

Product Monograph

^{Pr}Kepivance®
(palifermin)

Keratinocyte Growth Factor

Sterile, Lyophilized Powder for Reconstitution
Intravenous Use Only

6.25 mg/vial

Manufactured by:
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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 <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

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: The safety and effectiveness of Kepivance[®] in pediatric patients have not been established.

CONTRAINDICATIONS

Kepivance[®] (palifermin) 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 non-hematologic malignancies.

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

Carcinogenesis and Mutagenesis

The carcinogenic potential of Kepivance[®] has not been evaluated in long-term animal studies. Because the KGF receptor is expressed on epithelial cells, there is a theoretical risk that Kepivance[®] could stimulate the proliferation of epithelial-derived tumor cells.

Kepivance[®] was negative in *in vitro* bacterial and mammalian mutagenicity assays, negative in the *in vitro* chromosome aberration assay, and negative in the *in vivo* mouse bone marrow micronucleus assay.

Ophthalmologic

There is also a theoretical risk of ocular toxicity as a result of Kepivance[®] interaction with KGFR-expressing cells on the lens of the eye. In clinical trials, with recommended dosage, ocular toxicity was not demonstrated. Long-term effects are not yet known.

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.

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.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Please refer to the WARNINGS AND PRECAUTIONS: Carcinogenesis and Mutagenesis and DESCRIPTION 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[®] (palifermin) 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 change in the established overall safety information for Kepivance[®].

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[®] (palifermin) 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 6 days following the first of 3 consecutive daily doses of Kepivance[®], with a median duration of 5 days.

The most common serious adverse reaction attributed to Kepivance[®] was skin rash, which was reported in less than 1% (3/409) of patients 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), study drug was discontinued due to skin rash. Other serious adverse reactions occurred at a similar rate in patients who received Kepivance[®] (20%) or placebo (21%). 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 \geq 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/ parasthesia	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		
Edema Peripheral	10 (4)	54 (14)
Edema Face	2 (1)	23 (6)
Edema	4 (2)	17 (4)
Edema Circumoral	1 (0)	11 (3)
Pain	2 (1)	11 (3)
Edema Genital	0 (0)	8 (2)
	0 (0)	4 (1)

BODY SYSTEM Preferred Term (WHOART)	Placebo (N=241) N (%)	Kepivance® (N=396) N (%)
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	2 (1)	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 $\geq 1\%$ 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 Kepivance[®]. 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 Kepivance[®] with the incidence of antibodies to other products may be misleading.

Post-Market Adverse Drug Reactions

There have been no new major findings necessitating change in the established overall safety information for Kepivance[®] based on the post marketing experience to date.

DRUG INTERACTIONS

Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted for Kepivance[®] with drugs that may be used in the intended patient population. Kepivance[®] has been shown to bind to heparin *in vitro*. Therefore, 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).

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[®] (palifermin) 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 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 at least 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 Kepivance[®] (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 Kepivance[®] takes less than 5 minutes. Visually inspect the solution for discoloration and particulate matter before administration. The solution should be essentially free of visible particles. Kepivance[®] should not be administered if discoloration 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 Kepivance[®], 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

The maximum amount of Kepivance[®] (palifermin) 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 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. 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

Pharmacodynamics

Epithelial cell proliferative effects of Kepivance[®] 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 postdosing, was highest at 48 hours, and remained elevated compared to baseline at 72 hours postdosing.

Pharmacokinetics

The pharmacokinetics (PK) of Kepivance[®] 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), Kepivance[®] 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. Kepivance[®] 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 (V_{ss}) 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 V_{ss} 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 Kepivance[®] occurred after 3 consecutive daily doses of 20 and 40 µg/kg (healthy subjects) or 60

µg/kg (cancer patients). Inter-subject variability is high with a CV% of about 50% for CL and 60% for V_{ss} .

Special Populations and Conditions

No gender-related differences were observed in the pharmacokinetics of Kepivance[®]. The pharmacokinetic profile in pediatric and geriatric populations (see WARNINGS AND PRECAUTIONS: Pediatric Use, Use in the Elderly), or in patients with hepatic impairment, has not been assessed.

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[®] (palifermin) 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 Kepivance[®] (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 a 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 ($\pm 95\%$ CI) WHO Oral Mucositis Grade – Study 1

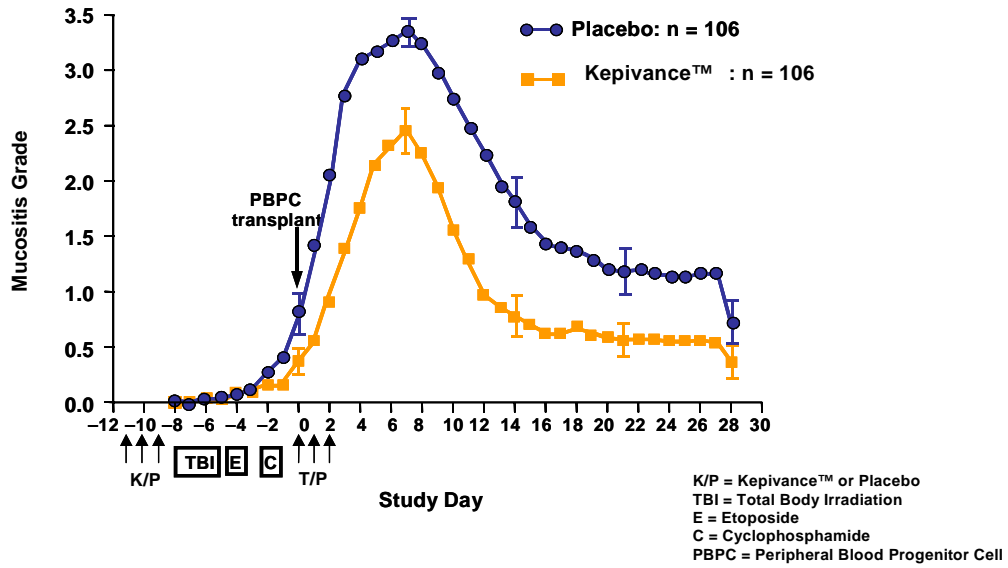
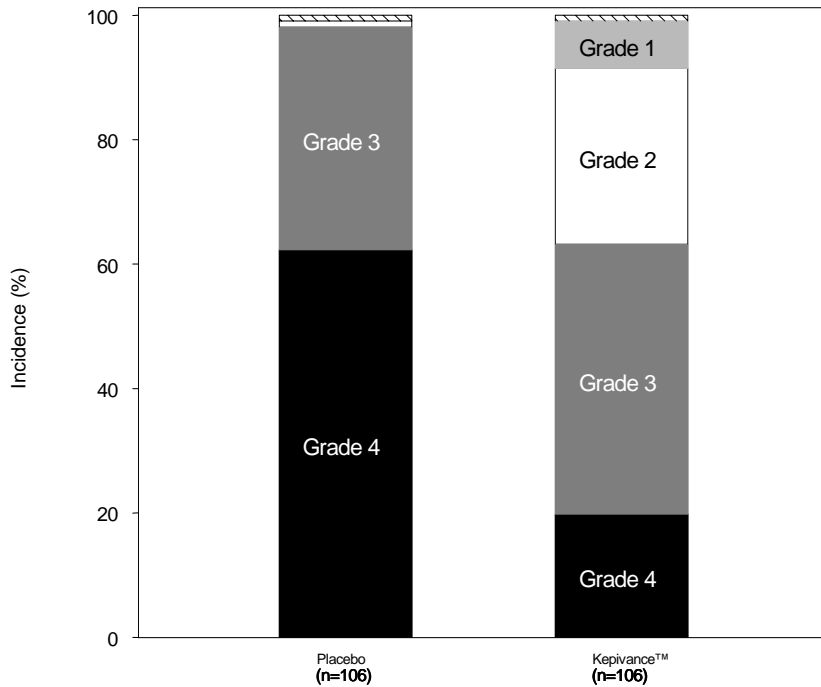


Figure 2. Incidence of Oral Mucositis by Maximum Grade –Study 1



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).

Long-term follow up (Study 960226)

In the hematology transplant setting, with a median follow-up of 23.1 months (range 0.2 to 83.8 months) for the placebo group and 23.8 months (range 0.8 to 81.6 months) 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 the same (6%) in both treatment groups.

DETAILED PHARMACOLOGY

The preclinical pharmacology of Kepivance[®] (palifermin) has been studied in mice, rats, and rhesus monkeys. In these studies, Kepivance[®] 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} Kepivance[®] has been extensively studied in murine models of chemotherapy and radiation-induced gastrointestinal injury. In such models, Kepivance[®] administered before cytotoxic insult improved survival and reduced weight loss, both of which were attributed to maintenance and regeneration of the gastrointestinal mucosa by Kepivance[®], 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 Kepivance[®] 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 $\geq 10,000$ 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 μ g/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.

Multidose Studies

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 \geq 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 \geq 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.

Reproductive Toxicity

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 \geq 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.

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.

PART III: CONSUMER INFORMATION

**PrKEPIVANCE®
(palifermin)**

This leaflet is part III of the three-part “Product Monograph” published when Kepivance® 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 ulcerations) that is a side effect of some cancer treatments. Kepivance® is used to treat the mouth and throat soreness thereby improving the patient’s ability to swallow, eat, drink, talk, and sleep.

What it does:

Kepivance® is a man-made form of keratinocyte growth factor (KGF). KGF is a substance that is naturally produced by the body. It stimulates the production and growth of epithelial cells in response to epithelial tissue injury.

When it should not be used:

Kepivance® should not be used in patients with known hypersensitivity to *E. coli*-derived proteins, palifermin, or any of the components of the product.

What the medicinal ingredient is:

The medicinal ingredient is palifermin.

What the important nonmedicinal ingredients are:

The nonmedicinal ingredients are L-histidine, mannitol, polysorbate 20, and sucrose.

What dosage forms it comes in:

Kepivance® is available as a sterile, freeze-dried powder for reconstitution. 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® treatment should be supervised by a physician experienced in the use of anticancer therapies.

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 fetus.

INTERACTIONS WITH THIS MEDICATION

Kepivance® has been known to bind to heparin *in vitro*; therefore, if heparin is used to maintain an IV line, saline should be used to rinse the line, prior to and after Kepivance® is used.

PROPER USE OF THIS MEDICATION

Usual dose:

The usual dose is 60 µg/kg/day. It is administered as an IV bolus injection, given 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.

Reconstitution:

Kepivance® should be reconstituted under sterile conditions with 1.2 mL of sterile water for injection (provided separately) to yield a solution containing 6.25 mg of Kepivance® (5 mg/mL). The sterile water 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 Kepivance® will dissolve in less than 5 minutes. Visually inspect the solution for discoloration and particulate matter before administration. The solution should be essentially free of visible particles. Kepivance® should not be administered if discoloration 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 Kepivance®, and do not dissolve Kepivance® with other liquids. Do not filter the solution during preparation or administration.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Possible side effects include skin and oral reactions (eg. rash, redness of the skin, itching, swelling, mouth/tongue thickness or discolouration, taste disorders). If you experience any of these reactions or other adverse reactions, you should report these to your doctor. Since the receptor for this drug is reported to be expressed on the lens of the eye, if you experience visual abnormalities 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 discolouration, taste disorders)		✓	

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.

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.

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 light. Shaking should be avoided. Do not freeze reconstituted solution.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
 toll-free fax 866-678-6789
 By email: cadtmp@hc-sc.gc.ca

By regular mail:
 National AR Centre
 Marketed Health Products Safety and Effectiveness
 Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Amgen Canada Inc., at: 1-866-502-6436.

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