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

Kapruvia 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

Kapruvia 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

Kapruvia should be restricted for in-centre haemodialysis use only.

Kapruvia 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

Weight range (Dry body weight in kg)	**Injection volume**[1] (mL)
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, Kapruvia should be administered at the next haemodialysis treatment at the same dose.

Extra treatment
If a 4th haemodialysis treatment is performed in a week, Kapruvia 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 Kapruvia 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 12-17 years has not yet been established. Currently available data are described in section 5.1.
The safety and efficacy of difelikefalin in children below 12 years has not yet been established. No data are available in patients below 12 years.

Method of administration

Kapruvia 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 Kapruvia. 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. Kapruvia 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 Kapruvia 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 Kapruvia 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

Kapruvia 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

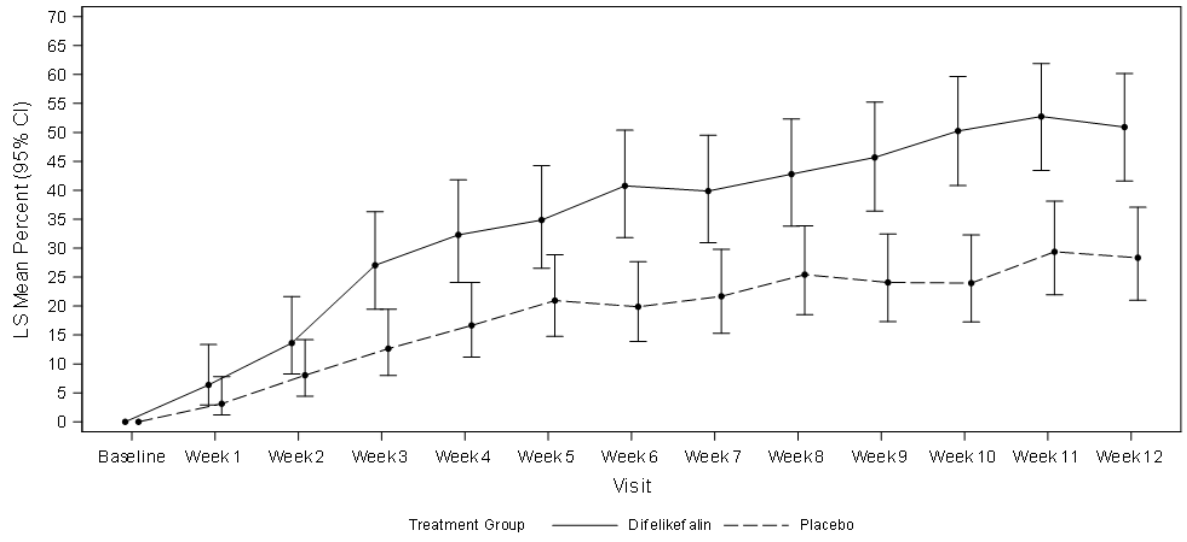
	KALM-1 (n = 378)		KALM-2 (n = 473)	
Endpoint by end of week 12	difelikefalin (n = 189)	Placebo (n = 189)	difelikefalin (n = 237)	Placebo (n = 236)
Primary endpoint				
WI-NRS				
Patients with ≥ 3-point improvement (%)	51.0% (p < 0.001)	27.6%	54.0% (p = 0.02)	42.2%
Secondary endpoints				
WI-NRS				
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.

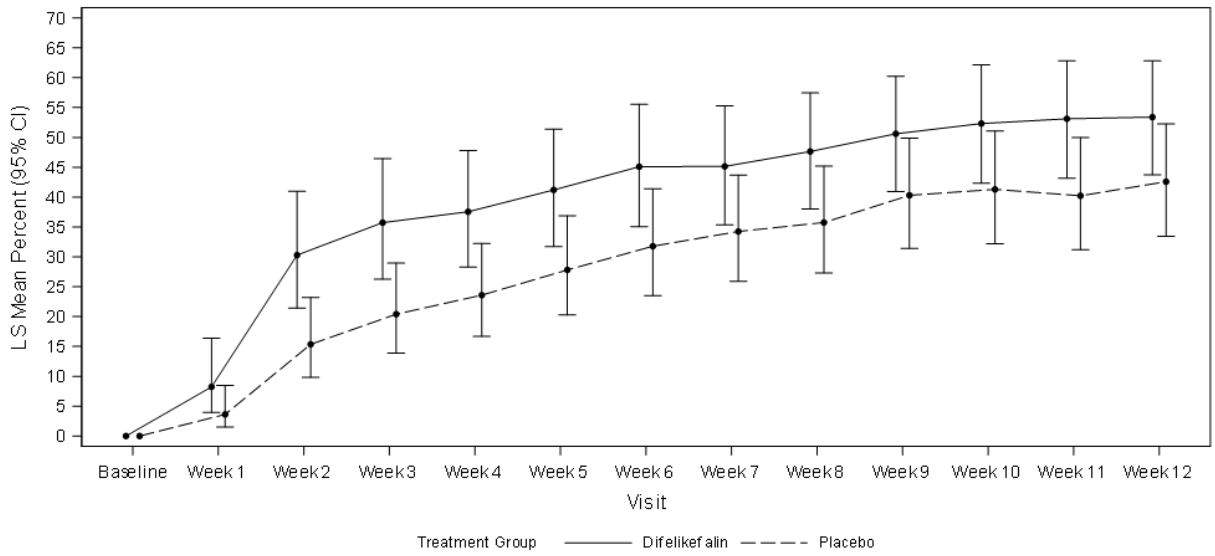
Figure 1 shows the mean percentage from KALM-1 and KALM-2 with a ≥ 3-point improvement from baseline in WI-NRS score by study week. Based on odds ratios, statistically significant improvements favouring the difelikefalin group were seen by week 3 in KALM-1 and by week 2 in KALM-2 and continued at each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



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.

Paediatric population

A total of 8 adolescents (12 to 17 years) on haemodialysis were enrolled in an open-label, single arm study to evaluate the pharmacokinetics of a single dose of intravenous difelikefalin. It has been demonstrated that the administration of a single dose of difelikefalin of 0.5 µg/kg, based on dry body weight provides comparable exposure between adolescents and adults on HD. The safety profile of difelikefalin 0.5 µg/kg of dry body weight, administered in adolescents as a single intravenous dose, was consistent with the known safety profile of difelikefalin in adults.

The European Medicines Agency has deferred the obligation to submit the results of studies with difelikefalin in one or more subsets of the paediatric population in the treatment of chronic kidney disease associated pruritus (see section 4.2 for information on paediatric use).

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

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Kapruvia 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

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1643/001
EU/1/22/1643/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kapruvia 50 micrograms/mL solution for injection
difelikefalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 micrograms difelikefalin.

3. LIST OF EXCIPIENTS

Excipients: Acetic acid and sodium acetate trihydrate (for pH adjustment), sodium chloride and water for injections.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
3 vials of 1 mL
12 vials of 1 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1643/001 – 3 vials
EU/1/22/1643/002 – 12 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kapruvia 50 mcg/mL injection
difelikefalin
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mcg/mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kapruvia 50 micrograms/mL solution for injection
difelikefalin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kapruvia is and what it is used for

Kapruvia contains the active substance difelikefalin. It is used to **treat itching** in adults with chronic kidney disease who need dialysis to clean their blood.

Kapruvia works at targets in the body called kappa-opioid receptors which are involved in controlling the perception of itching. By stimulating these receptors on nerves and immune cells outside the brain, Kapruvia relieves the sensation of itch caused by chronic kidney disease. The active substance difelikefalin does not pass the blood-brain barrier (the natural protective barrier between blood vessels and the brain), which reduces the risk of side effects.

2. What you need to know before you use Kapruvia

Do not use Kapruvia
- if you are allergic to difelikefalin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before you are given Kapruvia if you:
- have an increased potassium level in the blood
- have or have had heart weakness or a heart rhythm disorder
- have reduced function of the blood-brain barrier (such as cancer in the brain or the central nervous system, or a disease of the central nervous system like multiple sclerosis or dementia) as this might increase your risk of side effects
- are 65 years of age or older, as you may be more likely to be made drowsy by the medicine
- are using medicines that could increase the risk of drowsiness or dizziness, such as:
  - medicines that slow down brain activity such as those that help with sleep disturbances and anxiety
  - medicines to treat allergies, cold, nausea and/or vomiting called sedating antihistamines
  - strong painkillers, called opioid analgesics

Talk to your doctor if you take any of these medicines.

Children and adolescents
Kapruvia is not recommended for children under 18 years, as it has not been studied in these patients.

Other medicines and Kapruvia
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given Kapruvia.

Kapruvia has not been studied in pregnant women. It is unknown whether Kapruvia can harm the unborn baby. Your doctor will discuss with you if you should use Kapruvia during pregnancy.

It is not known whether difelikefalin can pass into breast milk. If you are breast-feeding your doctor will advise you on whether to stop breast-feeding or using Kapruvia, considering the benefit of breast-feeding to the baby and Kapruvia to you, the mother.

Driving and using machines
Kapruvia can cause drowsiness and dizziness which may affect your ability to react. Do not drive or use machines if your ability to react is reduced or you do not know the effect of Kapruvia on your ability to react.

Kapruvia contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

3. How to use Kapruvia

The doctor will work out the right dose of Kapruvia for you, based on your body weight. It will be given as an injection into a vein by a doctor or nurse at the end of your dialysis treatment through the tube that connects you to the dialysis machine.

Kapruvia will be given 3 times per week. This increases to 4 times per week in case of a fourth dialysis. No more than 4 doses are recommended, even if the number of dialysis treatments in a week is more than 4.

If a dialysis treatment is unfinished, your doctor will decide whether it is better for you to receive Kapruvia after the unfinished dialysis session or wait until your next dialysis treatment.
If a dialysis treatment is missed, the usual dose of Kapruvia will be given to you at the next dialysis treatment.

Itching is expected to decrease after 2-3 weeks treatment with Kapruvia.

Patients with reduced liver function
No dose adjustment is required for patients with mild or moderate reduced liver function. Kapruvia is not recommended for patients with severely reduced liver function, as use has not been studied in these patients.

If you have been given more Kapruvia than you should
This increases the occurrence of side effects listed in section 4. Inform your doctor if you think this applies to you.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported in patients receiving this medicine:

Common, may affect up to 1 in 10 people:
- drowsiness
- sensation disorder in the skin such as tingling, prickling, burning or numbness, decreased feeling or sensitivity

Uncommon, may affect up to 1 in 100 people:
- dizziness
- headache
- changes in mental status (alertness and clarity of thought), including confusion
- nausea, vomiting
- diarrhoea

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kapruvia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

6. Contents of the pack and other information

What Kapruvia contains
- The active substance is difelikefalin.
  Each vial contains 50 micrograms of difelikefalin (as acetate) in 1.0 mL solution.
- The other ingredients are acetic acid (for pH adjustment), sodium acetate trihydrate (for pH adjustment), sodium chloride, water for injections. See section 2 “Kapruvia contains sodium”.

What Kapruvia looks like and contents of the pack
Kapruvia is a clear, colourless solution and free from particles (pH 4.5). It is supplied in a glass vial with rubber stopper, an aluminium seal and a blue flip-off plastic cap.

Pack sizes of 3 and 12 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
France

Manufacturer
Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
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France

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.