KEPIVANCE®
(palifermin)

NAME OF THE MEDICINE

Palifermin is a human keratinocyte growth factor (KGF) produced by recombinant DNA technology in *Escherichia coli*. KEPIVANCE is the Swedish Orphan Biovitrum AB (publ) trademark for the palifermin (rbe) product.

DESCRIPTION

Palifermin 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 a sterile, white, preservative-free, lyophilised powder for reconstitution and administration as an intravenous (IV) injection. 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. Vials of KEPIVANCE are reconstituted with 1.2 mL of sterile Water for Injections to yield a palifermin concentration of 5 mg/mL. Reconstitution yields a clear, colourless solution of palifermin with a pH of 6.5.

PHARMACOLOGY

Pharmacodynamics

Keratinocyte growth factor (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, oesophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, skin (hair follicles and sebaceous gland) and the lens and cornea of the eye. The KGF receptor has not been detected on cancer cells of the haematopoietic lineage. Endogenous KGF is produced by mesenchymal cells and is up-regulated in response to epithelial cell injury.

Palifermin has been studied in murine models of chemotherapy- and radiation-induced oral/gastrointestinal injury. In such models, administration of palifermin prior to and/or after the cytotoxic insult generally improved survival, reduced weight loss and increased epithelial thickness of the tongue, oral cavity and oesophagus compared to control animals.

In an *in-vitro* study, palifermin did not inhibit the cytotoxic effects of radiation on epithelial tumour cell lines. In murine xenograft studies, palifermin did not affect the efficiency of radiotherapy or chemotherapy (5-FU) to reduce the rate of tumour growth.

In humans, evidence of increased epithelial cell proliferation was observed in buccal biopsies from healthy subjects given palifermin at 40 µg/kg/day intravenously 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 post dosing, was highest at 48 hours and remained elevated compared to baseline at 72 hours post dosing.

Pharmacokinetics

The pharmacokinetics of palifermin was studied in healthy volunteers and patients with haematologic malignancies. After single IV doses of 20 to 250 µg/kg (healthy volunteers) and 60 µg/kg (cancer patients), palifermin exhibited extravascular distribution and an average terminal half-life of 4.5 hours. Approximately dose-linear pharmacokinetics were observed in the dose-ranging studies in healthy volunteers. No accumulation of palifermin occurred after 3 consecutive daily doses of 20 and 40 µg/kg (healthy volunteers) or 60 µg/kg (adult patients) or 40 to 80 µg/kg (paediatric patients).

Special Populations

Geriatric Use

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

Paediatric use

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

Hepatic and renal insufficiency

The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed. Bilateral nephrectomy of rats led to a 2-fold increase in serum palifermin AUC values. Varying degrees of renal impairment has little or no influence on the pharmacokinetics of palifermin.

CLINICAL TRIALS

The palifermin clinical program in the setting of myelotoxic therapy requiring haematopoietic stem cell (HSC) support included patients with haematologic malignancies (non-Hodgkin's lymphoma [NHL], Hodgkin's disease [HD], acute myeloid leukaemia [AML], acute lymphoblastic leukaemia [ALL], chronic myeloid leukaemia [CML], chronic lymphocytic leukaemia [CLL] or multiple myeloma [MM]) enrolled in randomised, placebo-controlled clinical studies (Phases 1/2 through 3) and one pharmacokinetic study.

The efficacy and safety of palifermin were established in a randomised, double-blind, placebo-controlled Phase 3 study 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 haematological malignancies (NHL, HD, AML, ALL, CML, CLL, or MM). In this study, 212 patients were randomised and received either palifermin or placebo. Palifermin 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 scale) 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.

The study met its primary objective of demonstrating that, across all patients, palifermin-treated patients had a clinically and statistically significant reduction in the number of days during which

they experienced severe oral mucositis (grade 3/4 on the WHO scale) compared to placebo-treated patients (Table 1).

In addition, use of palifermin 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 (Table 1). Although not prospectively defined endpoints of the Phase 3 study, the requirement for total parenteral nutrition (TPN) and incidence of febrile neutropoenia (absolute neutrophil count [ANC] < 0.5×10^9/L with a concurrent temperature ≥ 38.5°C) were significantly improved (Table 1).

Table 1. Oral Mucositis & Related Clinical Sequelae – HSC Transplant Study

	Placebo n = 106	**Palifermin (60 µg/kg/day) n = 106**	**p-value***
Mean (SD) Days of WHO Grade 3/4 Oral Mucositis**	10.4 (6.2)	3.7 (4.1)	<0.001
Patient Incidence of WHO Grade 3/4 Oral Mucositis	98%	63%	<0.001
Mean (SD) Days of WHO Grade 3/4 Oral Mucositis in affected patients	10.6 (6.1) (n = 104)	5.9 (3.6) (n = 67)	
Patient Incidence of WHO Grade 4 Oral Mucositis	62%	20%	<0.001
Mean (SD) Days of WHO Grade 2/3/4 Oral Mucositis	15.7 (7.8)	8.4 (5.8)	<0.001
Opioid Analgesia for Oral Mucositis:			
Mean (SD) Days	11.8 (5.6)	6.7 (5.5)	<0.001
Mean (SD) Cumulative Dose (morphine mg equivalents)	1146.5 (1702.1)	699.5 (1749.3)	<0.001
Patient Incidence of TPN***	55%	31%	<0.001
Patient Incidence of Febrile Neutropoenia***	92%	75%	<0.001

* Using Cochran-Mantel-Haenszel (CMH) test stratified for study centre
** WHO Oral Mucositis Scale: Grade 1 = soreness/erythema; Grade 2 = erythema, ulcers, can eat solids; Grade 3 = ulcers, requires liquid diet only; Grade 4 = alimentation not possible
**** Not prospectively defined endpoints of Phase 3 study

In this randomised study, patient-reported outcomes associated with oral mucositis, including mouth and throat soreness and its impact on swallowing, drinking, eating, talking and sleeping were collected using 5-point Likert-like scales with zero representing no soreness or limitation and four representing extreme soreness or inability to perform the functional activity. Compared to placebo-treated patients, palifermin-treated patients demonstrated clinically meaningful and statistically significant differences in all of these patient-reported outcomes (Table 2). These patient-reported outcomes were highly correlated to the clinician grading of oral mucositis using the WHO scale.

Table 2. Patient-Reported Outcomes – HSC Transplant Study

	% Improvement - Palifermin vs. Placebo	p-value*
Mouth & Throat Soreness	38%	<0.001
Ability to Swallow	38%	<0.001
Ability to Drink	38%	<0.001
Ability to Eat	40%	<0.001
Ability to Talk	47%	<0.001
Ability to Sleep	40%	<0.001

* Using CMH test stratified for study centre

A randomised, placebo-controlled, double-blind trial (study 20050219) was conducted to evaluate the efficacy of palifermin given pre-versus pre- and post-chemotherapy in patients with multiple myeloma receiving conditioning with melphalan 200 mg/m^2 (day-2) prior to autologous haematopoietic stem cell transplantation (day 0). Patients were randomised 2:2:1 to palifermin 60 µg/kg/day on day -6, -5, -4, 0, 1, 2 ("pre-post chemotherapy"), palifermin 60 µg/kg/day on day -6, -5, -4 ("pre-chemotherapy") or placebo. The number of subjects in each group were 115, 109 and 57 respectively.

The primary endpoint was maximum severity of oral mucositis assessed on the 5-point WHO scale. Secondary endpoints included the incidence of severe oral mucositis (WHO grade 3-4) and mouth and throat soreness (MTS) scored daily by patients using a 5-point scale. Neither palifermin regimen significantly reduced the severity of oral mucositis, incidence of severe oral mucositis nor MTS compared with placebo. The incidence of severe oral mucositis was 38% with the pre-post chemotherapy palifermin regimen, 24% with the pre-chemotherapy palifermin regimen and 37% with placebo.

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

Paediatric population

The safety and efficacy of palifermin in paediatrics has not been established as limited clinical studies have been performed. A small, non-controlled, phase I dose escalation study was conducted in paediatric patients aged 1-16 years. A total of 27 paediatric patients with leukaemia were randomised to 40, 60 or 80 micrograms/kg/day of palifermin for 3 days pre- and post-hematopoietic stem cell transplantation (HSCT). The conditioning regimen consisted of total body irradiation (TBI), etoposide and cyclophosphamide. The incidence of severe (WHO Grade 3 or 4) oral mucositis was 44% with 40 micrograms/kg/day, 56% with 60 micrograms/kg/day, and 11% with 80 micrograms/kg/day. Although palifermin was safe at all doses tested the incidence of skin reactions increased with the dose. See Precautions – Paediatric Use.

INDICATIONS

KEPIVANCE is indicated to decrease oral mucositis in patients with haematological malignancies receiving myelotoxic therapy requiring haematopoietic stem cell support.

CONTRAINDICATIONS

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

PRECAUTIONS

Use with Chemotherapy

Palifermin should not be administered in the period 24 hours before and after cytotoxic chemotherapy nor during infusion of cytotoxic chemotherapy (see **DOSAGE AND ADMINISTRATION**). In clinical studies, administration of palifermin within 14 hours prior to high-dose etoposide was not efficacious and possibly resulted in an increased severity and duration of oral mucositis.

Patients should be monitored following haematopoietic stem cell infusion until platelet recovery.

The safety and efficacy of palifermin have not been established in patients with nonhaematologic malignancies.

Patients with haematologic malignancies receiving Total Body Irradiation are at a higher risk of developing cataracts because of the treatment regimen received. As KGF receptors are present on the lens of the eye, the possibility of cataract formation cannot be excluded (see **CLINICAL TRIALS**).

Skin Cancer

The safety and efficacy of palifermin in patients with a history of squamous cell carcinoma has not been established.

Potential for Stimulation of Tumour Growth

Palifermin has been shown to enhance the growth of some human epithelial tumour cell lines *in-vitro* at concentrations ≥ 10 µg/mL. Palifermin treatment (1500 or 4000 µg/kg/day IV for 3days then 4 days of no treatment, for 4 cycles) of athymic mice bearing xenografts of human cancer cell lines increased tumour growth in 1 of 7 KGF-responsive cell lines (hypopharyngeal squamous cell carcinoma, FaDu cells). These doses represented about 2- and 5-fold the proposed clinical dose (calculated on a body surface area basis) and double the duration of clinical treatment (4 vs. 2 cycles).

The safety and efficacy of palifermin have not been established in patients with non-haematological malignancies. Cell culture and animal models of non-haematopoietic human tumours have shown tumour growth and stimulation. The effects of palifermin on stimulation of KGF receptor-expressing, non-haematopoietic tumours in patients are unknown.

Lack of Efficacy and Risk of Infection with High- dose Melphalan conditioning regimen

Use of palifermin with melphalan prior to autologous haematopoietic stem cell transplantation in multiple myeloma is not recommended (see CLINICAL TRIALS).

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

In addition, there was a higher incidence of infections in patients administered palifermin pre- and post-chemotherapy (49.5%) compared with patients who received placebo (24.6%). Compared with the placebo group, the pre/post-chemotherapy group had a higher incidence of herpes virus infection (9% vs 0%), oral fungal infection (7% vs 2%) and sepsis/septic shock (12% vs 2%).

The efficacy and safety of palifermin have only been established in association with conditioning regimens for autologous haematopoietic stem cell support that comprise total body irradiation and high dose chemotherapy (cyclophosphamide and etoposide). Palifermin should not be used in association with myeloablative chemotherapy-only conditioning.

Effects on Fertility

When palifermin was administered IV daily to male and female rats prior to and during mating, reproductive performance and sperm assessment parameters were not affected at doses up to 100 µg/kg/day. Systemic toxicity (clinical signs and effects on body weight), decreased epididymal sperm counts and increased post-implantation loss were observed at doses ≥ 300 µg/kg/day (about 20-fold higher than the recommended human dose based on serum AUC values). Increased pre-implantation loss and decreased fertility were observed at a palifermin dose of 1000 µg/kg/day.

Use in Pregnancy (Category B3)

There are no adequate and well-controlled studies in pregnant women. Palifermin should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

No evidence of developmental toxicity was observed when pregnant rats were given palifermin at IV doses up to 300 µg/kg/day. Increased post-implantation loss, decreased foetal weights and/or increased skeletal variations were observed at doses ≥ 500 µg/kg/day (about 30 times the clinical exposure based on serum AUC values). Although these doses were maternotoxic (altered serum biochemistry, increased liver weight) and there was little/no evidence of placental transfer, a possible effect of palifermin on placental function cannot be ruled out.

Increased post-implantation loss and decreased foetal weights were observed at IV doses ≥ 5 µg/kg/day in rabbits (about 0.1 times the clinical exposure based on serum AUC values). These doses were also maternotoxic (clinical signs, reductions in food consumption/body weight gain). Increased incidences of small or absent gall bladders were observed at 150 µg/kg/day (about 5 times the clinical exposure based on serum AUC values).

Use in Lactation

It is not known whether palifermin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when palifermin is administered to women who are breast-feeding.

Paediatric Use

The safety and effectiveness of palifermin in paediatric patients have not been established. No studies in juvenile animals have been performed.

Use in the Elderly

Few subjects over the age of 65 years have been treated with palifermin. Caution is recommended in this group.

Genotoxicity

Palifermin was negative in *in-vitro* bacterial and mammalian mutagenicity assays, an *in-vitro* chromosome aberration assay and an *in-vivo* mouse micronucleus assay.

Carcinogenicity

The carcinogenic potential of palifermin has not been evaluated in long-term animal studies. In a short-term study of the tumour enhancement potential in transgenic rasH2 mice treated with palifermin once weekly for 9 weeks, no unequivocal treatment-related increases in the incidences of neoplastic lesions were observed.

INTERACTIONS WITH OTHER MEDICINES

In the Phase 3 study patients received NEUPOGEN® (filgrastim) support following haematopoietic stem cell transplant. The absolute neutrophil count (ANC) recovery was similar between patients who received palifermin or placebo.

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

ADVERSE EFFECTS

Safety data are based upon patients with haematologic malignancies (NHL, HD, AML, ALL, CML, CLL or MM) enrolled in randomised, placebo-controlled clinical studies and one pharmacokinetic study. Patients received palifermin either before or before and after myelotoxic chemotherapy with or without TBI and haematopoietic stem cell support. Most adverse events were attributable to the underlying malignancy, cytotoxic chemotherapy or TBI and occurred at similar rates in patients who received palifermin or placebo.

Those that occurred with at least a 5% higher incidence in palifermin-treated patients are listed in Table 3.

Most of these adverse events were consistent with the pharmacologic action of palifermin on skin and oral epithelium (e.g. rash, pruritus, erythema, oedema, mouth discolouration and tongue/taste disorders). These events were primarily mild to moderate in severity and were reversible. Median time to onset was 6 days following the first of 3 consecutive daily doses of palifermin, with a median duration of 5 days. Some adverse events (i.e. pain and arthralgia) are consistent with palifermin-treated patients having received less opioid analgesia than placebo-treated patients (see **CLINICAL TRIALS: Table 1**).

Serious adverse events occurred at a similar rate in patients who received palifermin (20%) or placebo (21%). The most frequently reported serious adverse events in both groups were fever, gastrointestinal and respiratory related. ANC recovery following haematopoietic stem cell transplant was similar between patients who received palifermin or placebo and there were no observed differences in disease progression or survival.

Table 3. Adverse Events Occurring with ≥ 5% Higher Incidence in Palifermin vs. Placebo

BODY SYSTEM Adverse Event	Placebo (N = 241)	Palifermin (N = 409)
BODY AS A WHOLE		
Fever	34%	39%
Oedema	21%	28%
Pain	11%	16%
GASTROINTESTINAL		
Mouth/Tongue Thickness or Discolouration	8%	17%
MUSCULO-SKELETAL		
Arthralgia	5%	10%
SKIN AND APPENDAGES		
Rash	50%	62%
Pruritus	24%	35%
Erythema	22%	32%
SPECIAL SENSES		
Taste Altered	8%	16%
NERVOUS SYSTEM		
Oral paresthesia	0.3%	1.7%

Laboratory values: 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. 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.

Post marketing Experience: The following adverse reactions have been identified during post marketing use of KEPIVANCE in the stem cell transplant setting: tongue disorder (e.g. redness, bumps, oedema), face oedema and mouth oedema; vaginal oedema and erythema, hyperpigmentation of the skin, Palmar-plantar Erythrodysaesthesia Syndrome (dysaesthesia, erythema, oedema on the palms and soles) and anaphylactic/allergic reactions.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. No antibodies were detected in subjects treated with KEPIVANCE in clinical studies.

DOSAGE AND ADMINISTRATION

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 chemotherapy for a total of 6 doses.

Pre-myelotoxic therapy: The first three doses should be administered prior to myelotoxic therapy, with the third dose 24 to 48 hours before myelotoxic therapy (see **PRECAUTIONS: Use in Chemotherapy**).

Post-myelotoxic therapy: The last three doses should be administered post myelotoxic therapy; the first of these doses should be administered within 24 hours of haematopoietic stem cell infusion and at least seven days after the most recent KEPIVANCE administration.

Reconstitution

KEPIVANCE should be reconstituted aseptically with 1.2 mL of sterile Water for Injections. When reconstituted with 1.2 mL sterile Water for Injections, the final concentration of palifermin is 5 mg/mL. During reconstitution, the diluent should be injected slowly into the KEPIVANCE vial. The contents should be swirled gently during dissolution. Do not shake or vigorously agitate the vial.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. The reconstituted solution should be clear and colourless; if particulates or discolouration are observed, the contents of the container should not be used.

KEPIVANCE must be used within 24 hours of reconstitution. If reconstituted KEPIVANCE is not used within 1 hour of reconstitution, the reconstituted solution should be stored as recommended in PRESENTATION AND STORAGE CONDITIONS. Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue. Do not save unused drug for later administration.

The contents of one vial of KEPIVANCE solution should not be mixed with the contents of another vial or transferred into 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.

Administration of KEPIVANCE

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 palifermin has been shown to bind to heparin *in-vitro* and *in-vivo*.

OVERDOSAGE

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

PRESENTATION AND STORAGE CONDITIONS

KEPIVANCE is supplied as a sterile, white, preservative-free, lyophilised 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 Injections.

KEPIVANCE is provided in dispensing packs containing 6 vials.

Lyophilised powder:

KEPIVANCE should be stored refrigerated at 2°C to 8°C (Refrigerate. Do not freeze.). Vials should be kept in their carton to protect from light until time of use. KEPIVANCE may be exposed to room temperature (up to 30°C) for a maximum single period of up to 72 hours. KEPIVANCE left at room temperature for more than 72 hours should be discarded.

Reconstituted solution:

Reconstituted solutions of KEPIVANCE may be stored refrigerated at 2°C to 8°C (Refrigerate. Do not freeze.) for up to 24 hours, in the original carton, to protect from light. However, for microbiological reasons the reconstituted solution should be used as soon as practicable after reconstitution/preparation. Before injection, KEPIVANCE may be allowed to reach room temperature for a maximum of 1 hour but should be protected from light. Reconstituted KEPIVANCE left at room temperature for more than 1 hour should be discarded.

Reconstituted product should not be frozen.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 August 2005

DATE OF MOST RECENT AMENDMENT

29 August 2016