VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

CSL Vifor

KAPRUVIA®
(difelikefalin) Injection

Formulary Application Support Pack

Moderate-to-severe pruritus associated with chronic kidney disease[1]

Kapruvia® is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis. Kapruvia® should be restricted for in-centre haemodialysis use only[1]

This medicine is subject to additional monitoring. Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Vifor Pharma UK Ltd. Tel: +44 1276 853633. Email: medicalinfo_UK@viforpharma.com

NICE RECOMMENDED TREATMENT

NICE recommends KAPRUVIA®, within its marketing authorisation, for treating moderate-to-severe CKD-associated pruritus in adults receiving in-centre haemodialysis[2]

SMC ACCEPTED TREATMENT

SMC accepts with restricted use KAPRUVIA®, for treating moderate-to-severe CKD-associated pruritus in adult patients on in-centre haemodialysis with an inadequate response to best supportive care for reducing itch[3]

PRESCRIBING INFORMATION CAN BE FOUND ON THE FINAL PAGE OF THIS DOCUMENT

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Purpose of this document

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Contents

1. Background

1.1 Burden of Chronic Kidney Disease-Associated Pruritus (CKD-aP)

Chronic kidney disease–associated pruritus (CKD-aP) is defined as itching directly related to kidney disease, which exists without another comorbid condition to explain it.[4] It is highly prevalent amongst patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) undergoing dialysis.[4] Based on data reported in the phase 5 (2012-2015) Dialysis Outcomes and Practice Patterns Study (DOPPS), the prevalence of patients on haemodialysis bothered by moderate to extreme pruritus was 48% in the UK.[5] See Section 1.2 for more detail on the study design and endpoints.

Although the pathophysiology is not well understood, there is increasing evidence that the cause of CKD-aP is multifactorial involving immune system dysfunction (including elevated proinflammatory activity), an imbalance in the endogenous opioid system (with overexpression of mu opioid receptors in dermal cells and lymphocytes and concomitant downregulation of kappa opioid receptors [KORs]).[6,7]

The clinical presentation of CKD-aP is highly variable, with both the onset of symptoms and severity of disease varying from patient to patient.[8] The itching is often accompanied by secondary skin lesions, such as crusts, papules, ulcerations, erosions, impetigo and prurigonodularis.[8] CKD-aP is generalised in almost 50% of patients, and when generalised, it frequently presents symmetrically.[7] However, it can also be localised, whereby the pruritus will occur predominantly on the face, back and shunt arm only.[7]

Patients with CKD-aP have significant comorbidity burden. Patients extremely bothered vs those not at all bothered by itchy skin had increased burden from: cardiovascular disease (32.7% vs 28.5%, p<0.0001*); chronic obstructive pulmonary disease (6.5% vs 3.4%, p<0.0001*); liver disease (2.7% vs 1.8%, p=0.0029*); infection-related conditions including: bacteraemia (33.9% vs 27.4%, p<0.0001*); septicaemia (7.9% vs 5.9%, p<0.0001*).[9]

Due to its distressing nature, CKD-aP has a large impact on patients' quality of life (QoL). 32.1% of 22,464 patients with severe† CKD-aP in the DOPPS reported at least 3 restless nights of sleep each week.[10] CKD-aP can also lead to patients avoiding social interactions due to the appearance of their skin and the need to scratch.[11,12] Severe CKD-aP is also strongly associated with depression among HD patients.[8] The impact on QoL increases with the severity of itch.[10]

In an observational study of over 1,700 HD patients, after adjusting for other clinical risk factors, severe CKD-associated pruritus was an independent predictor of death.[13] The DOPPS found that rates of all-cause,‡ cardiovascular- and infection-related deaths§ were higher for patients extremely bothered by pruritus versus those not at all bothered by pruritus.[10] CV-related mortality may be associated with

* P-value for trend in comorbid disease characteristics by itchiness score (1, "not at all bothered"; 2, "somewhat bothered"; 3, "moderately bothered"; 4, "very much bothered"; 5, "extremely bothered") among haemodialysis patients in the US (n=38,315).[9]

† In DOPPS, severe CKD-aP was based on self-reported degree to which patients were bothered by itchy skin in the past 4 weeks: very much and extremely.[10]

‡ Primary clinical outcome; HR, 1.24 vs no bothersome itch; 95% CI 1.08, 1.41; Total number of patients with event across all severities of itch 11,204/23,264.[10]

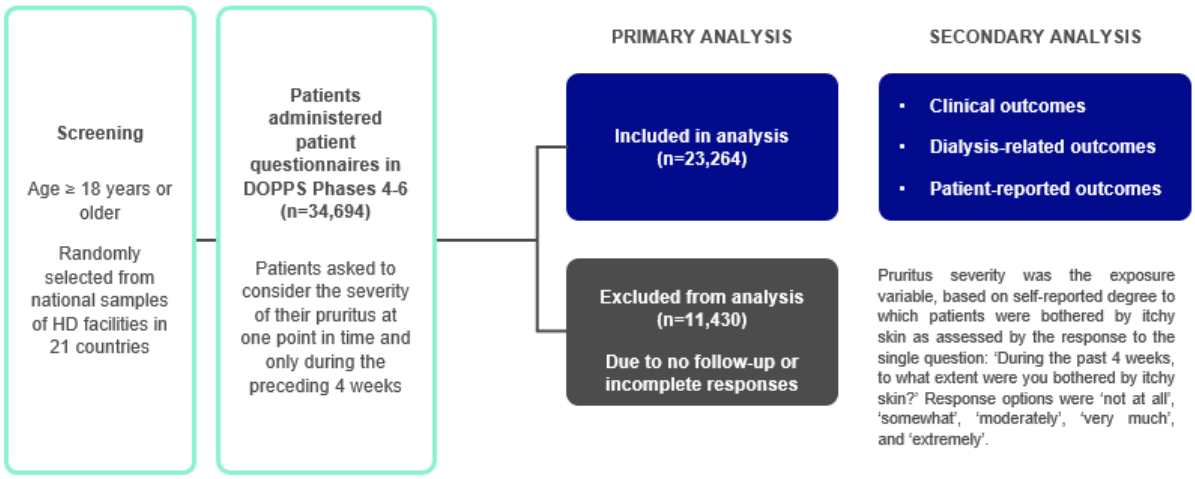
§ HR for patients extremely bothered by itch for CV-related mortality was 1.29 (95% CI, 1.06–1.57, N patients with event = 3,060/23,264). HR for infection-related mortality was 1.44 (95% CI, 1.05–1.96, N events = 2,215/23,264).[10]

higher levels of inflammation in these patients or possibly the prevalence of heart failure.[10] Infection-related mortality may also relate to immune system pathology or central venous catheter presence.[10]

1.2 Dialysis Outcomes and Practice Patterns Study (DOPPS)

Study design

The DOPPS was a multinational, prospective cohort study which aimed to explore the relationship between pruritis and several key outcomes in haemodialysis (HD) patients. Phases 4-6 were conducted between 2009 and 2018.[10]



The primary clinical outcomes were the time to all-cause mortality. Other clinical outcomes included cardiovascular and infection-related death as well as all-cause and cause-specific hospitalisations, including cardiovascular, infection, skin-related and mental status change/confusion admissions.[10]

Dialysis-related outcomes included withdrawal from dialysis, miss/skipped HD treatments, employment and recovery time from an HD session. Patient-reported outcomes consisted of physical and mental health related quality of life, depression, sleep quality, faintness/dizziness and feeling washed out/drained.[10]

1.3 Kapruvia (difelikefalin) summary

Kapruvia® is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on in-centre haemodialysis. Kapruvia is a selective kappa opioid (k-opioid) receptor agonist with low central nervous system penetration and is administered 3 times per week by intravenous bolus injection into the venous line of the dialysis circuit.[1] The physicochemical properties of Kapruvia (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.[1] Kapruvia should be restricted for in-centre haemodialysis use only.[1] Kapruvia is the only approved therapy specifically licensed for treatment of moderate-to-severe CKD-associated pruritus in adult patients receiving in-centre HD in the UK.[1]

In two pivotal clinical phase 3 clinical studies of similar double-blind, randomised, placebo-controlled design (KALM-1 and KALM-2), Kapruvia significantly reduced itch intensity and improved itch-related QoL over 12 weeks.[1] The primary endpoint, percentage of patients achieving ≥3-point improvement in Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores at Week 12, was met in both trials.[14]

Kapruvia is generally well tolerated. In placebo controlled and uncontrolled phase III clinical studies (n=1306), approximately 6.6% of patients experienced at least one adverse reaction during Kapruvia treatment. Most of these events were mild or moderate in severity, did not lead to deleterious consequences, and resolved with ongoing therapy.[1]

2. Kapruvia product characteristics

2.1 Product

Kapruvia 50 micrograms/mL solution for injection.[1]

2.2 Qualitative and quantitative composition

Each vial of 1 mL contains 50 micrograms Kapruvia (as acetate).[1]

2.3 Pharmaceutical form

Solution for injection.[1]

Clear, colourless solution, free from particles (pH 4.5).[1]

2.4 Posology

Kapruvia should be restricted for in-centre haemodialysis only. Causes of pruritus other than chronic kidney disease should be excluded before initiating treatment with Kapruvia. Kapruvia is administered 3 times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the HD treatment during rinse-back or after rinse-back.[1]

The recommended dose of Kapruvia is 0.5 micrograms/kg dry body weight (i.e., the target post-dialysis 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). Please refer to the table 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:[1]

Weight range (Dry body weight in kg)	Injection volume (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

*A minority of patients will require two vials per dose (only patients with a dry body weight ≥105kg will require more than one 1ml vial).

An effect of difelikefalin is expected after 2-3 weeks of treatment.[1]

Missed doses:

If a regularly scheduled HD treatment is missed, Kapruvia should be administered at the next HD treatment at the same dose.[1]

Extra treatment:

If a 4th haemodialysis dose is performed in a week, Kapruvia should be administered at the end of haemodialysis per the recommended dose. **No more than 4 doses are recommended**, even if the number of dialysis treatments in a week is more than 4. A 4th dose of Kapruvia is unlikely to lead to accumulation of Kapruvia that would be of concern for safety, as the majority of remaining Kapruvia from the previous treatment will be cleared by HD. However, safety and efficacy of a 4th dose has not been fully established due to insufficient data.[1]

Please refer to the full Summary of Product Characteristics before prescribing and administration.

Patients with incomplete HD treatment:

For haemodialysis treatments less than 1 hour, administration of Kapruvia should be withheld until the next HD session.[1]

Following administration of Kapruvia in haemodialysis subjects, up to 70% is eliminated from the body prior to the next haemodialysis session. Kapruvia plasma level remaining at the time of the next haemodialysis is reduced by about 40-50% within one hour of haemodialysis.[1]

Patients with hepatic impairment:

No dose adjustment is required for patients with mild or moderate hepatic impairment. Kapruvia 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.[1]

Elderly population (≥ 65 years of age):

Dosing recommendations for elderly patients are the same as for adult patients.[1]

Paediatric population:

The safety and efficacy of Kapruvia in children aged 0-17 years has not yet been established.[1]

No data are available.[1]

2.5 Pharmacokinetic properties

In patients with severe renal impairment undergoing haemodialysis, total body clearance of Kapruvia is reduced compared to healthy subjects and plasma concentrations decrease slowly until cleared during dialysis. As 70-80% of Kapruvia is removed during dialysis, Kapruvia is administered after each haemodialysis session in these patients. The available data on interindividual variability in haemodialysis subjects receiving 0.5 microgram/kg Kapruvia suggest that variability of area under the curve (AUC) can exceed 30%.[1]

Distribution

Plasma protein binding of Kapruvia is low-to-moderate, ranging from 24-32%, and remains unaffected by renal impairment. Mean volume of distribution at steady state ranged from 145 to 189 mL/kg in healthy subjects and from 214 to 301 mL/kg in haemodialysis patients with moderate-to-severe pruritus. Kapruvia penetration into the central nervous system is limited (below limit of quantification) as shown by physico-chemical, in-vitro and animal data.[1]

Elimination

In healthy subjects, the primary route of elimination for Kapruvia 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 Kapruvia with minor quantities of putative metabolites, none exceeding 2.5%. Mean total clearance ranged from 54 to 71 mL/h/kg and mean half-lives from 2 to 3 hours. By contrast, in renally impaired haemodialysis patients, elimination was predominantly via faeces, accounting on average for about 59% of the dose; about 19% were recovered in dialysate and about 11% were found in urine. As compared to subjects with normal renal function, mean total clearance decreased and half-lives increased about 10-fold with ranges of 5.3 to 7.5 mL/h/kg and 23 to 31 hours, respectively.[1]

Interaction with other medicinal products

Kapruvia 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).[1]

In addition, Kapruvia 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.[1]

Linearity/non-linearity

Pharmacokinetics of Kapruvia 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 AUC0-48h and 1.33 in another study, based on AUC0-44h; showing that variability for accumulation parameters can exceed 30%.[1]

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 Kapruvia.[1]

2.6 Method of administration

Kapruvia should not be diluted and should not be mixed with other medicinal products.[1]

Kapruvia is removed by the dialyzer membrane and must be administered after blood is no longer circulating through the dialyzer. Kapruvia is administered 3 times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the HD treatment during rinse-back or after rinse-back.[1]

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.[1]

Please refer to the full Summary of Product Characteristics before prescribing and administration.

2.7 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2.6.[1]

2.8 List of excipients

- Acetic acid (for pH adjustment)[1]
- Sodium acetate trihydrate (for pH adjustment)[1]
- Sodium chloride[1]
- Water for injections[1]

2.9 Special warnings and precautions for use

Hyperkalaemia:

Hyperkalaemia frequently occurs in chronic kidney disease patients on HD. In the placebo-controlled clinical studies a numerically higher rate of adverse events of hyperkalaemia was reported for the Kapruvia 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.[1]

Cardiac failure and atrial fibrillation:

Kapruvia 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 Kapruvia 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.[1]

Patients with impaired blood-brain barrier:

Kapruvia 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 minimising Kapruvia uptake into the CNS. 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 Kapruvia 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.[1]

Dizziness and somnolence:

Dizziness and somnolence have occurred in patients taking Kapruvia and may subside over time with continued treatment. 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 Kapruvia.[1]

Compared to placebo, the incidence of somnolence was higher in Kapruvia treated subjects 65 years of age and older (7.0%) than in Kapruvia treated subjects less than 65 years of age (2.8%).[1]

Excipients with known effect:

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

2.10 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed. Kapruvia does not inhibit or induce CYP450 enzymes and is not a substrate of CYP450 enzymes. It is not an inhibitor of glucuronidating enzymes either. Kapruvia is not a substrate or an inhibitor of human transporters. Therefore, interactions of Kapruvia with other medicinal products are unlikely.[1]

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.[1]

2.11 Fertility, pregnancy and lactation

Pregnancy:

There are no or limited amount of data from the use of Kapruvia in pregnant women.[1]

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.[1]

As a precautionary measure, it is preferable to avoid the use of Kapruvia during pregnancy.[1]

Breast-feeding:

It is unknown whether Kapruvia is excreted in human breast milk.[1]

A risk to the newborns/infants cannot be excluded.[1]

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.[1]

Animal studies have shown excretion of Kapruvia in breast milk.[1]

Fertility:

There are no data on the effect of Kapruvia on fertility in humans. In rat studies with Kapruvia, there was no effect on fertility.[1]

2.12 Effects on ability to drive and use machines

Kapruvia has minor influence on the ability to drive and use machines.[1]

Somnolence and/or dizziness have been reported in patients receiving Kapruvia. Patients should be cautioned about driving or operating hazardous machinery until the effect of Kapruvia 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.[1]

2.13 Mechanism of Action

Kapruvia is a selective kappa opioid receptor agonist with low central nervous system penetration.
The physicochemical properties of Kapruvia (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.[1]

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).[1]

Opioid receptors are known to modulate itch signals and inflammation, with kappa opioid receptor activation reducing itch and producing immunomodulatory effects.[1]

The activation of kappa opioid receptors on peripheral sensory neurons and immune cells by Kapruvia are considered mechanistically responsible for the antipruritic and anti-inflammatory effects.[1]
No signs of potential physical dependence or AEs related to withdrawal were observed in the KALM-1 study or reported in the Phase 3 KALM-2 study of Kapruvia in HD patients with moderate-to-severe pruritus.[15]

2.14 Shelf life

2 years.[1]

2.15 Storage requirements

This medicine does not require any special storage conditions.[1]

3. Kapruvia positioning in the treatment pathway

3.1 Current treatment options

Among the treatments currently used to manage CKD-aP, no single treatment is shown to be overwhelmingly effective.[17] Previously, the standard of care has been to optimise dialysis and use emollients before considering other treatment strategies.[17] However, NICE has recommended Kapruvia for treating moderate-to-severe CKD-aP in adults receiving in-centre haemodialysis.[18] Additionally, SMC accepts with restricted use Kapruvia, for treating moderate-to-severe CKD-associated pruritus in adult patients on in-centre haemodialysis with an inadequate response to best supportive care for reducing itch.[3]

In an international study of UK patients on haemodialysis (n=39,452) who were bothered by itch, 29% were found to have no relief treatment.[5]

Topicals:

Topical analgesics, such as capsaicin (0.025% and 0.075% cream), are sometimes used for treating patients suffering with CKD-aP. These products alleviate pruritus through conduction blocking of nerve impulses from the skin, leading to numbness and decreased sensation.[19] Capsaicin is often used to reduce localised pruritus symptoms but its effectiveness is still yet to be evaluated due to insufficient clinical trial data.[8] Furthermore, many patients report unpleasant side effects such as burning, and stinging.[11]

In addition to analgesics, traditional emollients may also be considered in patients experiencing pruritus.[19]

Antihistamines:

Antihistamines are prescribed to CKD-aP patients despite displaying limited efficacy within the CKD-aP population.[20] The mechanism of itching associated with kidney disease is different from allergic itching and so antihistamines are usually not effective.[20] Several studies on the efficacy of antihistamines have been conducted and found that oral antihistamines provide no extra benefit to emollients alone.[19] Although the effectiveness in treating itch is relatively low, they can be useful for patients who are experiencing nocturnal exacerbations as a means of sedation.[19]

Gabapentinoids:

Gabapentinoids are used in the UK and act by modulating the alpha-2-delta subunit of voltage-gated ion channels and/or inhibition of calcitonin gene-related peptide release (a mediator of itch) from reduction of neural sensitisation and sensory neurons.[19]

Five studies have shown that gabapentin or pregabalin had a statistically significant benefit when compared with placebo.[19] However, the efficacy of gabapentinoids must be weighed against side effects that may limit its use.[19]

3.2 Unmet need

There is an unmet need for an effective treatment option with a tolerable safety profile accompanied by long-term efficacy in patients on HD suffering from moderate-to-severe CKD-aP.[14]

Despite the clear burden of CKD-aP, there is a lack of effective treatments and other than Kapruvia, there are no approved drugs in Europe for the treatment of CKD-aP. Currently, Kapruvia is the only specifically licensed treatment for CKD-aP, and other treatments used for CKD-aP have limited and low-grade clinical evidence to support their use in this condition. Consequently, there is a lack of robust treatment recommendations with no established standard of care.[21] This results in a high level of unmet need among HD patients with moderate-to-severe CKD-aP.

In a recent international prospective cohort survey (n=23,264), 43% of HCPs declared they had no specific therapy of choice whilst 72% agreed that treatment options for CKD-aP are limited. Many felt major treatment improvements were needed in terms of improved efficacy for reduction of itch intensity (62%) and ability to improve a patient's QoL (57%).[14]

Additionally, consultant nephrologists underestimated the prevalence of CKD-aP in 69% of dialysis units (n=233/237).[5*†] This is accompanied by 25% of patients with CKD-aP who were bothered by itch did not report it to their HCP (n=631/2,522).[22‡]

3.3 Rationale for Kapruvia use

In two, double-blind, placebo-controlled phase 3 trials (KALM-1 and KALM-2), Kapruvia provided a continuous and clinically meaningful reduction in itch intensity to HD patients with CKD-aP. During KALM-1 involving patients with CKD (n=378) who had been on haemodialysis for 12 weeks, 51.0% of the Kapruvia cohort and 27.6% of the placebo cohort reported a reduction of at least three points on the weekly mean WI-NRS score at week 12 ($P < 0.001$).[1] In KALM-2, which involved patients with CKD (n=473) who had been on dialysis for at least 12 weeks, 54.0% of participants in the Kapruvia group achieved a ≥3 point reduction in the weekly mean WI-NRS score at week 12, versus 42.2% in the placebo group (P=0.02).[1] The categorical threshold of a decrease of at least 3 points was selected on the basis of a psychometric analysis of data from a previous phase 2 trial that showed that a 3-point decrease represented a clinically meaningful improvement in itch intensity in this patient population.[16,23]

Itch severity and itch-related QoL were also measured by the total Skindex-10 and the 5-D Itch scale. The effects of treatment with Kapruvia 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.[1] A summary of secondary endpoints can be found in Section 5.1.

Kapruvia tolerability was assessed in placebo controlled and uncontrolled phase 3 clinical studies (n=1306), where approximately 6.6% of the patients experienced at least one adverse reaction during Kapruvia treatment. Most of these events were mild or moderate in severity, did not lead to deleterious consequences, and resolved with ongoing therapy.[1] A summary of adverse events in the clinical trials can be found in Section 6.

* DOPPS Phases 1–5 was a prospective cohort study of 51,062 HD patients from up to 21 countries between 1996–2015. Pruritus data were collected from 35,452 of these HD patients.[5]

† In year 2 of DOPPS Phase 5 (2013) 268 Consultant Nephrologists (medical directors of 337 participating study sites) were asked to estimate the prevalence of pruritus among their patients and describe their typical treatment practices.[5]

‡ In year 2 of DOPPS Phase 5 (2013) patients 'nearly always' or 'always' bothered by their itchy skin (2,522 patients) were asked 'What health care providers have you spoken about with your itchy skin'.[22]

3.4 National guidance and recommendations for Kapruvia

NICE Technology Appraisal Guidance [TA890 Published: 17th May 2023]

Final draft guidance from NICE recommends the use of Difelikefalin within its marketing authorisation, for treating moderate to severe pruritus in adults with CKD having in-centre haemodialysis. Difelikefalin is only recommended if the company provides it according to the commercial agreement.[2]

The committee has made this decision as evidence from clinical trials shows that difelikefalin reduces itching compared with usual treatment and the cost-effectiveness estimates for difelikefalin are within the range that NICE usually considers an acceptable use of NHS resources.[2]

The company has a commercial arrangement – simple discount patient access scheme. This makes difelikefalin available to the NHS with a discount. The size of the discount is commercial in confidence.

SMC Treatment Advice [SMC2623 Published: 12th February 2024]

SMC has accepted Kapruvia for restricted use. The restriction means that Kapruvia is accepted to treat adult in-centre haemodialysis patients with moderate-to-severe CKD-aP, where the best available commonly used treatments have not worked well enough to control their itch.[3]

3.5 Anticipated positioning of Kapruvia in the treatment algorithm

There are currently no approved treatments of CKD-aP in the UK although treatments for other conditions are sometimes used off-label, such as antihistamines including cetirizine or the gamma aminobutyric acid (GABA) analogues gabapentin and pregabalin.[2,20,24] Kapruvia should be positioned as an adjunct to current clinical management/treatment (which could include: optimised dialysis, lifestyle measures, emollients, antihistamines, gabapentinoids), where the patient has moderate to severe symptoms despite their current treatment.

4. Cost Considerations

4.1 Estimated number of eligible patients per 100,000[25]

	Per 100,000 adults (aged 18 and over) population	
	Percentage (%)	Number
Patients on KRT for renal failure[25]	0.13%	130
Patients on KRT receiving in-centre HD[25]	36%	47*
Prevalence of moderate-to-extreme pruritus[10]	48%	23*
Patients diagnosed with CKD-aP[26]	41%	9*
Total number of eligible patients for treatment	9 patients*	

KRT = Kidney replacement therapy
**Rounded to whole number*

4.2 Pricing

Cost of Kapruvia:

The list price of Kapruvia is £35 per vial sold as a pack of 12 vials at a list price of £420.00.[27] A simple discount patient access scheme (PAS) for Kapruvia has been agreed with NHS England (NHSE). NHS England is the responsible commissioner via a passthrough payment.

Resource impact

NICE anticipates no significant resource impact with the introduction of Kapruvia.[18]

As the cost of treatment is relatively low, NICE expect the resource impact of implementing the recommendations in England will be less than £5 million per year in England (or approximately £8,800 per 100,000 population, based on population for England of 56.6m people).[18]

5. Clinical Efficacy and Safety Data

5.1 Placebo controlled studies

Study designs

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 Kapruvia 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.[1]

Please refer to schematic diagrams below showing the study designs for KALM-1, KALM-2 and open label extension (OLE) (see figures 1,2 and 3).[16,23,28,29]

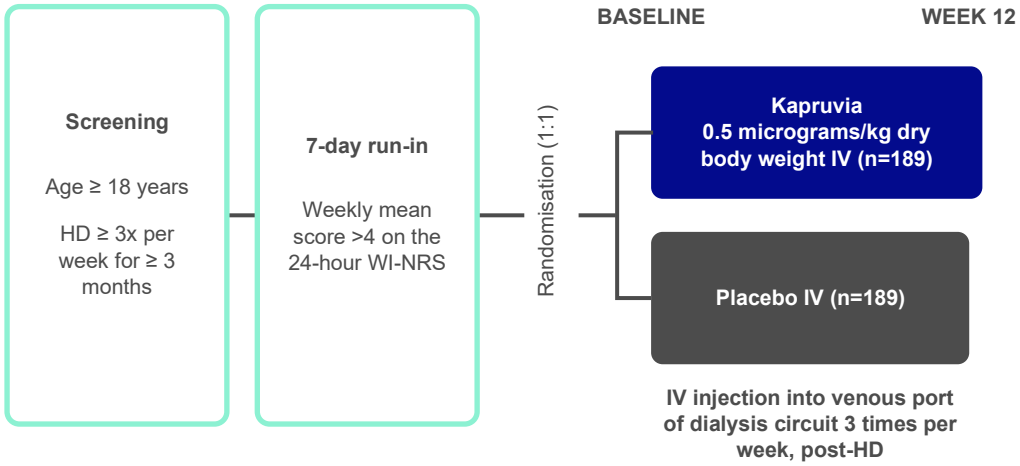


Figure 1: Schematic diagram showing the study design for KALM-1.

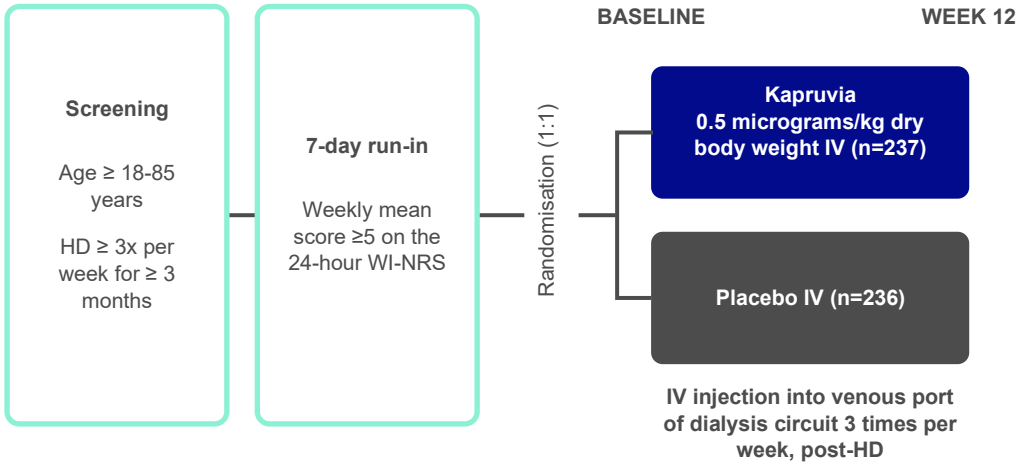


Figure 2: Schematic diagram showing the study design for KALM-2.

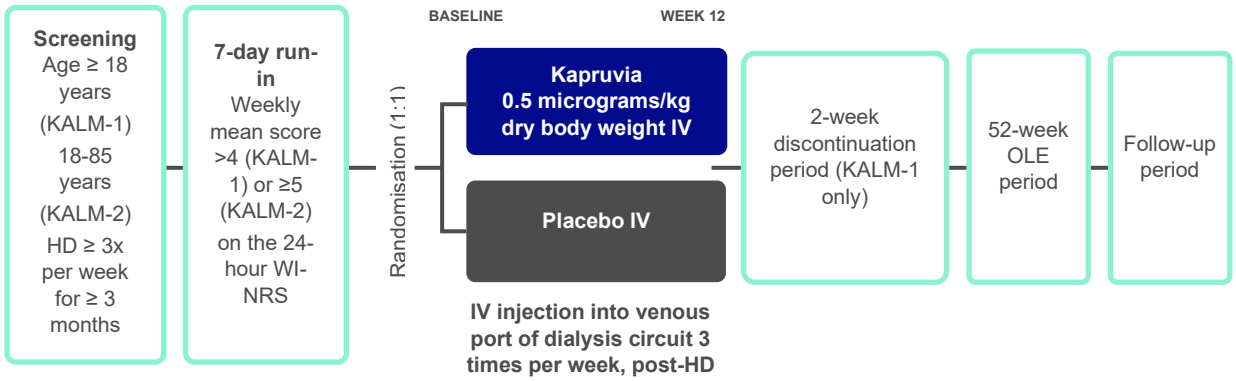


Figure 3: Schematic diagram showing the study design for KALM-1 and KALM-2 OLE.

Study endpoints

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.[1] The categorical threshold of a decrease of at least 3 points was selected on the basis of a psychometric analysis of data from a previous phase 2 trial that showed that a 3-point decrease represented a clinically meaningful improvement in itch intensity in this patient population.[16,23]

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.[1]

Eligibility criteria

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.[1]

Patient characteristics at baseline

The baseline mean WI-NRS scores were 7.18 in both, Kapruvia and placebo arms; baseline median WI-NRS scores were 7.13 (range 4.2 to 10) in Kapruvia and 7.13 (range 4.1 to 10) in placebo arm.[1]

Other disease characteristics at baseline were comparable in Kapruvia 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%).[1]

Results

Across studies, Kapruvia significantly reduced itch intensity and improved itch-related QoL over 12 weeks as shown in Table 1.[1]

Table 1: Adapted from Kapruvia SmPC. Summary of primary and key secondary endpoints in KALM-1 and KALM-2 at week 12.[1]

	KALM-1 (n=378)		KALM-2 (n=473)	
	Kapruvia®▼ (n=189)	Placebo (n=189)	Kapruvia®▼ (n=237)	Placebo (n=236)
Primary endpoint				
WI-NRS Patients with a ≥3-point improvement (%)	51.0% (p<0.001)	27.6%	54.0% (p=0.02)	42.2%
WI-NRS Patients with a ≥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†	-3.8

†*Was not tested based on the hierarchical testing order.*

The mean percentage from KALM-1 and KALM-2 with a ≥3-point improvement from baseline in WI-NRS score by study week is shown in figures 4 and 5 (see below). The categorical threshold of a decrease of at least 3 points was selected on the basis of a psychometric analysis of data from a previous phase 2 trial that showed that a 3-point decrease represented a clinically meaningful improvement in itch intensity in this patient population.[16,23] Based on odds ratios, statistically significant improvement favouring the Kapruvia 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.[1]

Pre-specified additional outcome: Proportion of patients achieving ≥3-point improvement in WI-NRS from Week 1 through to Week 12 with Kapruvia vs. placebo in KALM-1 (intent to treat (ITT) population).[1]

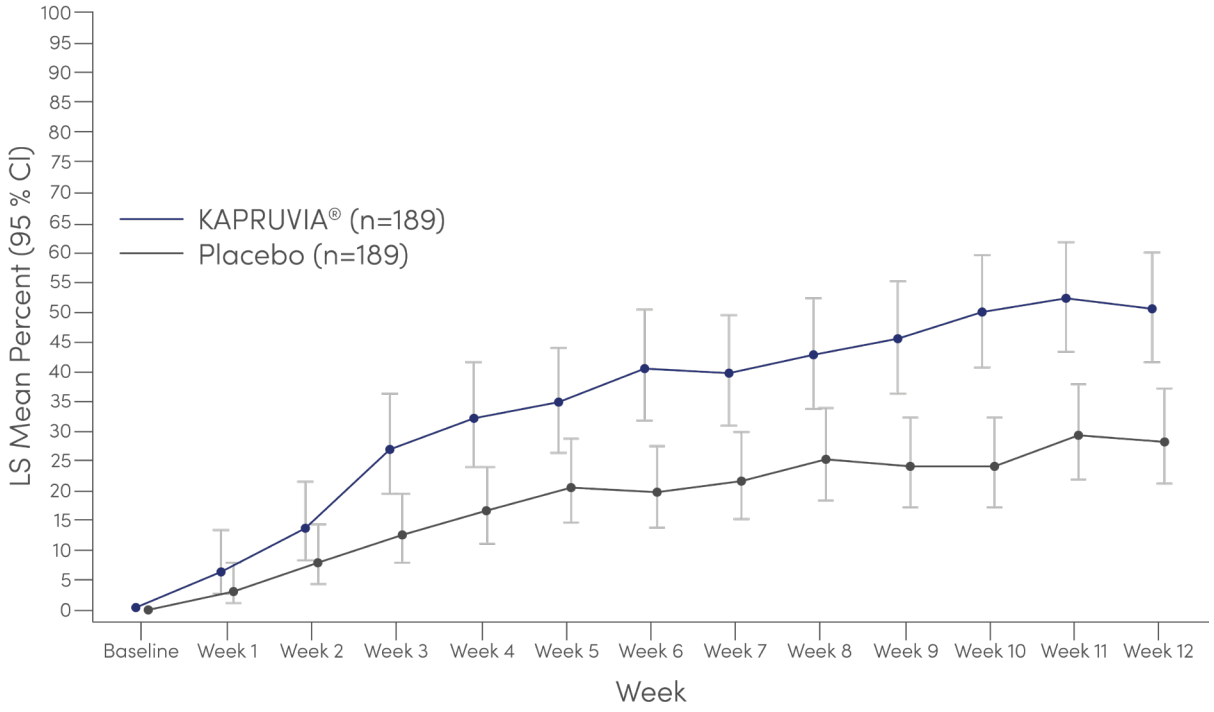


Figure 4: Adapted from Kapruvia® SmPC. [1]

Additional outcome: Proportion of patients achieving a >= 3-point improvement in WI-NRS from Week 1 through to Week 12 with Kapruvia vs. placebo in KALM-2 (ITT population).[1]

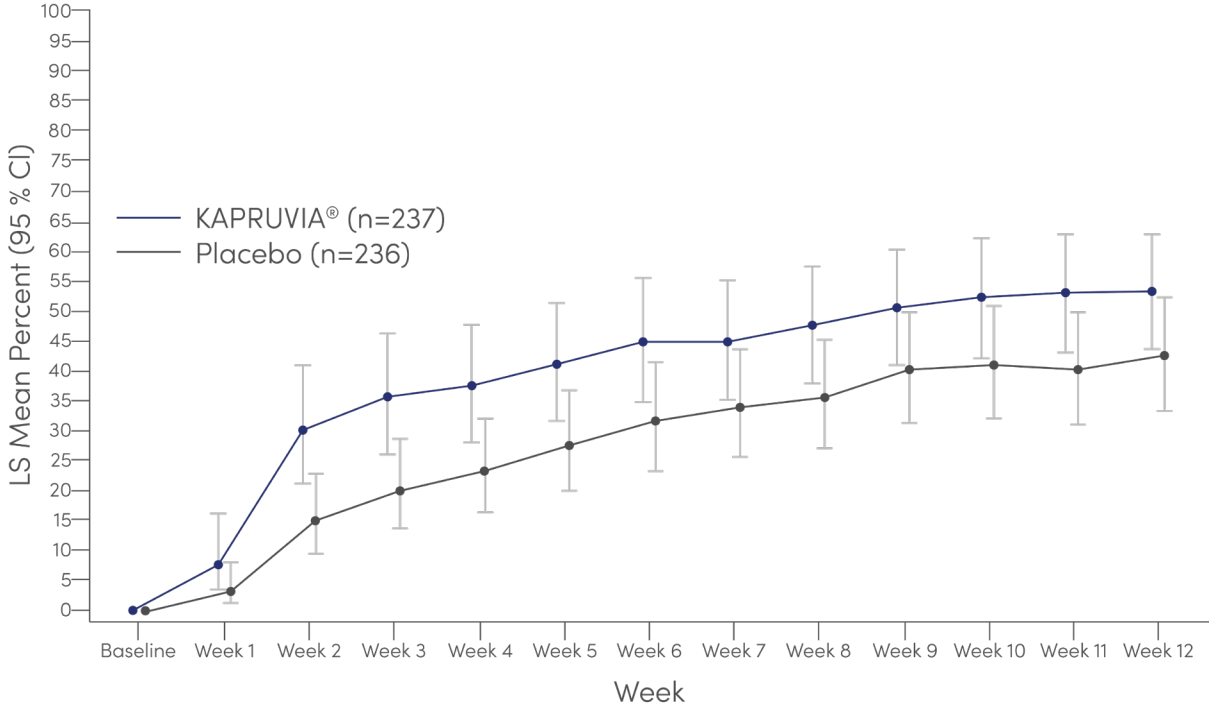


Figure 5: Adapted from Kapruvia® SmPC.[1]

Open label extension studies

The effect of treatment with Kapruvia 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.[1]

In patients switching from placebo to Kapruvia 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 Kapruvia 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.[1]

Additional study information

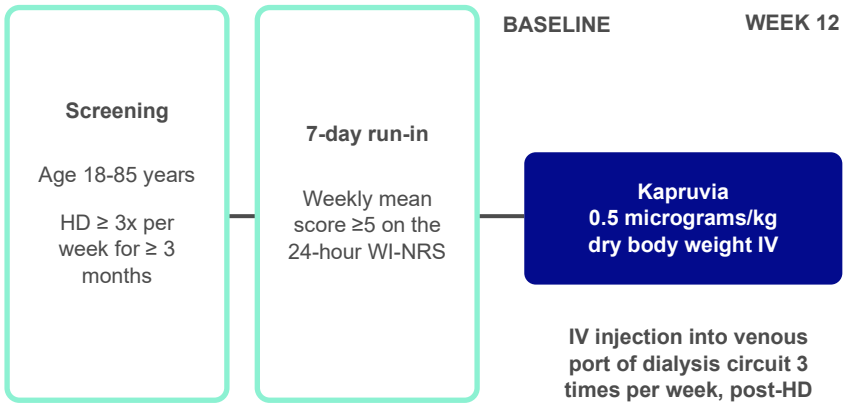
For additional study endpoints and analysis for KALM-1 and KALM-2, please refer to the following references:

1. Fishbane, S., Jamal, A., Munera, C., et al. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. *N Engl J Med.* 2020; 382: 222-232.
2. Topf, J., Wooldridge, T., McCafferty, K., et al. Efficacy of Difelikefalin for the Treatment of Moderate to Severe Pruritus in Hemodialysis Patients: Pooled Analysis of KALM-1 and KALM-2 Phase 3 Studies. *Kidney Med.* 2022.
3. Fishbane S., Wen, W., Munera, C., et al. Safety and Tolerability of Difelikefalin for the Treatment of Moderate to Severe Pruritus in Hemodialysis Patients: Pooled Analysis From the Phase 3 Clinical Trial Program. *Kidney Med.* 2022; 4(8); 100513.

5.2 Open-label safety study

Study design

The open-label safety study (n=222) was a multicentre study conducted at 31 facilities in the United States and 12 facilities in Europe to evaluate the safety and effectiveness of intravenous (IV) Kapruvia in haemodialysis patients aged 18-85, at a dose of 0.5 micrograms/kg administered after each dialysis session (3 times/week) for 12 weeks. Patient enrolment criteria regarding itching intensity was maintenance HD patients with moderate-to-severe CKD-aP, defined as a baseline Worst Itching Intensity Numerical Rating Scale (WI-NRS) score ≥5 points.[30]



Eligibility criteria

Eligible patients were 18-85 years of age and had been receiving HD three times weekly for at least 3 months before screening. Individuals were also required to demonstrate dialysis adequacy (at least 2 single-pool Kt/V* measurements of at least 1.2 or at least 2 urea reduction ratio measurements ≥65% over the 3-month period before screening).[30]

Patient characteristics at baseline[30]

	Kapruvia (n=222)
Age, mean (SD) years	58.1 (12.8)
Male, n (%)	121 (54.5)
Female, n (%)	101 (45.5)
Race, n (%)	
Black or African American	110 (49.5)
White	96 (43.2)
Other*	16 (7.2)
Prescription dry body weight, mean (SD), kg	86.6 (23.5)
Years on chronic HD, mean (SD), years	5.4 (4.4)
Duration of pruritus, mean (SD), years	3.9 (3.3)
Blood chemistry	
Calcium, mean (SD), mg/dL	8.8 (0.8)
Phosphate, mean (SD), mg/dL	5.9 (1.9)
Baseline use of anti-itch medications, n (%)	71 (32.0)
WI-NRS score, mean (SD)	7.6 (1.3)
Sleep Quality score, mean (SD)	6.6 (2.2)
5-D Itch scale total score, mean (SD)	17.1 (3.5)
Skindex-10 scale total score, mean (SD)	32.9 (14.3)

SD, standard deviation; WI-NRS, Worst Itch Intensity-Numerical Rating Scale.

* Includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and other.

* The parameter Kt/V is a measurement of the efficacy of a haemodialysis session.

Study endpoints

The primary objective was to observe the safety of Kapruvia assessed through monitoring of adverse events, vital signs, 12-lead electrocardiogram (ECG) and laboratory values.[30]

Secondary objectives were to evaluate the efficacy of Kapruvia in reducing the intensity of itch (change from mean baseline weekly 24-hour WI-NRS score to Week 12 and percentage of patients achieving ≥3-point and ≥4-point improvements from baseline to Week 12); sleep quality improvement (change from mean baseline weekly 24-hour Sleep Quality NRS score to Week 12 and percentage of patients achieving ≥3-point and ≥4-point improvements from baseline to Week 12); itch-related quality of life improvement (change from baseline at Week 12 in 5-D Itch and Skindex-10 scales).[30]

Results

A clinically meaningful (≥3-point) reduction in itch intensity was reported by 73.7% of participants, while 59.3% had a ≥4-point improvement with a mean change from baseline at Week 12 of -4.5 points (95% CI, -4.9 to -4.2; p< 0.001) (see Figure 6 & 7). Additionally, 29.4% and 19.1% of participants achieved complete resolution* in WI-NRS scores and Sleep Quality NRS scores respectively at Week 12 (see Figure 7).[30]

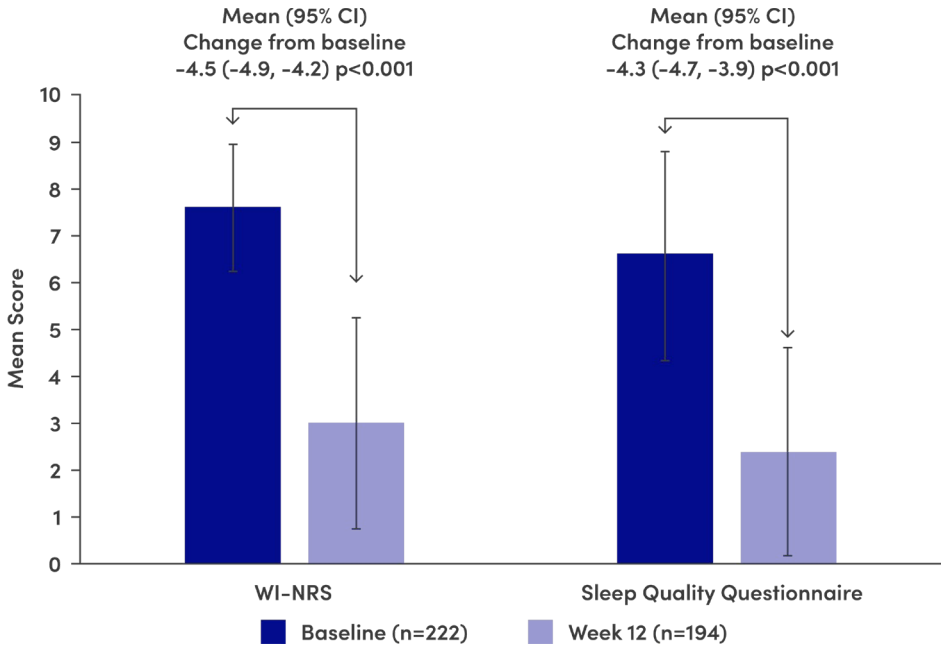


Figure 6: Adapted from Weiner, et al. 2022. Chart showing mean (95% CI) change from baseline to Week 12 using WI-NRS and Sleep Quality Questionnaire. Mean baseline scores shown are 7.6 ± 1.3 (WI-NRS), 6.6 ± 2.2 (Sleep quality NRS).
***Study limitations:** The majority of participants were enrolled in the US (91%), 49% were Black or African American, and all participants were required to have adequate dialysis; the results may not be generalisable to other populations.*

* Complete resolution is defined as ≥75% of weekly mean WI-NRS scores equal to 0 or 1 or all Sleep Quality NRS scores equal to 0.[30]

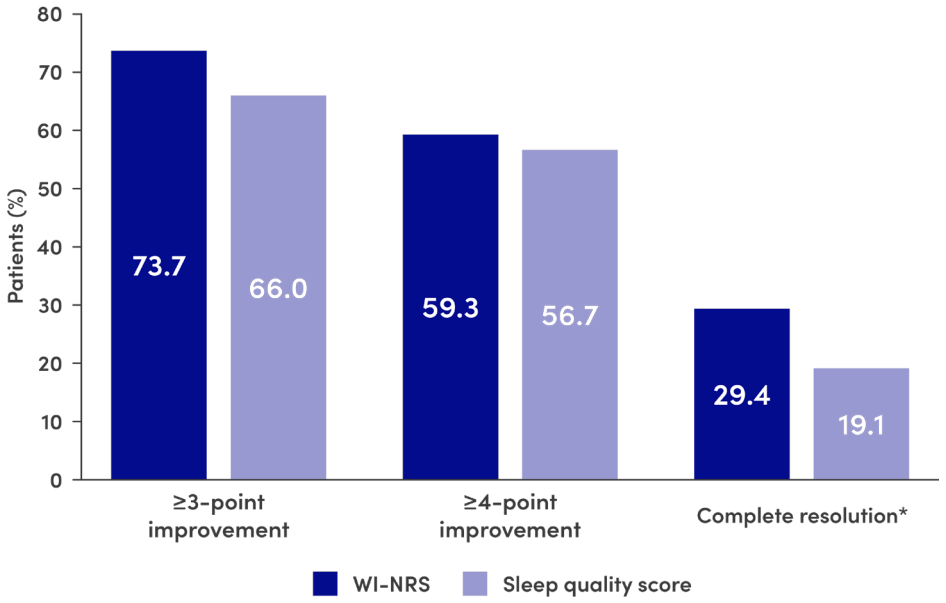


*Figure 7: Adapted from Wiener, et al. 2022. Percentage of patients achieving a ≥3 and ≥4-point improvement in WI-NRS and Sleep quality scores alongside percentage of patients who achieved complete resolution. *Complete resolution is defined as ≥75% of weekly mean WI-NRS scores equal to 0 or 1 or all Sleep Quality NRS scores equal to 0.*[30]

Study limitations: *A minimum clinically meaningful change for the Sleep Quality NRS has not yet been established for this patient population; however, the substantial improvements reported suggest that these changes are likely to be of clinical relevance. The majority of participants were enrolled in the US (91%), 49% were Black or African American, and all participants were required to have adequate dialysis; the results may not be generalisable to other populations. This was a single-arm, open-label trial design with no placebo control group.*

Mean Sleep-Quality NRS scores decreased (improved) from 6.6 ± 2.2 at baseline to 2.4 ± 2.2 at Week 12 (see Figure 7), with a mean change from baseline of -4.3 (95% CI, -4.7 to -3.9; p<0.001); 66.0% had a ≥3-point improvement from baseline and 56.7% had a ≥4-point improvement (see Figure 7).[30]

The mean change from baseline to Week 12 in 5-D Itch scale total score was -7.1 (95% CI, -7.7 to -6.5; p<0.001). A clinically meaningful (≥5-point) improvement in 5-D Itch total score at Week 12 was achieved by 69.8% of participants. Additionally, improvements were seen in all 5 domains: disability, 1.5 ± 1.3; distribution, -1.0 ± 1.1; duration, -1.5 ± 1.0; degree -1.3 ± 1.1; and direction, -1.7 ± 1.1.[30]

The mean change from baseline to Week 12 in Skindex-10 was -21.0 (95% CI, -23.2 to -18.7; p<0.001). A clinically meaningful (≥15-point) improvement in Skindex-10 total score at Week 12 was achieved by 63.0% of participants. Improvements were also seen in all domains: disease total -7.4 ± 5.2, mood and emotional distress -6.5 ± 5.6 and social functioning -6.9 ± 6.8.[30]

Kapruvia was generally well tolerated with no serious treatment related treatment-emergent adverse events (TEAEs).[30]

6. Safety

In placebo controlled and uncontrolled phase 3 clinical studies, approximately 6.6% of the patients experienced at least one adverse reaction during Kapruvia 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.[1]

6.2 Tabulated list of adverse reactions

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

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.[1]

MedDRA System Organ Class	Common	Uncommon
Psychiatric disorders		Mental status changes*
Nervous system disorders	Somnolence, Paraesthesia†	Dizziness; Headache
Gastrointestinal disorders		Vomiting, Nausea; Diarrhoea

*Table 2 Adverse reactions attributed to the treatment with KAPRUVIA® in haemodialysis patients. *Mental status changes included MedDRA preferred terms of confusional state and mental status changes.[1] †Paraesthesia included MedDRA preferred terms of paraesthesia, hypoesthesia, paraesthesia oral and hypoesthesia oral.[1]*

Description of selected adverse reactions

Somnolence

Somnolence was reported as a TEAE in 2.2% of subjects randomised to Kapruvia. The vast majority of these events were mild or moderate in severity. In 0.3% of patients, somnolence led to discontinuation of treatment with Kapruvia. Somnolence was reported as a serious adverse event (SAE) in <0.1% of Kapruvia-treated subjects.[1]

Dizziness

Dizziness was reported as a TEAE in 7.9% of subjects randomised to Kapruvia. The vast majority of these events were mild or moderate in severity. In 0.5% of patients, dizziness led to discontinuation of treatment with Kapruvia. Dizziness was reported as an SAE in 0.5% of Kapruvia-treated subjects.[1]

Mental status change*

Mental status change (including confusional state) was reported as a TEAE in 4.4% of subjects randomised to Kapruvia. The majority of these events were mild or moderate in severity. Mental status changes were reported as an SAE in 2.2% of Kapruvia-treated subjects.[1]

*Mental status changes included MedDRA preferred terms of confusional state and mental status changes.[1]

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Prescribing information

KAPRUVIA®▼
(difelikefalin) Injection

Prescribing Information – United Kingdom
For full prescribing information refer to the Summary of Product Characteristics (SmPC)

Active ingredient
Difelikefalin

Presentation
50 microgram/mL solution for injection. Available as a 2mL vial (containing 1 mL of solution for injection)

Indication
Treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis

Dosage and Administration
Difelikefalin should be restricted for in-centre haemodialysis use only. 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).

Difelikefalin is removed by the dialyzer membrane and must be administered after blood is no longer circulating through the dialyzer. 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 difelikefalin. 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. Difelikefalin should not be diluted and should not be mixed with other medicinal products. For patients with a dry body weight equal to or above 195 kg the recommended dose is 100 micrograms (2 mL). Please refer to SmPC for a table detailing injection volumes of difelikefalin. If a regularly scheduled haemodialysis treatment is missed, difelikefalin should be administered at the next haemodialysis treatment at the same dose. If a 4th haemodialysis treatment is performed in a week, difelikefalin 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. Safety and efficacy of a 4th dose has not been fully established due to insufficient data. For haemodialysis treatments less than 1 hour, administration of difelikefalin should be withheld until the next haemodialysis session. No clinical interaction studies have been performed. 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.

Contraindications
Hypersensitivity to active substance or to any of the excipients.

Special warnings and precautions
In the placebo-controlled clinical studies a numerically higher rate of adverse events of hyperkalaemia was reported for the difelikefalin treated patients compared to placebo. No causal relationship was established. Frequent monitoring of potassium levels is recommended. 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.

Difelikefalin is a peripherally acting kappa opioid receptor agonist with restricted access to the central nervous system (CNS). 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. Difelikefalin 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 have occurred in patients taking difelikefalin and may subside over time with continued treatment. 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.

Difelikefalin has minor influence on the ability to drive and use machines. 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. This medicinal product contains less than 1 mmol sodium per vial.

Overdose
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.

Special populations
No dose adjustment is required for patients with mild or moderate hepatic impairment. Difelikefalin has not been studied in subjects with severe hepatic impairment and is therefore not recommended for use in this patient population. Dosing recommendations for elderly patients (≥ 65 years of age) are the same as for adult patients. The safety and efficacy of difelikefalin in children aged 0-17 years has not yet been established. There are no or limited amount of data from the use of difelikefalin in pregnant women. As a precautionary measure, it is preferable to avoid the use of difelikefalin during pregnancy. It is unknown whether difelikefalin is excreted in human breast milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from difelikefalin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. There are no data on the effect of difelikefalin on fertility in humans..

Undesirable effects
Common (≥1/100 to <1/10): Somnolence and paraesthesia. Please consult the SmPC in relation to other undesirable effects.

Legal category
POM

Price
Pack size of 12 x 2 ml vials (containing 1 mL of solution for injection) = £420.00

MA Number
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MA Holder
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This medicine is subject to additional monitoring. Adverse events should be reported. Reporting forms and information for United Kingdom can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Vifor Pharma Ltd.

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