HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Kepivance safely and effectively. See full prescribing information for Kepivance.

Kepivance® (palifermin)
For injection, for intravenous use
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Postmarketing Experience (6.2)	[3/2009]
Drug Interactions (7)	[4/2009]
Geriatric Use (8.5)	[4/2009]
Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)	[4/2009]

----------INDICATIONS AND USAGE----------

- Kepivance is a mucocutaneous epithelial human growth factor indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support (1)
- The safety and efficacy of Kepivance have not been established in patients with non-hematologic malignancies (1, 5)

----------DOSAGE AND ADMINISTRATION----------

Administer as an intravenous bolus injection at a dose of 60 mcg/kg/day for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses (2.1)

- Administer the first 3 doses prior to myelotoxic therapy with the third dose 24 to 48 hours before myelotoxic therapy (2.1)
- Administer the last 3 doses after myelotoxic therapy is complete with the first of these doses on the day of hematopoietic stem cell infusion after the infusion is completed, and at least 4 days after the most recent administration of Kepivance (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

6.25 mg lyophilized powder in single-use vials (3)

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

- Potential for stimulation of tumor growth — Kepivance is not indicated for non-hematologic tumors. The effects of Kepivance on stimulation of keratinocyte growth factor (KGF) receptor-expressing, non-hematopoietic tumors in patients are not known (1, 5.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥20% and 5%≥placebo) are rash, fever, elevated serum amylase (Grade 3/4), pruritus, erythema, and edema (6)

To report SUSPECTED ADVERSE REACTIONS, contact Biovitrum at 1-866-546-3738 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Heparin may increase systemic exposure (7)
- Myelotoxic chemotherapy (7, 14)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Consider discontinuation of drug or nursing, taking into account the importance of drug to mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION
Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

The safety and efficacy of Kepivance have not been established in patients with non-hematologic malignancies *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Regimen

The recommended dose of Kepivance is 60 mcg/kg/day, administered as an intravenous bolus injection for 3 consecutive days before and 3 consecutive days after myelotoxic therapy, for a total of 6 doses.

Administer the first 3 doses prior to myelotoxic therapy. Administer the third dose 24 to 48 hours prior to beginning myelotoxic therapy *[see Drug Interactions (7)]*.

Administer the last 3 doses after myelotoxic therapy is complete; Administer the first of these doses on the day of hematopoietic stem cell infusion after the infusion is completed, and at least 4 days after the most recent administration of Kepivance *[see Drug Interactions (7)]*.

2.2 Preparation and Administration

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Reconstitute Kepivance lyophilized powder with Sterile Water for Injection, USP (not supplied) by slowly injecting 1.2 mL of Sterile Water for Injection, USP to yield a final concentration of 5 mg/mL.
- Swirl the contents gently during dissolution. Do not shake or vigorously agitate the vial. Dissolution of Kepivance can take up to 3 minutes.
- Visually inspect the solution for discoloration and particulate matter before administration. The reconstituted solution should be clear and colorless. Do not administer Kepivance if discoloration or particulates are observed. Do not filter the reconstituted solution during preparation or administration. Do not freeze the reconstituted solution. Protect from light.

Administration

- Administer Kepivance by intravenous bolus injection. If heparin is used to maintain an intravenous line, rinse the line with saline prior to and after Kepivance administration *[see Drug Interactions (7)]*.
- The reconstituted solution contains no preservatives and is intended for single use only. Discard any unused portion.
- Following reconstitution, it is recommended that the product be used immediately. If not used immediately, the reconstituted solution of Kepivance may be stored refrigerated in its carton at 2° to 8°C (36° to 46°F) for up to 24 hours.
- Prior to injection, allow Kepivance to reach room temperature for a maximum of 1 hour protected from light. Discard Kepivance left at room temperature for more than 1 hour.

3 DOSAGE FORMS AND STRENGTHS

6.25 mg lyophilized powder in single-use vials.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 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-hematopoietic 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 *[see Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The most common adverse reactions attributed to Kepivance were skin toxicities (rash, erythema, edema, pruritus), oral toxicities (dysesthesia, tongue discoloration, tongue thickening, alteration of taste), pain, arthralgias, and dysesthesia. The 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. In patients receiving Kepivance, dysesthesia (including hyperesthesia, hypoesthesia, and paresthesia) was usually localized to the perioral region, whereas in patients receiving placebo dysesthesias were more likely to occur in extremities.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in Table 1 and the discussion below reflect exposure to Kepivance in 409 patients with hematologic malignancies who were enrolled in 3 randomized, placebo-controlled clinical trials and a pharmacokinetic study. Patients received Kepivance either before, or before and after, regimens of myelotoxic chemotherapy, with or without total body irradiation (TBI), followed by hematopoietic stem cell support. Kepivance was administered in daily doses ranging from 5 to 80 mcg/kg/day. The total dose of Kepivance ranged from 15 to 480 mcg/kg with a median of 360 mcg/kg. The population had a median age of 48 years (range: 41 to 60 years), 62% were male and 83% were White with 7.4 % Black and 6.2 % Hispanic. Non Hodgkin's lymphoma (NHL) was the most common malignancy followed by Hodgkin's disease, multiple myeloma, and leukemia.

The most common serious adverse reaction attributed to Kepivance was skin rash, reported in less than 1% (3/409) of patients treated. Grade 3 skin rashes occurred in 3% of patients (9/409) receiving Kepivance and 2% (5/241) receiving placebo.

Table 1. Incidence of Adverse Reactions Occurring with a Between-Group Difference of ≥ 5%

BODY SYSTEM Adverse Event	Kepivance (n = 409) %	Placebo (n = 241) %
BODY AS A WHOLE		
Edema	28	21
Pain	16	11
Fever	39	34
GASTROINTESTINAL		
Mouth/Tongue Thickness or Discoloration	17	8
MUSCULOSKELETAL		
Arthralgia	10	5
SKIN AND APPENDAGES		
Rash	62	50
Pruritus	35	24
Erythema	32	22
SPECIAL SENSES		
Taste Altered	16	8
CENTRAL NERVOUS SYSTEM / PERIPHERAL NERVOUS SYSTEM		
Dysesthesia – Hyperesthesia / hypoesthesia/ paresthesia	12	7
METABOLIC		
Elevated serum lipase		
All grades	28	23
Grade 3 and 4	11	5
Elevated serum amylase		
All grades	62	54
Grade 3 and 4	38	31

Laboratory Test Findings: Reversible elevations in serum lipase and amylase, which did not require treatment, were reported in 28% and 62% of patients receiving Kepivance and 23% and 54%of patients receiving placebo. In general, peak increases were observed during the period of cytotoxic therapy and returned to baseline by the day of hematopoietic stem cell infusion. Amylase was mainly salivary in origin.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The clinical significance of antibodies to Kepivance is unknown but may include decreased activity and/or cross reactivity with other members of the FGF family of growth factors.

In clinical trials, serum samples from patients treated with Kepivance were tested for antibodies to Kepivance using an electrochemiluminescence-based binding assay. Twelve of 645 patients (2%) tested positive; none 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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Kepivance in the stem cell transplant setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Vaginal edema and erythema;
- Palmar-plantar Erythrodysaesthesia Syndrome (also known as “hand-foot syndrome”)

7 DRUG INTERACTIONS

In vitro and *in vivo* data showed that palifermin interacts with unfractionated as well as low molecular weight heparins. Heparin co-administration resulted in a 5-fold increase in palifermin systemic exposure. Avoid co-administration of palifermin with heparin. If heparin is used to maintain an intravenous line, rinse the line with saline prior to and after Kepivance administration *[see Clinical Pharmacology (12.3)]*.

Do not administer Kepivance within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy *[see Dosage and Administration (2.1) and Clinical Studies (14)]*. In a clinical trial, administration of Kepivance within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.

8 USE IN SPECIFIC POPULATIONS

No gender-related differences were observed in the pharmacokinetics of Kepivance at doses ≤ 60 mcg/kg.

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of Kepivance in pregnant woman. Palifermin is embryotoxic in rabbits and rats. In reproductive toxicology studies, increased post-implantation loss and decrease in fetal body weight were observed in both rabbit (2.5 times the maximum recommended human dose [MRHD], adjusted for body weight) and rat (8 times the MRHD, on a mcg/kg basis) *[see Nonclinical Toxicology (13.3)]*. Kepivance should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether Kepivance is secreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Kepivance, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Kepivance have not been established in children.

8.5 Geriatric Use

Clinical studies of Kepivance did not include sufficient numbers of subjects aged 65 years and older to determine whether they responded differently from younger subjects. [*see Clinical Pharmacology (*12.*3)]*.

8.6 Patients with Renal Impairment

No dose adjustment is recommended for patients with renal impairment [*see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment

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

10 OVERDOSAGE

No data are available regarding overdosage with Kepivance.

11 DESCRIPTION

Kepivance (palifermin) is a truncated human KGF produced by recombinant DNA technology in *E coli.* Kepivance 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 is supplied as a sterile, white, preservative-free, lyophilized powder for intravenous injection after reconstitution with 1.2 mL of Sterile Water for Injection, USP. Reconstitution yields a clear, colorless solution of Kepivance (5 mg/mL) with a pH of 6.5. Each single use vial of Kepivance contains palifermin (6.25 mg),with L histidine (1.94 mg), mannitol (50 mg), polysorbate 20 (0.13 mg or 0.01% w/v), and sucrose (25 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KGF is an endogenous protein in the fibroblast growth factor (FGF) family that binds to the KGF receptor. Binding of KGF to its receptor has been reported to result in proliferation, differentiation, and migration of epithelial cells. The KGF receptor, one of four receptors in the FGF 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. The KGF receptor has been reported to not be present on cells of the hematopoietic lineage. Endogenous KGF is produced by mesenchymal cells and is upregulated in response to epithelial tissue injury.

In mice and rats, Kepivance enhanced proliferation of epithelial cells (as measured by Ki67 immunohistochemical staining and BrDU uptake) and demonstrated an increase in tissue thickness of the tongue, buccal mucosa, and gastrointestinal tract. Kepivance has been studied in murine models of chemotherapy and radiation-induced gastrointestinal injury. In such models, administration of Kepivance prior to and/or after the cytotoxic insult improved survival and reduced weight loss compared to control animals.

Kepivance has been shown to enhance the growth of human epithelial tumor cell lines *in vitro* at concentrations ≥ 10 mcg/mL (> 15-fold higher than average therapeutic concentrations in humans). In nude mouse xenograft models, three consecutive daily treatments of Kepivance at doses of 1,500 and 4,000 mcg/kg (25- and 67-fold higher than the recommended human dose, respectively) repeated weekly for 4 to 6 weeks were associated with a dose-dependent increase in the growth rate of 1 of 7 KGF receptor-expressing human tumor cell lines.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

The pharmacokinetics of Kepivance were studied in healthy subjects and patients with hematologic malignancies. After single intravenous doses of 20 to 250 mcg/kg in healthy subjects and 60 mcg/kg in cancer patients, Kepivance concentrations declined over 95% 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. In cancer patients compared with healthy subjects, after a 60 mcg/kg single dose of Kepivance the average total body clearance (CL) was 2- to 4-fold higher, and volume of distribution at steady state (Vss) was 2-fold higher. 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 mcg/kg in healthy subjects or 60 mcg/kg in cancer patients.

The potential pharmacokinetic interaction between palifermin and heparin was evaluated in a single-dose study in 27 healthy subjects receiving palifermin (60 mcg/kg) co-administered with and without therapeutic levels of unfractionated heparin. This co-administration resulted in a 5-fold increase in palifermin AUC and an 80% decrease in the mean CL. There was no significant effect of palifermin on heparin activity with respect to activated partial thromboplastin time (aPTT). The clinical relevance of this observed increase in palifermin systemic exposure is unclear *[see Drug Interactions (7)]*.

Results from a pharmacokinetics study in 24 subjects with varying degrees of renal impairment demonstrated that renal impairment has little or no influence on Kepivance pharmacokinetics *[see Use in Specific Populations (8.6)]*.

In a single-dose study, subjects received a 180-mcg/kg or 90-mcg/kg dose of palifermin administered by intravenous bolus injection. Subjects over the age of 65 (n=8) had an approximately 30% lower rate of CL on average than those 65 and younger (n=19). No dose adjustment is recommended for the geriatric population *[see Use in Specific Populations (8.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: No treatment-related increase in the incidence of neoplastic lesions occurred in transgenic rasH2 mice treated with 9 weekly intravenous doses of palifermin, at 167-fold higher than the recommended human dose (on a mcg/kg basis).

Mutagenicity: No clastogenic or mutagenic effects of palifermin were observed in mammalian chromosomal aberration or Ames genotoxicity assays.

Impairment of Fertility: Reproductive performance, fertility, and sperm assessment parameters were not affected when palifermin was administered intravenously to male and female rats prior to and during mating at doses up to 100 mcg/kg/day. Decreased epididymal sperm counts, and increased post-implantation losses were observed at doses ≥ 300 mcg/kg/day (5-fold higher than the recommended human dose, on a mcg/kg basis). Increased pre-implantation loss and a decreased fertility index were observed at a palifermin dose of 1000 mcg/kg/day.

13.3 Reproductive and Developmental Toxicology

In animal reproductive toxicity studies, palifermin is embryotoxic at doses that are 2.5 times (rabbits) and 5 to > 8 times (rats) the MRHD, based on body weight (mcg/kg). Pregnant rabbits received intravenous palifermin during organogenesis at doses equivalent to 1.0 and 2.5 times the MRHD, based on body weight (mcg/kg). Increased post-implantation loss and decreased fetal body weights occurred along with maternal toxicity (clinical signs and reductions in body weight gain/food consumption) at doses 2.5 times the MRHD.

In pregnant rats, animals received intravenous palifermin during organogenesis at doses of 5 to >8 times the MRHD based on body weight (mcg/kg). Increased post-implantation loss, decreased fetal body weight, and/or increased skeletal variations occurred in the presence of maternal toxicity at doses > 8 times the MRHD.

14 CLINICAL STUDIES

The safety and efficacy of Kepivance in decreasing the incidence and duration of severe oral mucositis in patients with hematologic malignancies (NHL, Hodgkin's disease, acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, or multiple myeloma) receiving myelotoxic therapy requiring hematopoietic stem cell support, were established in a randomized placebo-controlled clinical trial of 212 patients (Study 1) and a randomized, schedule-ranging, placebo-controlled clinical trial of 169 patients (Study 2).

In Study 1, 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 hematopoietic stem cell support. Patients were randomized to receive either Kepivance (n = 106) or placebo (n = 106). Kepivance 60 mcg/kg was administered as a daily intravenous injection for 3 consecutive days prior to initiation of cytotoxic therapy and for 3 consecutive days following infusion of hematopoietic stem cells. The major efficacy outcome was the number of days during which patients experienced severe oral mucositis (Grade 3/4 on the WHO [World Health Organization] scale)[1]. Other analyses included the incidence, duration, and severity of oral mucositis and the use of opioid analgesia. There was no evidence of a delay in time to hematopoietic recovery in patients who received Kepivance as compared to patients who received placebo. The results of Study 1 are presented in Table 2 and Figure 1.

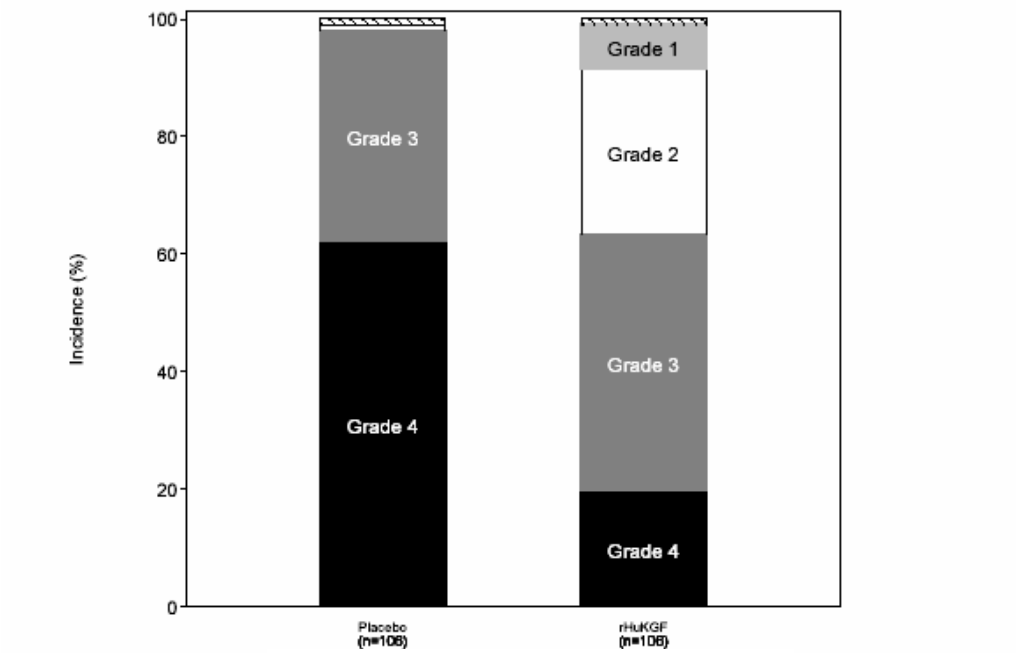
Table 2: Study 1 Efficacy Outcomes

Efficacy Variable	Kepivance (60 mcg/kg/day) (n = 106)	Placebo (n = 106)
Median (25^{th}, 75^{th} percentile) Days of WHO Grade 3/4 Oral Mucositis*	3 (0, 6)	9 (6, 13)
Incidence of WHO Grade 3/4 Oral Mucositis	63% (67/106)	98% (104/106)
Median (25^{th}, 75^{th} percentile) Days of WHO Grade 3/4 Oral Mucositis in Affected Patients	6 (3, 8) (n = 67)	9 (6, 13) (n = 104)
Incidence of WHO Grade 4 Oral Mucositis	20%	62%
Median (25^{th}, 75^{th} percentile) Cumulative Opiod Dose (morphine mg equivalents)	212 (3, 558)	535 (269, 1429)

* P < 0.001 compared to placebo, using Generalized Cochran-Mantel-Haenszel (CMH) test stratified for study center.

[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.

Figure 1: Study 1 Incidence of Oral Mucositis by Maximum Grade WHO Oral Mucositis Scale



Placebo
(n = 106)

Kepivance®
(n = 106)

Study 2 was a randomized, multi-center, placebo-controlled trial 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 hematopoietic stem cell support. The results for Study 1 were supported by results observed in the subset of patients in Study 2 who received the same dose and schedule of Kepivance administered in Study 1. One arm of Study 2 that included patients who received 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 hematopoietic stem cells was prematurely closed by the Safety Committee for lack of efficacy and a trend towards increased severity and duration of oral mucositis as compared to placebo-treated patients. The Safety Committee attributed the safety finding to Kepivance having been administered within 24 hours of chemotherapy, which resulted in an increased sensitivity of the rapidly dividing epithelial cells in the immediate post-chemotherapy period *[see Dosage and Administration (2.1) and Drug Interactions (7)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Kepivance is supplied as a lyophilized powder in single use vials containing 6.25 mg of palifermin.

Kepivance vials are supplied in:

- a dispensing pack containing 6 vials (NDC 66658-112-06)
- a distribution case containing 4 dispensing packs (NDC 66658-112-24) [4 x 6 vial dispensing packs (24 x 6.25 mg/vial)].

Store Kepivance vials in the dispensing pack in its carton refrigerated at 2° to 8°C (36° to 46°F) until time of use. Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise patients to report the following to healthcare providers:

- Rashes and reddening of skin *[see Adverse Reactions (6.1)]*
- Itchiness *[see Adverse Reactions (6.1)]*
- Swelling of tongue *[see Adverse Reactions (6.1)]*
- Changes in mouth and tongue sensation *[see Adverse Reactions (6.1)]*
- Alteration in taste *[see Adverse Reactions (6.1)]*

Inform patients

- That the safety and efficacy of Kepivance have not been established in patients with non-hematologic malignancies *[see Indications and Usage (1) and Warnings and Precautions (5.1)]*
- Of the evidence of tumor growth and stimulation in cell culture and in animal models of non-hematopoietic human tumors *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.1)]*

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