcinogenic potential of Kepivance® has not been evaluated in long-term animal studies. However, the potential of palifermin to enhance the incidence of spontaneous tumours has been evaluated in the transgenic mice which overexpressed the human c-Ha-ras oncogene (Tg.rasH2). Palifermin was administered once per week for nine weeks to four groups of rasH2 transgenic mice (25/sex/group) as a single intravenous injection of 0 (vehicle), 0.1, 1.0 or 10 mg/kg followed by a 17 week untreated period. Satellite groups of the wild type strain were used for toxicokinetic and immunological evaluation.
The toxicokinetic analysis demonstrated that systemic exposure (AUC) to palifermin increased with increasing doses. The maximum plasma level and AUC increased after multiple dosing, indicating an accumulation of palifermin in serum. The presence of antibodies to palifermin was demonstrated in the majority of the treated animals.

Gross necropsy revealed a thickening of the mucosal lining of the stomach in the females of the high-dose groups, This was defined histopathologically as an epithelial hyperplasia (non-neoplastic) of the non-glandular stomach at the intersection of the glandular and non-glandular stomach. This is consistent with the biological activity of palifermin. No meaningful increase in the incidence of neoplastic lesions was observed among treated animals. Thus, palifermin treatment of the transgenic mice prone to developing spontaneous tumors was not associated with toxicity or an increase in the incidence of neoplastic lesions.

REFERENCES

1. Osslund TD, Syed R, Singer E, et al. Correlation between the 1.6 Angstrom crystal structure and mutational analysis of keratinocyte growth factor. Prot Sci. 1998;7(8):1681-90.

2. Danilenko DM. Preclinical and early clinical development of keratinocyte growth factor, an epithelial-specific tissue growth factor. Toxicol Pathol. 1999;27:64-71.

3. Werner S. Keratinocyte growth factor: a unique player in epithelial repair processes. Cytokine Growth Factor Rev. 1998;9:153-65.

4. Lu JZ, Chow G, Scully S, et al. Keratinocyte growth factor (KGF) ameliorates salivary gland function in rat models of irradiation injury. Proc Am Assoc Cancer Res. 2002;43:580. Abstract 2873.

5. Liguang C, Larrier N, Rabbani ZN, et al. Assessment of the protective effect of keratinocyte growth factor on radiation-induced pulmonary toxicity in rats. Int J Radiat Oncol Biol Phys. 2003;57(supp 2):S162. Abstract 65A.

6. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. NEJM. 2004;351:2590-8.

7. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer. 1981;47:207-14.

8. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer. 2004;4:277-84.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr KEPIVANCE ®
(palifermin)

This leaflet is part III of the three-part "Product Monograph" published when Kepivance® ([*KEP ih vans]*) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Kepivance®.

Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Kepivance® (palifermin) is used to decrease the incidence and duration of oral mucositis (severe mouth sores) that is a side effect of some cancer treatments. Kepivance® is used to treat the mouth and throat soreness, which can improve your ability to swallow, eat, drink, talk, and sleep.

What it does:
Kepivance® is a man-made form of keratinocyte growth factor (KGF). KGF, also known as palifermin, is a substance that is naturally produced by the body. It stimulates the production and growth of certain skin cells, called epithelial cells that form the lining of your mouth, digestive tract and other skin tissues in the body.

When it should not be used:
Kepivance® should not be used in patients with known hypersensitivity (allergy) to certain proteins derived from *E. coli*, to palifermin, or any of the components of the product. For a complete listing, see **What the important nonmedicinal ingredients are**.

What the medicinal ingredient is:
The medicinal ingredient is palifermin.

What the important nonmedicinal ingredients are:
The nonmedicinal ingredients are L-histidine (an amino acid), mannitol (a type of sugar), polysorbate 20 (a moisturising agent) and sucrose (a type of sugar).

What dosage form it comes in:
Kepivance® is available as a sterile freeze-dried powder for reconstitution and intravenous injection. Each vial contains 6.25 mg of palifermin.

WARNINGS AND PRECAUTIONS

Kepivance® should not be used within 24 hours before, during infusion of, or within 24 hours after administration of chemotherapy. Kepivance® should also not be used in combination with heparin.

Kepivance should not be used in children under 18 years of age

There may be a risk that Kepivance treatment could lead to cataracts (a clouding of your vision) in some patients.

Your doctor will be experienced in the use of Kepivance® and anti-cancer medicines.

There have not been studies on the use of Kepivance® in pregnant women. Kepivance® should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the unborn infant.

The safety and efficacy of Kepivance® have not been established in patients with all types of cancers. The effect of Kepivance® on some types of tumors which may react to KGF stimulation is also not known. The use of Kepivance with melphalan (a drug used to treat multiple myeloma, a type of cancer), is not recommended.

INTERACTIONS WITH THIS MEDICATION

Kepivance® has been observed to interact with heparin (a blood thinner) in the laboratory, but this interaction is not known to decrease the effectiveness of Kepivance®. Nevertheless, *;* heparin and Kepivance® should generally not be used together.

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dose is 60 μg/kg/day, given by intravenous injection for 3 days before and 3 days after chemotherapy.

At least 24 hours should be allowed between the administration of Kepivance® and the chemotherapy infusion.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Possible side effects include skin and oral (mouth) reactions (eg., rash, redness of the skin, itching, swelling, mouth / tongue thickness or discoloration, taste disorders). If you experience any of these reactions or other adverse reactions, you should report them to your doctor. Also, if you experience any changes in vision, please notify your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common: Skin and oral reactions (eg., rash, redness of the skin, itching, swelling, mouth / tongue thickness or discoloration, taste disorders);		√	
Uncommon: Anaphylaxis (a severe allergic reaction that can occur rapidly);		√	
Hypersensitivity (another type of allergic reaction)		√	

This is not a complete list of side effects. For all other common / uncommon side effects, please refer to the Product Monograph. For any unexpected effects while taking Kepivance®, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free to 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
- - Fax toll-free to 1-866-678-6789
- - Mail to:
  Canada Vigilance Program
  Health Canada
  Postal Locator 00701D
  Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Kepivance® should be stored refrigerated at 2° to 8°C (36° to 46°F); vials should be kept in their carton to protect them from light until time of use.

When dissolved, Kepivance® contains no preservative and is intended for single use only; therefore, it should be administered immediately (within 3 hours). However, when handled by a health care professional under very clean conditions, Kepivance® may be kept in the refrigerator, in the carton, at 2° to 8°C (36° to 46°F) for up to 24 hours. Before injection, Kepivance® may be allowed to reach room temperature for a maximum of 1 hour, but should be protected from light. It should not be shaken or frozen. Keep out of reach of children.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be obtained by contacting the sponsor,

Swedish Orphan Biovitrum AB (publ) at 1-866-773-5274
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