

## **ANNEX I**

### **SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

#### **1. NAME OF THE MEDICINAL PRODUCT**

KORSUVA 50 micrograms/mL solution for injection

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial of 1 mL contains 50 micrograms difelikefalin (as acetate).

For the full list of excipients, see section 6.1.

#### **3. PHARMACEUTICAL FORM**

Solution for injection.

Clear, colourless solution, free from particles (pH 4.5).

#### **4. CLINICAL PARTICULARS**

##### **4.1 Therapeutic indications**

KORSUVA is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis (see section 5.1).

##### **4.2 Posology and method of administration**

KORSUVA should be restricted for in-centre haemodialysis use only and by health care professionals trained in haemodialysis administration.

KORSUVA is intended for use by healthcare professionals experienced in the diagnosis and treatment of conditions for which difelikefalin is indicated. Causes of pruritus other than chronic kidney disease should be excluded before initiating treatment with difelikefalin.

##### Posology

Difelikefalin is administered 3 times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the haemodialysis treatment during rinse-back or after rinse-back.

The recommended dose of difelikefalin is 0.5 micrograms/kg dry body weight (i.e., the target postdialysis weight). The total dose volume (mL) required from the vial should be calculated as follows:  $0.01 \times \text{dry body weight (kg)}$ , rounded to the nearest tenth (0.1 mL). For patients with a dry body weight equal to or above 195 kg the recommended dose is 100 micrograms (2 mL). Injection volumes are detailed in the table below:

<b>Weight range</b> (Dry body weight in kg)	<b>Injection volume<sup>1</sup></b> (mL)
40 – 44	0.4
45 – 54	0.5
55 – 64	0.6
65 – 74	0.7
75 – 84	0.8
85 – 94	0.9
95 – 104	1.0
105 – 114	1.1
115 – 124	1.2
125 – 134	1.3
135 – 144 <sup>†</sup>	1.4
145 – 154 <sup>†</sup>	1.5
155 – 164 <sup>†</sup>	1.6
165 – 174 <sup>†</sup>	1.7
175 – 184 <sup>†</sup>	1.8
185 – 194 <sup>†</sup>	1.9
≥ 195 <sup>†</sup>	2.0

<sup>1</sup> More than 1 vial may be necessary if an injection volume of more than 1 mL is required.

<sup>†</sup> The maximum target dry body weight of patients treated with difelikefalin evaluated in the placebo-controlled Phase 3 clinical trials was 135.0 kg. Population pharmacokinetic simulations demonstrated comparable difelikefalin exposure up to 200 kg.

#### Missed doses

If a regularly scheduled haemodialysis treatment is missed, KORSUVA should be administered at the next haemodialysis treatment at the same dose.

#### Extra treatment

If a 4th haemodialysis treatment is performed in a week, KORSUVA should be administered at the end of the haemodialysis per the recommended dose. No more than 4 doses per week should be administered even if the number of haemodialysis treatments in a week exceeds 4. A 4th dose of KORSUVA is unlikely to lead to accumulation of difelikefalin that would be of concern for safety, as the majority of remaining difelikefalin from the previous treatment will be cleared by haemodialysis (see sections 4.9 and 5.2). However, safety and efficacy of a 4th dose has not been fully established due to insufficient data (see section 5.1)

#### Patients with incomplete haemodialysis treatment

For haemodialysis treatments less than 1 hour, administration of difelikefalin should be withheld until the next haemodialysis session.

Following administration of difelikefalin in haemodialysis subjects, up to 70% is eliminated from the body prior to the next haemodialysis session (see sections 4.9 and 5.2). Difelikefalin plasma level remaining at the time of the next haemodialysis is reduced by about 40-50% within one hour of haemodialysis.

#### Patients with hepatic impairment

Metabolism by hepatic enzymes does not significantly contribute to elimination of difelikefalin. While faecal excretion contributes to elimination, it is not known whether hepatic impairment has a clinically

relevant effect on overall difelikefalin clearance in haemodialysis patients. Evaluation of available population pharmacokinetic data in HD patients concluded that no adjustment of intravenous difelikefalin dosage is needed in patients with mild to moderate hepatic impairment; however, clinical data following IV dosing in patients with moderate hepatic impairment is currently limited (see section 5.2). Difelikefalin has not been studied in subjects with severe hepatic impairment (National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG)) and is therefore not recommended for use in this patient population.

Elderly population ( $\geq 65$  years of age)

Dosing recommendations for elderly patients are the same as for adult patients.

Paediatric population

The safety and efficacy of difelikefalin in children aged 0-17 years has not yet been established. No data are available.

#### Method of administration

Inspect KORSUVA for particulate matter and discoloration prior to administration. The solution should be clear and colourless. Do not use KORSUVA vials if particulate matter or discolouration is observed.

KORSUVA should not be diluted and should not be mixed with other medicinal products.

The dose must be administered within 60 minutes of the completion of the syringe preparation.

Difelikefalin is removed by the dialyzer membrane and must be administered after blood is no longer circulating through the dialyzer. Difelikefalin is administered by intravenous bolus injection into the venous line of the dialysis circuit at the end of the haemodialysis treatment during rinse-back or after rinse-back.

When given after rinse-back, at least 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection rinse-back volume should be administered after injection of KORSUVA. If the dose is given during rinse-back, no additional sodium chloride 9 mg/mL (0.9%) solution for injection is needed to flush the line.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Hyperkalaemia

Hyperkalaemia frequently occurs in chronic kidney disease patients on haemodialysis. In the placebo-controlled clinical studies a numerically higher rate of adverse events of hyperkalaemia was reported for the difelikefalin treated patients (4.7%; 20 / 424 patients) compared to placebo (3.5%; 15 / 424 patients). The incidence of hyperkalemia was higher in patients who took concomitant opioids regardless of study treatment and was almost doubled in the difelikefalin group (11.7%) compared to the placebo group (6.2%). No causal relationship was established. Frequent monitoring of potassium levels is recommended.

#### Cardiac failure and atrial fibrillation

Difelikefalin has not been studied in patients with New York Heart Association class IV heart failure. In the clinical studies a small numerical imbalance of cardiac failure events (4.7%; 20/424 for the difelikefalin treated patients compared to placebo 3.3%; 14/424) and atrial fibrillation events was observed in the difelikefalin (1.4%; 6/424) treated patients compared to placebo (0.5%; 2/424), in particular among patients with a medical history of atrial fibrillation, some of whom had discontinued or missed their atrial fibrillation treatment. The clinical significance of these findings is unknown as no causal relationship was established.

#### Patients with impaired blood-brain barrier

Difelikefalin is a peripherally acting kappa opioid receptor agonist with restricted access to the central nervous system (CNS). The blood-brain barrier (BBB) integrity is important for minimizing difelikefalin uptake into the CNS (see section 5.1). Patients with clinically important disruptions to the BBB (e.g., primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease) may be at risk for difelikefalin entry into the CNS. KORSUVA should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects.

#### Dizziness and somnolence

Dizziness and somnolence have occurred in patients taking difelikefalin and may subside over time with continued treatment (see section 4.8). Concomitant use of sedating antihistamines, opioid analgesics or other CNS depressants may increase the likelihood of these adverse reactions and should be used with caution during treatment with difelikefalin (see section 4.5).

Compared to placebo, the incidence of somnolence was higher in difelikefalin treated subjects 65 years of age and older (7.0%) than in difelikefalin treated subjects less than 65 years of age (2.8%). Therefore, the use of difelikefalin in this patient population should take into account individual benefit-risk assessment and be carefully monitored.

#### Excipients with known effect

This medicinal product contains less than 1 mmol sodium per vial, that is to say essentially sodium-free.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No clinical interaction studies have been performed. Difelikefalin does not inhibit or induce CYP450 enzymes, and is not a substrate of CYP450 enzymes. It is not an inhibitor of glucuronidating enzymes either. Difelikefalin is not a substrate or an inhibitor of human transporters (see section 5.2).

Therefore, interactions of difelikefalin with other medicinal products are unlikely.

Concurrent administration of medicinal products such as sedating antihistamines, opioid analgesics or other CNS depressants (e.g., clonidine, ondansetron, gabapentin, pregabalin, zolpidem, alprazolam, sertraline, trazodone) may increase the likelihood of dizziness and somnolence (see section 4.4).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data from the use of difelikefalin in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of KORSUVA during pregnancy.

## Breast-feeding

It is unknown whether difelikefalin is excreted in human breast milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from KORSUVA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Animal studies have shown excretion of difelikefalin in breast milk.

## Fertility

There are no data on the effect of difelikefalin on fertility in humans. In rat studies with difelikefalin, there was no effect on fertility (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Somnolence and/or dizziness have been reported in patients receiving difelikefalin (see section 4.8). Patients should be cautioned about driving or operating hazardous machinery until the effect of difelikefalin on the patient's ability to drive or operate machinery is known.

### **4.8 Undesirable effects**

#### Thyroid Stimulating Hormone (TSH) and Free Thyroxine Levels

In a Phase 2 placebo-controlled, randomized, double-blind study (14 day study drug administration period) conducted in Japanese patients with CKD and pruritus undergoing haemodialysis, dose-dependent decreases in serum TSH and free thyroxine levels were observed on the fourth dialysis day in patients administered IV difelikefalin three times per week at doses ranging from 0.25 micrograms per kg to 1.5 micrograms per kg, with a return to baseline levels following treatment discontinuation. There was also an increase in treatment-emergent adverse events of decreased TSH in patients administered IV difelikefalin (0.25 micrograms per kg [9.5% of patients], 0.50 micrograms per kg [0% of patients], 1.0 microgram per kg [31.6% of patients], 1.5 micrograms per kg [30.4% of patients]), compared to no events in patients administered placebo. Treatment-emergent adverse events of decreased free thyroxine were also reported in all IV difelikefalin dose groups (0.25 micrograms per kg [4.8% of patients], 0.50 micrograms per kg [4.8% of patients], 1.0 micrograms per kg [5.3% of patients], 1.5 micrograms per kg [8.7% of patients]) compared to no events in patients administered placebo.

TSH and free thyroxine were not assessed in the placebo-controlled Phase 3 trials. In pooled safety analyses from Phase 2/3 placebo-controlled studies in patients with CKD undergoing haemodialysis, there was one treatment-emergent adverse event of free thyroxine decreased in a patient treated with difelikefalin that was considered by the investigator to be related to study treatment; however, there was no overall imbalance in thyroid-related adverse events in in haemodialysis patients treated with difelikefalin compared to placebo in the Phase 3 trials. The clinical relevance of this is unknown.

#### Summary of the safety profile

In placebo controlled and uncontrolled phase 3 clinical studies, approximately 6.6% of the patients experienced at least one adverse reaction during difelikefalin treatment. The most common adverse reactions were somnolence (1.1%), dizziness (0.9%), headache (0.6%), nausea (0.7%), diarrhoea (0.2%) and mental status changes (including confusional state) (0.3%). Most of these events were mild or moderate in severity, did not lead to deleterious consequences, and resolved with ongoing therapy.

No event was serious and the incidence of events leading to treatment discontinuation was  $\leq 0.5\%$  for any of the adverse reactions listed above.

#### Tabulated list of adverse reactions

The adverse reactions observed in the placebo-controlled and uncontrolled phase 3 clinical studies in patients (N = 1306) treated with difelikefalin are listed in Table 1 by MedDRA system organ class, preferred term and frequency.

The frequency is classified as common ( $\geq 1/100$  to  $< 1/10$ ) and uncommon ( $\geq 1/1,000$  to  $< 1/100$ ).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 1: Adverse reactions attributed to the treatment with difelikefalin in haemodialysis patients**

MedDRA System Organ Class	Common	Uncommon
Psychiatric disorders		Mental status changes <sup>1</sup>
Nervous system disorders	Somnolence	Dizziness; Headache
Gastrointestinal disorders		Nausea; Diarrhoea

<sup>1</sup> Mental status changes included MedDRA preferred terms of confusional state and mental status changes.

#### Description of selected adverse reactions

##### Somnolence

Somnolence was reported as treatment emergent adverse event in 2.2% of subjects randomised to difelikefalin. The vast majority of these events was mild or moderate in severity. In 0.3% of patients, somnolence led to discontinuation of treatment with difelikefalin. Somnolence was reported as serious adverse event in  $<0.1\%$  of difelikefalin treated subjects. In 1.1% of patients, somnolence was reported to have a causal relationship to difelikefalin treatment. Somnolence occurred within the first 3 weeks of treatment and tended to subside with continued dosing.

The likelihood of somnolence may increase when difelikefalin is concomitantly used with other medicinal products (see sections 4.4 and 4.5).

##### Dizziness

Dizziness was reported as treatment emergent adverse event in 7.9% of subjects randomised to difelikefalin. The vast majority of these events was mild or moderate in severity. In 0.5% of patients, dizziness led to discontinuation of treatment with difelikefalin. Dizziness was reported as serious adverse event in 0.5% of difelikefalin treated subjects. In 0.9% of patients, dizziness was reported to have a causal relationship to difelikefalin treatment. Dizziness occurred within the first 9 weeks of treatment and was generally transient.

The likelihood of dizziness may increase when difelikefalin is concomitantly used with other medicinal products (see sections 4.4 and 4.5).

##### Mental status changes

Mental status change (including confusional state) was reported as treatment emergent adverse event in 4.4% of subjects randomised to difelikefalin.

The majority of these events was mild or moderate in severity. In less than 0.2% of patients, mental status changes led to discontinuation of treatment with difelikefalin.

Mental status changes were reported as serious adverse event in 2.2% of difelikefalin treated subjects. In 0.3% of patients, mental status changes were reported to have a causal relationship to difelikefalin treatment.

## 4.9 Overdose

Single dose of difelikefalin up to 12 times and multiple doses of difelikefalin up to 5 times the clinical dose of 0.5 micrograms/kg were administered in clinical studies in patients undergoing haemodialysis. A dose-dependent increase in adverse events including dizziness, somnolence, mental status changes, paraesthesia, fatigue, hypertension and vomiting, was observed.

In the event of overdose, the appropriate medical attention based on patient's clinical status should be provided. Haemodialysis for 4 hours using a high-flux dialyzer effectively cleared approximately 70-80% of difelikefalin from plasma, and difelikefalin was not detectable in plasma at the end of the second of two dialysis cycles (see section 5.2).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: all other therapeutic products, other therapeutic products, ATC code: V03AX04

#### Mechanism of action

Difelikefalin is a selective kappa opioid receptor agonist with low central nervous system penetration. The physicochemical properties of difelikefalin (hydrophilic, synthetic D-amino acid peptide with high polar surface area and charge at physiological pH) minimize its passive diffusion (permeability) and active transport across membranes, thus limiting penetration into the central nervous system. The pathophysiology of chronic kidney disease-associated pruritus is thought to be multifactorial, including systemic inflammation and an imbalance in the endogenous opioid system (e.g., overexpression of mu opioid receptors and concomitant downregulation of kappa opioid receptors). Opioid receptors are known to modulate itch signals and inflammation, with kappa opioid receptor activation reducing itch and producing immunomodulatory effects. The activation of kappa opioid receptors on peripheral sensory neurons and immune cells by difelikefalin are considered mechanistically responsible for the antipruritic and anti-inflammatory effects.

#### Clinical efficacy and safety

##### Placebo-controlled studies

In two pivotal clinical phase-3 studies of similar double-blind, randomised, placebo-controlled design (KALM-1 and KALM-2), chronic kidney disease patients on haemodialysis with moderate-to-severe pruritus received either placebo or 0.5 micrograms/kg difelikefalin intravenously 3 times a week following haemodialysis for 12 weeks. A maximum of 4 doses per week was allowed in patients receiving an additional dialysis during a given week. The primary endpoint in both studies was the percentage of patients who achieved at least a 3-point reduction from baseline in the Worst Itching-Numerical Rating Scale (WI-NRS) at 12 weeks. The main secondary endpoints in both studies were the percentages of patients with an improvement in the WI-NRS of at least 4 points after 12 weeks and the changes in itch severity and itch-related quality of life (QoL) as measured by the total Skindex-10 and the 5-D Itch scale. A responder analysis based on Patient Global Impression of Change was also included.

A total of 851 patients with moderate-to-severe pruritus (baseline WI-NRS >4) were enrolled in the pivotal studies. Mean age was 59 years, 33.1% were aged 65 and over and 11.1% were aged 75 and over; 60% of patients were male. The baseline mean WI-NRS scores were 7.18 in both, difelikefalin and placebo arms; baseline median WI-NRS scores were 7.13 (range 4.2 to 10) in difelikefalin and 7.13 (range 4.1 to 10) in placebo arm. Other disease characteristics at baseline were comparable in difelikefalin and placebo arms: time from diagnosis of chronic kidney disease (8.22 years vs.

8.54 years), duration of pruritus (3.20 years vs. 3.31 years) and use of medicinal products intended to relieve pruritus such as antihistamines, corticosteroids, gabapentin or pregabalin (37.5% vs. 38%). Only a limited number (74, 17.4%) of patients received a 4th dose of difelikefalin within a one-week period (i.e., 1 single extra dose during 12 weeks), and only 5 patients (1.2%) received a 4th dose of difelikefalin in a week 3 times during 12 weeks.

Across studies, difelikefalin significantly reduced itch intensity and improved itch-related QoL over 12 weeks as shown in Table 2.

**Table 2: Summary of primary and key secondary outcomes in KALM-1 and KALM-2 at week 12**

Endpoint by end of week 12	KALM-1 (n = 378)		KALM-2 (n = 473)	
	difelikefalin (n = 189)	Placebo (n = 189)	difelikefalin (n = 237)	Placebo (n = 236)
<b>Primary endpoint</b>				
<b>WI-NRS</b>				
Patients with $\geq$ 3-point improvement (%)	51.0% (p < 0.001)	27.6%	54.0% (p = 0.02)	42.2%
<b>Secondary endpoint</b>				
<b>WI-NRS</b>				
Patients with $\geq$ 4-point improvement (%)	38.9% (p < 0.001)	18.0%	41.2% (p = 0.01)	28.4%
<b>Skinindex-10</b>				
Change from baseline [total score]	-17.2 (p < 0.001)	-12.0	-16.6 (p = 0.171)	-14.8
<b>5-D Itch</b>				
Change from baseline [total score]	-5.0 (p < 0.001)	-3.7	-4.9 Not applicable <sup>1</sup>	-3.8

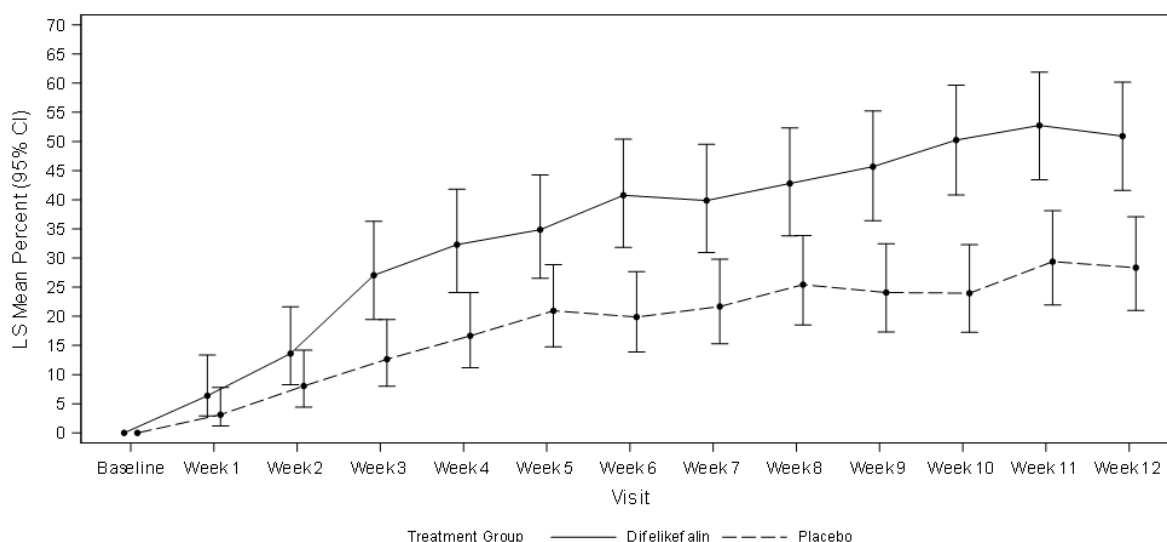
<sup>1</sup> Was not tested based on the hierarchical testing order.

Figure 1 shows the mean percentage from KALM-1 and KALM-2 with a  $\geq$  3-point improvement from baseline in WI-NRS score by study week. Based on odds ratios, statistically significant improvements favouring the difelikefalin group were seen by week 3 in KALM-1 and by week 2 in KALM-2 and continued at each subsequent week through week 12 in both studies.

**Figure 1: Percentage of patients with  $\geq$  3-point improvement with respect to WI-NRS score by week in KALM-1 and KALM-2 (ITT population)**

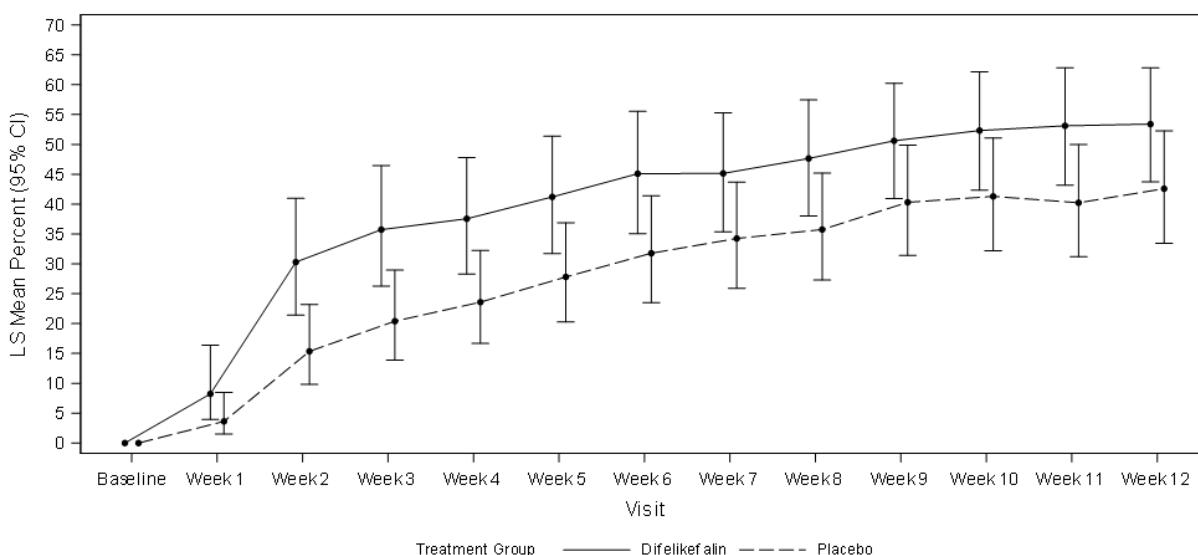


## KALM-1



CI = confidence interval; ITT = intent to treat; LS = least squares; WI-NRS = Worst Itching-Numerical Rating Scale

## KALM-2



CI = confidence interval; ITT = intent to treat; LS = least squares; WI-NRS = Worst Itching-Numerical Rating Scale

## Open label extension studies

The effect of treatment with difelikefalin for up to 52 weeks was evaluated using the 5-D Itch Scale in single arm, open label extensions of studies KALM-1 and KALM-2 including 712 patients.

In patients switching from placebo to difelikefalin at the end of the double-blind phase, an improvement in 5-D Itch score was observed after 4 weeks of treatment, with an LS mean (SE) of the change from baseline comparable to the patients receiving difelikefalin from study start: -6.0 (0.22) vs. -5.7 (0.23). The improvement in 5-D Itch score was maintained in both treatment groups throughout the 52-week treatment.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of intravenous difelikefalin are dose proportional over a single and multiple dosage range of 0.5 to 2.5 mcg/kg (1 to 5 times the recommended dosage) in chronic kidney disease patients undergoing HD. Steadystate was reached after the second administered dosage and the mean accumulation ratio was up to 1.6.

## Distribution

Plasma protein binding of difelikefalin is low to moderate, ranging from 24-32%, and remains unaffected by renal impairment. Mean volume of distribution at steady state ranged from 145 to 189 mL/kg in healthy subjects and from 214 to 301 mL/kg in haemodialysis patients with moderate-to-severe pruritus. Difelikefalin penetration into the central nervous system is limited (below limit of quantification) as shown by physico-chemical, in-vitro and animal data.

### Elimination

In healthy subjects, the primary route of elimination for difelikefalin is renal, accounting for about 81% of the dose being excreted in urine as compared to 11% via faecal excretion. In both healthy volunteers and subjects on haemodialysis, most of the dose excreted into urine and faeces was unchanged difelikefalin with minor quantities of putative metabolites, none exceeding 2.5%. Mean total clearance ranged from 54 to 71 mL/h/kg and mean half-lives from 2 to 3 hours. By contrast, in renally impaired haemodialysis patients, elimination was predominantly via faeces, accounting on average for about 59% of the dose; about 19% were recovered in dialysate and about 11% were found in urine. As compared to subjects with normal renal function, mean total clearance decreased and half-lives increased about 10-fold with ranges of 5.3 to 7.5 mL/h/kg and 23 to 31 hours, respectively.

### Interaction with other medicinal products

Difelikefalin is neither a substrate for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4, nor an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 and has minimal to no potential for induction of human CYP1A2, CYP2B6, or CYP3A. It is not an inhibitor of glucuronidation enzymes either (UGT1A3, UGT1A9, or UGT2B7).

In addition, difelikefalin is not an inhibitor of BCRP, BSEP, LAT1, MATE1, MATE2-K, MRP2, OAT1, OAT3, OATP1A2, OATP1B1, OATP1B3, OCT1, OCT2, OCT3, P-glycoprotein, PEPT1 or PEPT2, and is not a substrate for ASBT, BCRP, BSEP, LAT1, MATE1, MATE2-K, MRP2, OAT1, OAT2, OAT3, OATP1A2, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, OCT3, OCTN1, OCTN2, OST $\alpha$  $\beta$ , P-glycoprotein, PEPT1 or PEPT2.

### Linearity/non-linearity

The pharmacokinetics of intravenous difelikefalin are dose proportional over a single dosage range from 1 to 3 mcg/kg (2 to 6 times the recommended dosage) and over a multiple dosage range from 0.5 to 2.5 mcg/kg (1 to 5 times the recommended dosage) in chronic kidney disease patients undergoing HD. Steady-state was reached after the second administered dosage and the mean accumulation ratio was up to 1.6.

### Characteristics in specific groups of subjects or patients

Based on available evidence, there is no indication that factors such as age, sex, ethnicity, or mild to moderate hepatic impairment have any impact on the pharmacokinetics of difelikefalin.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity and carcinogenic potential.

### Reproductive toxicity

In rats, male and female fertility, early embryonic, and prenatal and postnatal development were not affected up to 2000-fold the human AUC. In the rabbit, prenatal development was neither impaired despite marked maternal toxicity at 30-fold the human AUC.

Difelikefalin crosses the placenta in rats.

#### Abuse and dependence potential

The abuse and dependence potential studies in the rat suggest that difelikefalin is not likely to present a risk of physical dependence or abuse potential.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Acetic acid (for pH adjustment)  
Sodium acetate trihydrate (for pH adjustment)  
Sodium chloride  
Water for injections

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

30 months

### **6.4 Special precautions for storage**

Store below 30 °C. Keep out of the sight and reach of children. Do not freeze.

### **6.5 Nature and contents of container**

KORSUVA is supplied in a single use 2 mL glass vial (type I), with a bromobutyl rubber stopper, an aluminium seal and a blue flip-off plastic cap.

Pack sizes of 3 and 12 vials containing 1 mL of solution for injection.  
Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

For single use only.

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

## **7. PRODUCT OWNER**

Vifor Fresenius Medical Care Renal Pharma Ltd.,  
Rechenstrasse 37,  
9014 St. Gallen  
Switzerland

## **8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:

**10. DATE OF REVISION OF THE TEXT**

MM/YYYY