Date: 14 September 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Kapruvia

International non-proprietary name: difelikefalin as difelikefalin acetate
Pharmaceutical form: solution for injection
Dosage strength(s): 50 µg/ml
Route(s) of administration: intravenous use
Marketing Authorisation Holder: Vifor Fresenius Medical Care
Marketing Authorisation No.: 68653
Decision and Decision date: approved on 16 August 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
CKD	Chronic kidney disease
C_{max}	Maximum observed plasma/serum concentration of drug
CPN	Chronic progressive nephropathy
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HD	Haemodialysis
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
IV	Intravenous
Ki	Inhibitory constant
KOR	Kappa opioid receptor
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetic
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance difelikefalin of the medicinal product mentioned above.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia, Singapore, Canada and Switzerland.
The Access NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic, and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of a NAS application that has been filed in at least two jurisdictions.

2.2 Indication and Dosage

2.2.1 Requested Indication

Kapruvia is indicated for the treatment of moderate to severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.

2.2.2 Approved Indication

Kapruvia is indicated for the treatment of moderate to severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended dose of difelikefalin is 0.5 µg / kg dry bodyweight (defined as targeted body weight after dialysis) to be administered as a bolus i.v. injection 3 times per week.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	7 September 2021
Formal control completed	21 October 2021
List of Questions (LoQ)	18 February 2022
Answers to LoQ	14 April 2022
Predecision	3 June 2022
Answers to Predecision	16 June 2022
Labelling corrections	13 July 2022
Answers to Labelling corrections	18 July 2022
Final Decision	16 August 2022
Decision	approval

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

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4 Nonclinical Aspects

Difelikefalin was developed according to the principles of ICH M3 (R2).

4.1 Pharmacology

In vitro, difelikefalin bound recombinant human kappa opioid receptor (KOR) with an inhibitory constant (K_i) of 0.32 nM, IC_{50} of 0.799 nM, and had a slow off-rate. In functional assays, difelikefalin showed an EC_{50} of 0.048 nM on mouse KOR, and EC_{50} of 0.16 nM in a reporter gene assay in human embryonic kidney 293 cells expressing human KORs. Activity on recombinant rat KOR was similar. Difelikefalin did not bind human delta or mu opioid receptors, and had no significant activity on a panel of receptors, ion channels, transporters, and enzymes at concentrations up to 10 µM.
Difelikefalin reduced lipopolysaccharide-induced cytokine production *in vitro* in human cells and *in vivo* in mice, and displayed anti-inflammatory activity in a murine paw swelling model. Difelikefalin exhibited antipruritic and antinociceptive activity in several mouse models, with ED_{50} values in the range of 0.03-0.08 mg/kg following intravenous (IV) administration. In a spinal nerve ligation mouse model, the anti-allodynic effect of difelikefalin was shown to depend mainly on peripheral KOR activity. There was no, or little, tolerance induction after repeated dosing.
Safety pharmacology studies did not indicate that human vital parameters (neurobehaviour, respiratory and cardiovascular function) and gastrointestinal transit are likely affected at the recommended dose of 0.5 µg/kg. Central nervous system (CNS) findings (e.g. decreased locomotor activity, abnormal postures) and decreased body temperature, blood pressure, and heart rate were considered related to exaggerated pharmacology and were also noted in the repeated dose toxicology studies at exposure multiples of at least 74-fold (C_{max}) and 18-fold (AUC). This indicates, that difelikefalin has some central KOR activity.

4.2 Pharmacokinetics

Difelikefalin showed a comparable PK and metabolic profile in mice, rats, dogs, monkeys, rabbits, and humans. Difelikefalin showed a biphasic PK profile. Exposures increased roughly dose-proportionally (single dose) and slightly more than dose-proportionally after repeated dosing following IV administration in the tested dose range of 0.25-25 mg/kg/day in rats, 0.06-4 mg/kg/day in monkeys, and 0.025-0.1 mg/kg/day in pregnant rabbits. Clearance and volume of distribution were low to moderate.
There was no, or only slight, accumulation after repeated dosing, except for an increase in AUC in the first 6 months during chronic treatment in monkeys. Elimination half-lives increased with higher doses and treatment duration. Terminal elimination half-lives were shorter in animals compared to chronic kidney disease (CKD) patients undergoing haemodialysis (HD) (≤5.5 h (single dose) and 10 h (repeated dosing) compared to 23-26 h).
Subcutaneous (SC) administration was applied in a chronic rat study with doses of 1 to 25 mg/kg/day, in carcinogenicity studies in transgenic mice with doses of 3 to 30 mg/kg/day, and in rats with doses of 0.25 to 1 mg/kg/day. Absorption was fast with t_{max} of 0.25-1 h. Exposure increased with increasing dose. There was a marked accumulation in C_{max} and AUC in rats in the first 3 months of treatment at lower doses up to 1 mg/kg/day.
There were no gender differences in exposure > 2-fold except for higher exposures in female rats in the carcinogenicity study.
Protein binding was low (<50%).
Difelikefalin distributed mainly into organs of excretion (kidney and, to a lesser extent, liver), showed low brain penetration and no preferential binding to melanin-containing tissues. Difelikefalin was very stable, with literally no metabolic elimination. Excretion was mainly via the urine in animals and healthy people. In CKD-associated pruritis patients undergoing HD, elimination occurred mainly via HD and biliary excretion.
Difelikefalin crossed the placenta and was detected in the milk of lactating rats.

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4.3 Toxicology

Pivotal toxicology studies were conducted with IV and SC administration in rats, and IV administration in monkeys, which are considered appropriate species based on the pharmacological responsiveness and ADME profile. The daily dosing scheme is considered a cautious measure to account for a potential low renal clearance in CKD-aP patients undergoing HD with 2-3 times weekly treatment. Chronic treatment was evaluated in a 26-week study in rats with doses up to 25 mg/kg/day and two 39-week studies in cynomolgus monkeys with maximal doses of 1 mg/kg/day. The conduct of the second chronic monkey study is questioned, including for 3R principles. The predominant difelikefalin-related effects were considered related to exaggerated pharmacodynamic activity of difelikefalin in both rodents and monkeys. Decreased spontaneous behaviour, lethargy and altered motor coordination, weight loss or decreased weight gain, lower body weights, and reduced food consumption, were noted usually from the lowest dose levels. These findings ceased after a few days of treatment, indicating adaptation. Urine volume was decreased in the initial dosing phase, probably due to decreased water and food intake. In rats, difelikefalin caused abnormalities in the male reproductive organs at the highest dose, including bilateral atrophy in the seminiferous tubules in the testis, decreased sperm in the epididymis, and cell debris in the lumen of the epididymis. In rats, renal tubular basophilia associated with changes of chronic progressive nephropathy (CPN) and hyaline droplet accumulation were noted. These increased with dose and treatment duration, particularly in male rats. In monkeys, deposits of brown pigment in the pars recta of the proximal tubule in the kidney were noted. The CPN was considered rat-specific and not to present a human risk factor, and the findings in monkeys were not considered adverse. The NOAEL in the chronic rat study was considered 2.5 mg/kg/day for males and 25 mg/kg/day for females, corresponding to safety margins of 211-fold and 2228-fold based on the clinical $AUC_{0\text{-}72h}$. The NOAEL for chronic treatment in monkeys was considered 0.25 mg/kg/day based on the moribund condition of one female in the 1 mg/kg/day dose group, a probable result of exaggerated pharmacology, corresponding to margins of > 650-fold the clinical AUC.
There was no evidence of immunotoxicity from the rat and monkey studies.
Difelikefalin tested negative in a standard battery of genotoxicity studies.
Difelikefalin was not carcinogenic in a 6-month transgenic mouse study and a 2-year rat study with SC administration at exposures greatly in excess of the clinical exposure.

In a rat IV fertility and early embryonic development study, difelikefalin prolonged diestrus that was associated with a slight increase in days to mating at ≥ 2.5 mg/kg/day. No effect on female mating was seen at exposures 15-fold the clinical exposure. There was no effect on male mating, male and female fertility, implantation, or early embryonic development at exposures 1905-fold to 2912-fold the clinical exposure at the recommended human dose.
Embryofoetal studies in rats and rabbits showed maternal toxicities (reduced body weight gain and gain loss, and behavioural changes) from the lowest dose at exposures 19-fold (rat) and 5-fold (rabbits) the clinical exposure. Maternal toxicity was likely the cause for fewer pregnancies in rabbits in the high dose group. In rats, at exposures 194-fold the clinical exposure, an increased incidence of wavy ribs and incompletely ossified ribs was noted. The developmental NOAEL was equal to exposures 2133-fold the clinical exposure in rats and 30-fold in rabbits. The maternal reproductive function in rabbits was not affected at exposures 13-fold the clinical exposure.
In the pre- and postnatal development study in rats, maternal toxicity (reduced body weight and behavioural changes) was most severe during the gestation phase. The NOAEL for maternal toxicity was at the lowest dose, corresponding to exposure multiples of 47 to the clinical exposure. There was a statistically significant increase in mean duration of gestation without an effect on delivery or growth and functional parameters of the offspring at exposures 776-fold the clinical exposure.
In summary, difelikefalin had no adverse effect on reproduction or development. As maternal toxicity may have consequences for the pregnancy outcome, as a precautionary measure difelikefalin should not be given during pregnancy. This is indicated in the Information for healthcare professionals.

Difelikefalin, as a small synthetic peptide, is considered to have a low risk of phototoxicity.

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Difelikefalin showed a reversible, slight irritancy potential, as noted in rats in the toxicology studies with SC administration and in a dedicated study in rabbits following perivascular SC administration.
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.
Based on the environmental risk assessment, difelikefalin is not expected to pose a risk to the environment. There are no concerns with regard to the impurities or excipients.
All nonclinical information is adequately mentioned in the RMP.

4.4 Nonclinical Conclusions

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Kapruvia with the new active substance difelikefalin in the proposed indication. The pharmacological activity and the toxicological profile of difelikefalin were well characterised. There were no particular safety issues identified in the nonclinical studies that would be of concern for human use.

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5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Kapruvia, solution for injection, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

KAPRUVIA

Composition

Active substances

Difelikefalin (as difelikefalin acetate).

Excipients

Acetic acid (for pH adjustment), sodium acetate trihydrate (for pH adjustment), sodium chloride, water for injection. It contains a total of approx. 3.3 mg sodium per ml.

Pharmaceutical form and active substance quantity per unit

Solution for injection for intravenous administration.
One vial of 1 ml contains 50 micrograms of difelikefalin (as difelikefalin acetate).
Clear, colourless solution, free from particles.

Indications/Uses

Kapruvia is indicated for the treatment of moderate-to severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.

Dosage/Administration

Usual dosage

The recommended dose of difelikefalin is 0.5 micrograms/kg dry body weight (i.e. the target postdialysis weight) and is to be administered by intravenous bolus injection three times per week. The total dose volume (ml) required from the vial should be calculated as follows: 0.01 x dry body weight (kg) as prescribed by a doctor, 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). The recommended doses are listed in the following table:

Weight range (dry body weight in kg)	**Dose*** (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

* More than 1 vial is to be used if a dose of more than 1 ml is required.

Missed doses

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

Additional treatment

If a 4th haemodialysis treatment is performed in the same 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 safety concern, as the majority of remaining difelikefalin from the previous treatment will be cleared by haemodialysis. The safety and efficacy of a 4th dose has however 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 treatment.
Following administration of difelikefalin in haemodialysis patients, up to 70% is eliminated from the body prior to the next haemodialysis treatment. Difelikefalin plasma levels remaining at the time of the next haemodialysis are reduced by about 40-50% within one hour of haemodialysis.

Elderly population

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

Patients with hepatic disorders

No dose adjustment is required for patients with mild or moderate hepatic impairment (see section "Pharmacokinetics"). The use of difelikefalin has not yet been studied in patients with severe hepatic impairment and is therefore not recommended for use in this patient population.

Children and adolescents

The safety and efficacy of Kapruvia in children and adolescents aged 0-17 years have not yet been demonstrated. No data are available.

Mode of administration

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

Kapruvia is administered 3 times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of 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 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 is needed to flush the line.

Contraindications

Hypersensitivity to the active substance or to any of the other components (see "Composition").

Warnings and precautions

Hyperkalaemia

Hyperkalaemia frequently occurs in chronic kidney disease patients on haemodialysis. In the placebo-controlled clinical studies a numerically higher incidence 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 stopped their atrial fibrillation treatment. No causal relationship was established.

Patients with impaired blood-brain barrier

Difelikefalin is a 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 "Properties/effects"). Patients with clinically important disorders of 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 difelikefalin treated patients. These symptoms may subside over time with continued treatment (see "Undesirable effects"). 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 "Interactions"). Compared to placebo, the incidence of somnolence was higher in difelikefalin treated patients 65 years of age and older (7.0%) than in difelikefalin treated patients less than 65 years of age (2.8%).

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

Interactions

No clinical interaction studies have been performed.
Difelikefalin is not a substrate of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4, nor an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5, and carries minimal to no potential for induction of human CYP1A2, CYP2B6, or CYP3A. It is also not an inhibitor of glucuronidation enzymes (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 of 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.
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 "Warnings and precautions" and "Undesirable effects").

Pregnancy, 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 adverse effects with respect to reproductive toxicity (see "Preclinical data").
As a precautionary measure, Kapruvia should not be used during pregnancy.

Lactation

It is unknown whether difelikefalin is excreted in human breast milk. Animal studies have shown excretion of difelikefalin in breast milk. A risk for 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 mother.

Fertility

There are no data on the effect of Kapruvia on fertility in humans. In rat studies with difelikefalin, there was no impairment of mating ability or fertility observed (see "Preclinical data").

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 "Undesirable effects"). Patients should be cautioned about driving or operating machines 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 treatment. Dizziness occurred within the first 9 weeks of treatment and was generally transient.

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%), 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.

List of adverse reactions

The adverse reactions are ordered by MedDRA system organ class and frequency according to the following convention:
"Very common" (≥1/10)
"Common" (≥1/100 to <1/10),
"Uncommon" (≥1/1,000 to <1/100)
"Rare" (≥1/10,000 to <1/1,000)
"Very rare" (<1/10,000)

Side effects reported with the use of Kapruvia in clinical studies at the target dose of 0.5 micrograms/kg in these patients (n = 1,306) are listed in Table 1.
Within each frequency category, side effects are listed in order of decreasing severity.

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

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

[1] 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 patients. 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 treatment.
The likelihood of somnolence may increase when difelikefalin is concomitantly used with other medicinal products (see "Warnings and precautions").

Dizziness

Dizziness was reported as treatment emergent adverse event in 7.9% of patients 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 patients. 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 "Warnings and precautions").

Mental state changes

Mental status change (including confusional state) was reported as treatment emergent adverse event in 4.4% of patients 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 patients. In 0.3% of patients, mental status changes were reported to have a causal relationship to difelikefalin treatment.

Reporting suspected adverse reactions after authorisation of the medicinal product is very 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 I ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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 cleared approximately 70-80% of difelikefalin from plasma, and difelikefalin was not detectable in plasma at the end of two dialysis cycles.

Properties/Effects

ATC-Code

ATC-Code: V03AX04

Mechanism of action

Difelikefalin is a selective kappa opioid receptor agonist with low CNS penetration.
Opioid receptors are known to modulate itch signals and inflammation processes, with kappa opioid receptor activation reducing itch and producing immunomodulatory effects.

Pharmacodynamics

The exposure-response relationship of difelikefalin and the time course of pharmacodynamic response are not known.

Influence on the electrocardiogram

When dosed at 6 times the recommended dose, there is no clinically significant prolongation of the QTc interval with difelikefalin.

Clinical Efficacy

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. This double-blind treatment period was followed by a

52-week open-label extension study with active treatment only. The primary endpoint in both studies was the percentage of patients who achieved at least a 3 point reduction in the Worst Itching Numerical Rating Scale (WI-NRS scores range from 0 to 10, with higher scores representing greater intensity of itching.) from baseline 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. The main inclusion criteria were chronic kidney disease with thrice weekly haemodialysis for at least 3 months, moderate to severe pruritus (WI-NRS baseline >4) and adequate haemodialysis. The main exclusion criteria were pruritus of a cause other than chronic kidney disease or associated complications, pruritus on the palms and pruritus exclusively during haemodialysis sessions.

The combined studies enrolled 851 patients. The mean age was 59 years, 33.1% were aged 65 and over, 60% of patients were male. Disease characteristics at baseline, such as use of medications to relieve pruritus, time since diagnosis of chronic kidney disease and duration of pruritus, were comparable in the active treatment and placebo arms. The baseline mean WI-NRS scores were 7.18 in both, difelikefalin and placebo arms; baseline mean WI-NRS scores were 7.13 (range 4.2 to 10) in the difelikefalin group and 7.13 (range 4.1 to 10) in the placebo group. Overall, 38% of the patients had previously used medicinal products to treat pruritus. Across studies, difelikefalin significantly reduced itch intensity and improved itch-related Quality of Life over 12 weeks as shown in Table 2.

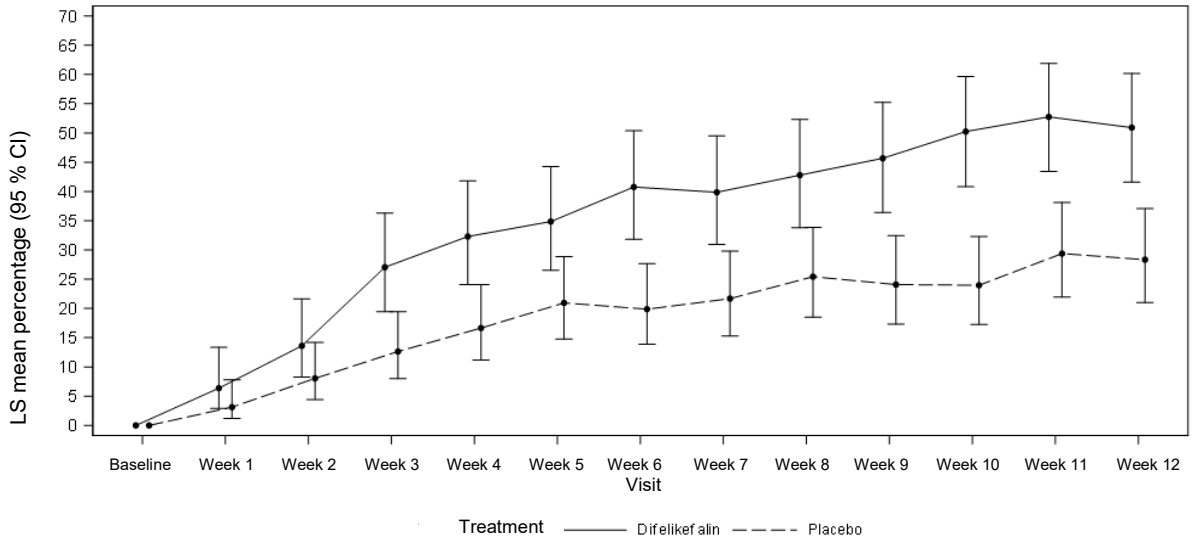
Table 2: Summary of primary and key secondary outcomes in KALM-1 and KALM-2 and the pooled database at week 12

	KALM-1 (n = 378)		KALM-2 (n = 473)	
Endpoint by the end of week 12	Difelikefalin (n = 189)	Placebo (n = 189)	Difelikefalin (n = 237)	Placebo (n = 236)
Primary endpoints				
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 [Score]	-17.2 (p <0.001)	-12.0	-16.6 (p = 0.171)	-14.8
5-D Itch Change from baseline [Score]	-5.0 (p <0.001)	-3.7	-4.9 (p = 0.002)	-3.8

Figure 1 shows the mean percentage from KALM-1 and KALM-2 with ≥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.

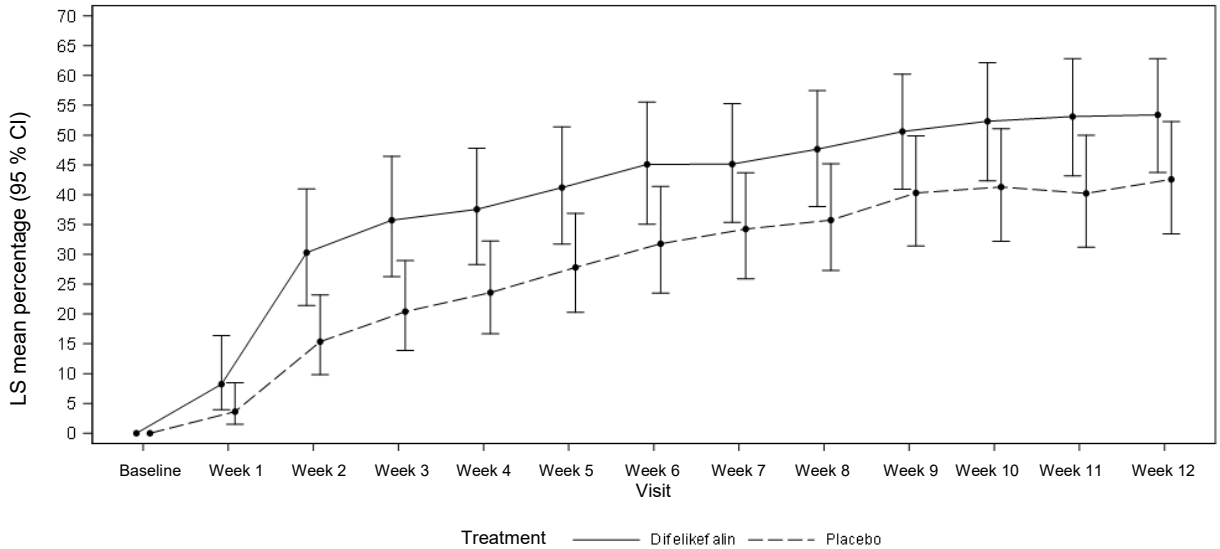
Figure 1: Percentage of patients with ≥3-point improvement with respect to WI-NRS-score by week in KALM-1 and KALM-2 (ITT population)

KALM-1



CI = confidence interval; ITT = intent to treat; LS = least squares (Method of Least Squares (MKQ)); WI-NRS = Worst Itching-Numerical Rating Scale

KALM-2



CI = confidence interval; ITT = intent to treat; LS = least squares (Method of Least Squares (MKQ)); WI-NRS = Worst Itching-Numerical Rating Scale

Open label extension studies

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 on 5-D Itch scale was maintained in both treatment groups throughout the 52-weeks treatment interval.

Pharmacokinetics

The pharmacokinetic properties of intravenously administered difelikefalin were studied in 319 healthy participants and 115 patients with chronic kidney disease, 91 of whom were on haemodialysis. The pharmacokinetic profile in patients with mild renal impairment was comparable to that of healthy participants. However, in patients with severe renal insufficiency, total body clearance of difelikefalin was reduced and plasma concentrations remained relatively constant until the drug was eliminated during dialysis.

Absorption

Not applicable.

Distribution

The plasma protein binding of difelikefalin is low to moderate. It is between 24 and 32% and remains unaffected by renal impairment. The mean distribution volume at steady state ranged from 145 to 189 ml/kg in healthy participants and from 214 to 301 ml/kg in haemodialysis patients with moderate to severe pruritus.

Metabolism

Difelikefalin is not a substrate of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

Elimination

In healthy participants, the primary route of elimination for difelikefalin is through the kidney, with approximately 81% of the dose excreted in the urine compared to 11% in the faeces. The mean total clearance ranged from 54 to 71 ml/h/kg and the mean half-life ranged from 2 to 3 hours. In contrast, elimination in renal insufficient haemodialysis patients was predominantly via faeces, in which on average approximately 59% of the dose was detected; approximately 19% was recovered in the dialysate and approximately 11% was found in the urine. Compared to participants with normal renal function, mean total clearance decreased and half-life increased 10-fold with values of 5.3 to 7.5 ml/h/kg and 23 to 31 hours, respectively. After administration of radiolabelled active substance, the parent compound accounted for >99% of the circulating radioactivity. Haemodialysis reduces the difelikefalin concentration by 70 to 80%. After 2 dialysis cycles, difelikefalin was no longer detectable in plasma.

Linearity/non-linearity

In haemodialysis patients with chronic kidney disease, the pharmacokinetics of difelikefalin are linear and dose-proportional in the single intravenous dose range of 1 to 3 micrograms/kg (2 to 6 times the

recommended dose) and in the multiple dose range of 0.5 to 2.5 micrograms/kg (1 to 5 times the recommended dose). The steady state was reached after the second administered dose and the mean accumulation ratio was up to 1.6.

Kinetics in specific patient groups

Currently, there is no evidence that factors such as age (25 to 80 years), gender, ethnicity or mild to moderate liver disorders have an influence on the pharmacokinetics of difelikefalin.

Relationship between pharmacokinetics and pharmacodynamics

In the target group of haemodialysis patients with renal insufficiency, no obvious dose-response relationship for antipruritic efficacy was observed. In persons with intact renal function, the risk of aquaresis is dose-dependent.

Preclinical data

Non-clinical data show no particular hazard to humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and abuse and dependence potential.

Reproductive and developmental toxicity

In rats, male and female fertility, early embryonic as well as prenatal and postnatal development were not affected at exposures at least 775-fold above the human AUC. In the rabbit, prenatal development was neither impaired despite marked maternal toxicity at 30-fold the human AUC.

In rats, difelikefalin crosses the placenta and is excreted in breast milk.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack

Special precautions for storage

Store at 15-30°C.
Keep out of the sight and reach of children.

Instructions for handling

The Kapruvia solution for injection in the vial is ready for use. Kapruvia must not be mixed or diluted with other medicinal products.

The sterile solution for injection in the vial contains no preservatives and is intended for a single injection in one patient only. Only solutions that are clear, colourless and free of visible particles may be injected.

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

Authorisation number

68653

Packs

Pack sizes of 3 vials (currently not marketed) and 12 vials containing each 1 ml of solution for injection. (B).

Marketing authorisation holder

Vifor Fresenius Medical Care Renal Pharma Ltd., St. Gallen

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