SUMMARY OF PRODUCT CHARACTERISTICS

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.

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 × 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:

Weight range (Dry body weight in kg)	**Injection volume**[1] (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	1.4
145 – 154	1.5
155 – 164	1.6
165 – 174	1.7
175 – 184	1.8
185 – 194	1.9
≥ 195	2.0

[1] More than 1 vial may be necessary if an injection volume of more than 1 mL is required.

An effect of difelikefalin in reducing pruritus is expected after 2-3 weeks of treatment.

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.

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
No dose adjustment is required for patients with mild or moderate hepatic impairment (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 (≥ 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

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

Difelikefalin is removed by the dialyzer membrane and must be administered after blood is no longer circulating through the dialyzer. 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.

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). 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 pivotal clinical studies, a small numerical imbalance of cardiac failure and atrial fibrillation events was observed in the difelikefalin treated patients compared to placebo, in particular among patients with a medical history of atrial fibrillation who discontinued or missed their atrial fibrillation treatment. 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%).

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 or limited amount of 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

Korsuva has minor influence on the 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. Somnolence occurred within the first 3 weeks of treatment and tended to subside with continued dosing. Dizziness occurred within the first 9 weeks of treatment and was generally transient.

4.8 Undesirable effects

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%), paraesthesia (including hypoesthesia, paraesthesia oral and hypoesthesia oral) (1.1%), headache (0.6%), nausea (0.7%), vomiting (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 ≤ 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 treated with difelikefalin (N = 1306) are listed in Table 1 by MedDRA system organ class, preferred term and frequency.

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

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

MedDRA System Organ Class	Common	Uncommon
Psychiatric disorders		Mental status changes[1]
Nervous system disorders	Somnolence, Paraesthesia[2]	Dizziness; Headache
Gastrointestinal disorders		Vomiting; Nausea; Diarrhoea

[1] Mental status changes included MedDRA preferred terms of confusional state and mental status changes.
[2] Paraesthesia included MedDRA preferred terms of paraesthesia, hypoesthesia, paraesthesia oral and hypoesthesia oral.

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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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

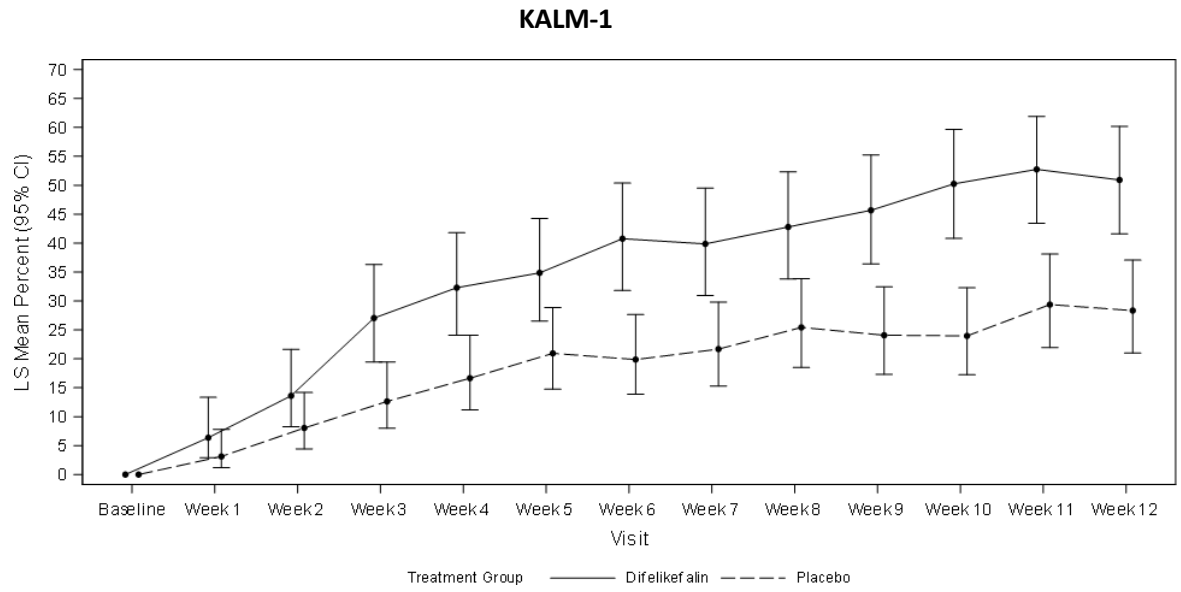
Table 2: Summary of primary and key secondary outcomes in KALM-1 and KALM-2 at week 12

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

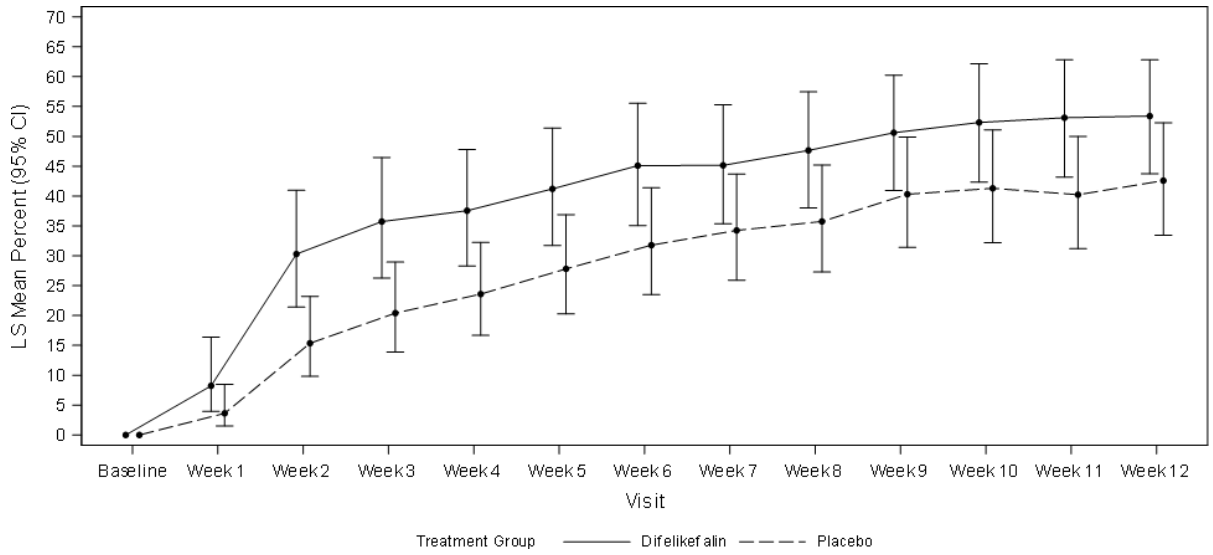
[1] Was not tested based on the hierarchical testing order.

Figure 1 shows the mean percentage from KALM-1 and KALM-2 with a ≥ 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 ≥ 3-point improvement with respect to WI-NRS score by week in KALM-1 and KALM-2 (ITT population)



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

In patients with severe renal impairment undergoing haemodialysis, total body clearance of difelikefalin is reduced compared to healthy subjects and plasma concentrations decrease slowly until cleared during dialysis. Due to the 70-80% of difelikefalin removed during dialysis, difelikefalin is administered after each haemodialysis session in these patients. The available data on interindividual variability in haemodialysis subjects receiving 0.5 microgram/kg difelikefalin suggest that variability of AUC can exceed 30%.

Distribution

Plasma protein binding of difelikefalin is low to moderate(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 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, OSTαβ, P-glycoprotein, PEPT1 or PEPT2.

Linearity/non-linearity

Pharmacokinetics of difelikefalin were demonstrated to be linear and dose-proportional in healthy subjects (tested over dose ranges of 1 to 40 and 1 to 20 micrograms/kg in single and repeated dose studies, respectively). Steady state dose proportionality was also established in chronic kidney disease patients on haemodialysis receiving repeated doses from 0.5 to 2.5 micrograms/kg, 3 times per week for 1 week. However, in another study dose proportionality was observed at doses of 0.5 and 1 micrograms/kg, but not at the dose of 1.5 micrograms/kg. Trough plasma concentration values reached steady state by the second dose and for the dose of 0.5 micrograms/kg, mean accumulation ratio was 1.144 in one study based on $AUC_{0\text{-}48h}$ and 1.33 in another study, based on $AUC_{0\text{-}44h}$; showing that variability for accumulation parameters can exceed 30%.

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

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 25C

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. MARKETING AUTHORISATION HOLDER

CTS Ltd. 4 Haharash St. Hod-Hasharon Israel

8. MARKETING AUTHORISATION NUMBER(S)

173-72-37475-99

Approved in 08/2023 by the MOH.