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ADIS DRUG Q&A

Difelikefalin in pruritus associated with chronic kidney disease: a profile of its use

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Abstract

Difelikefalin (Kapruvia®; Korsuva™), a novel peripheral kappa opioid receptor (KOR) agonist, is a promising emerging treatment for moderate-to-severe pruritus associated with chronic kidney disease (CKD) in adults undergoing haemodialysis. Evidence thus far indicates that difelikefalin is effective and generally well tolerated in these patients. In randomized, double-blind, placebo-controlled, multicentre phase 3 trials, difelikefalin produced clinically meaningful improvements in the intensity of itch in patients with moderate-to-severe CKD-associated pruritus. Difelikefalin was also associated with improved itch-related quality of life relative to placebo. Limited data suggest that clinical benefits are maintained over longer-term treatment. The most common treatment-emergent adverse events in difelikefalin recipients are diarrhoea, dizziness and nausea, typically of mild or moderate severity.

Plain Language Summary

Chronic kidney disease (CKD)-associated pruritus (itching that is directly related to advanced CKD and/or end-stage kidney failure) is common in patients undergoing haemodialysis and negatively impacts quality of life. Imbalances in endogenous opioid receptor activity may drive CKD-associated pruritus. Difelikefalin (Kapruvia®; Korsuva™) targets peripheral kappa opioid receptors and, in the USA and Europe, is the first drug to be specifically approved for the treatment of moderate-to-severe pruritus associated with CKD in patients undergoing haemodialysis. Difelikefalin therapy reduces itch severity in this frail patient population, based on results from clinical trials. Difelikefalin may also improve itch-related quality of life and quality of sleep. Common adverse events in recipients include diarrhoea, dizziness and nausea, which rarely require treatment discontinuation. Effective and generally well tolerated, difelikefalin is a promising emerging treatment for moderate-to-severe pruritus associated with CKD.

Digital Features for this Adis Drug Q&A can be found at https://doi.org/10.6084/m9.figshare.20445828.

Adis evaluation of difelikefalin in the treatment of pruritus associated with CKD in adults undergoing haemodialysis

Administered as an intravenous bolus injection at the end of each haemodialysis treatment

Reduces itch intensity and potentially improves itch-related quality of life in patients with moderate-to-severe pruritus

Generally well tolerated, with most treatment-emergent adverse events being of mild or moderate severity

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What is the rationale for developing difelikefalin in CKD-associated pruritus?

Chronic kidney disease (CKD)-associated pruritus (previously referred to as uraemic pruritus) is defined as itching that is directly related to CKD and not explained by any alternate cause [1–3]. It is highly prevalent in patients with end-stage kidney disease (ESKD) undergoing haemodialysis, affecting up to 80% and being of moderate-to-severe intensity in ≈ 40% [3]. Clinical presentations of CKD-associated pruritus vary with respect to severity, persistence, timing in relation to dialysis, and distribution pattern [1–3]. The itch may be localized (with areas commonly impacted including the back, face and shunt arm) or generalized [1–3]. CKD-associated pruritus is associated with sleep disruption, poor quality of life and depression, as well as adverse medical outcomes including a higher rate of mortality [1, 2, 4].

While the pathogenesis of CKD-associated pruritus is yet to be fully understood, endogenous opioid dysfunction

is potentially involved [1, 2, 5]. Pruritus may result from an imbalance of mu opioid receptor (MOR) and kappa opioid receptor (KOR) activity due to central MOR over-stimulation or KOR under-stimulation [2, 5]. Opioid receptors have therefore been identified as potential targets in the treatment of pruritus. However, agents targeting MORs appear to be of limited therapeutic benefit for CKD-associated pruritus [1, 2, 6, 7]. Furthermore, adverse effects, including opioid withdrawal-like symptoms and gastrointestinal complaints, may restrict their use [6, 8–10]. Centrally acting KOR agonists also have use-limiting adverse effects (e.g. sedation, dysphoria, hallucinations) [11]. In response to these concerns, agents that exclusively activate peripheral KORs have been developed [11].

Difelikefalin [Kapruvia® (EU); Korsuva™ (USA)], a novel peripheral KOR agonist, is approved in the EU [12] and USA [13] for the treatment of moderate-to-severe pruritus associated with CKD in adult patients undergoing haemodialysis. Table 1 provides a summary of the prescribing information for difelikefalin in these regions. Consult local prescribing information for further details.

How should difelikefalin be used?

Difelikefalin should be restricted to use after in-centre haemodialysis treatment [12] and is intended to be administered as an intravenous bolus injection into the venous line of the dialysis circuit at the conclusion of each haemodialysis treatment (see Table 1 for details) [12, 13]. Prior to initiating difelikefalin therapy, clinicians should exclude causes of pruritus other than CKD [12]. The use of difelikefalin in patients on peritoneal dialysis has not been investigated and is not recommended [13].

How does difelikefalin work?

Difelikefalin is a peripheral KOR agonist that binds with high affinity and selectivity to KOR (Ki 0.32 nmol/L for human KOR) in vitro [14]. As the pathophysiology of CKD-associated pruritus likely involves systemic inflammation and endogenous opioid system imbalance (including KOR down-regulation), the anti-pruritic and anti-inflammatory effects of difelikefalin are attributed to its KOR activation on peripheral sensory neurons and immune cells [12]. Difelikefalin has low CNS penetration, with its physicochemical properties limiting its active transport and passive diffusion across membranes [12].

Difelikefalin potently alleviated visceral pain, inflammatory pain, neuropathic pain, evoked itch and writhing behaviour in rodent models [14]. In addition, difelikefalin was shown to inhibit cytokine release in a mouse model of sepsis. Unlike morphine (an MOR agonist), difelikefalin was not associated with any adverse gastrointestinal effects [14].

Difelikefalin administered intravenously to healthy, non-smoking volunteers ($n = 15$) at two-fold or ten-fold higher than the recommended dose did not produce respiratory depression in a randomized, double-blind, placebo-controlled, three-way crossover study [15]. Similarly, difelikefalin did not produce any clinically meaningful prolongation of the corrected QT interval when administered at a supratherapeutic dose six-fold higher than that recommended [13].

What potential is there for difelikefalin to be abused?

Difelikefalin appears to have low abuse potential [16]. In a dedicated human abuse potential study in healthy recreational drug users with opioid and hallucinogenic drug experience, the abuse potential profile of difelikefalin administered at supratherapeutic doses did not meaningfully differ from that of placebo and was significantly lower than that of a centrally acting opioid analgesic (a partial MOR agonist and KOR agonist). Difelikefalin had no dysphoric or hallucinogenic effects associated with CNS-penetrant KOR agonists [16].

What is the efficacy of difelikefalin in CKD-associated pruritus?

Intravenous difelikefalin is an effective treatment for moderate-to-severe CKD-associated pruritus in adults undergoing haemodialysis. Its efficacy at the recommended dosage was demonstrated in the randomized, double-blind, placebo-controlled, multicentre, phase 3 KALM-1 and KALM-2 trials [17–19], and supported by data from phase 2 trials [20, 21] and an open-label phase 3 study [22].

Patients eligible for enrolment in the US-only KALM-1 trial and global KALM-2 trial were adults ≥ 18 years with moderate-to-severe pruritus due to ESKD who were undergoing haemodialysis three times per week for ≥ 3 months prior to screening [17]. Moderate-to-severe pruritus was defined as a Worst Itching Intensity Numerical Rating Scale (WI-NRS) score of > 4 (KALM-1) or ≥ 5 (KALM-2). Exclusion criteria included pruritus attributed to a cause other than ESKD or its complications, localized itch restricted to the palms, or pruritus only during haemodialysis sessions. In each trial, patients were randomized to receive difelikefalin 0.5 μg/kg or placebo following haemodialysis three times per week for 12 weeks. A fourth dose per week was permitted in patients who received an additional haemodialysis treatment during a given week. Randomization was stratified by the use or non-use of concomitant medications

Table 1 Summary of the prescribing information of difelikefalin (Kapruvia®; Korsuva™) in pruritus associated with chronic kidney disease in the EU [12] and USA [13]

What is the approved indication for difelikefalin?	
Treatment of moderate-to-severe pruritus associated with CKD in adults on HD	
How is difelikefalin available?	
Solution for injection (50 µg/mL): 1 mL vials containing 50 µg difelikefalin (EU) or 1.3 mL vials containing 65 µg difelikefalin (USA)	
How should difelikefalin be administered?	
Recommended dose	0.5 µg/kg dry body weight (i.e. target post-dialysis weight)
	Calculate total dose volume (mL) required from vial as 0.01 × dry body weight (kg), rounded to nearest 0.1 mL
	For pts with dry body weight ≥ 195 kg, recommended dose is 100 µg (i.e. 2 mL) [EU]
Administration frequency	Three times per week (EU)
Administration method	IV bolus injection into venous line of dialysis circuit at conclusion of each HD treatment (during or after rinse-back); remove by dialyser membrane and administer once blood no longer circulating through dialyser
	If giving difelikefalin after rinse-back, administer ≥ 10 mL saline flush into venous line after difelikefalin; if giving during rinse-back, no additional saline is needed to flush venous line
	Administer difelikefalin within 60 min of completing syringe preparation (USA)
	Do not dilute difelikefalin nor mix it with other medicinal agents
Missed doses	If a regular HD treatment is missed, administer difelikefalin at the recommended dose at the end of the next HD treatment
Incomplete HD treatment	If HD treatment is < 1 h, withhold difelikefalin until next HD session (EU)
Additional treatments	If pt undergoes a 4th HD treatment in a week, administer difelikefalin at the recommended dose at the end of the HD; data on 4th doses are limited (efficacy and safety not fully established) [EU]
	Administer no more than 4 doses/week, even if pt undergoes > 4 HD treatments (EU)
What are the contraindications to the use of difelikefalin?	
Hypersensitivity to the active substance or to any of the excipients (EU)	
How should difelikefalin be used in special populations?	
Paediatric pts < 18 yrs	Efficacy and safety not established
Geriatric pts ≥ 65 yrs	No dosage adjustment required
Pts with hepatic impairment	No dosage adjustment required for pts with mild or moderate hepatic impairment
	Use in pts with severe hepatic impairment not recommended (lack of data)
Pregnant pts	Limited data on use in pregnant pts insufficient to evaluate risks; no harmful effects in animal studies
	Preferable to avoid use during pregnancy as a precaution (EU)
Breastfeeding pts	Human data not available; difelikefalin excreted in breast milk in animal studies
	Decide whether to discontinue breastfeeding or difelikefalin, giving consideration to benefit of breastfeeding for child and of difelikefalin for pt (EU)
	Consider benefits of breastfeeding alongside maternal clinical need for difelikefalin and any possible adverse effects of difelikefalin or underlying maternal condition on breastfed child (USA)
What are the pharmacokinetic properties of difelikefalin?	
Linearity	Dose proportional over dose range 0.5 to 2.5 µg/kg (multiple IV doses) in pts with CKD undergoing HD
Accumulation	Steady state achieved after 2nd dose; mean accumulation ratio up to 1.6
Distribution	Mean volume of distribution ≈ 238 mL/kg; 23–28% bound to plasma proteins in pts undergoing HD
Elimination	Half-life 23–31 h in pts prior to dialysis; HD reduced plasma concentrations by 70–80% (difelikefalin not detected in plasma after 2 HD cycles)
	Not metabolized by major CYP enzymes in human hepatic microsomes or hepatocytes
	In pts undergoing HD, 59% of given dose was excreted in faeces, 11% in urine and 20% in dialysate fluid
Pharmacokinetics in specific populations	No clinically relevant differences in difelikefalin pharmacokinetics based on age (25–80 yrs), sex, race/ethnicity or mild-to-moderate hepatic impairment
What clinically relevant drug interactions may potentially occur with difelikefalin?	
While no clinical drug interaction studies have been conducted, interactions with other medicinal products are considered unlikely	

Unless otherwise indicated, data are derived from both the EU [12] and US [13] prescribing information; pharmacokinetic data are from US

CKD chronic kidney disease, *HD* haemodialysis, *pt(s)* patient(s)

to treat pruritus during the run-in period prior to randomization and the presence or absence of specific medical conditions (e.g. falls or fractures due to falls, gait disturbance, mental status change). Both trials included an open-label extension (OLE) phase of up to 52 weeks for patients who met certain eligibility criteria. During the OLEs, all patients received difelikefalin [17].

At baseline, disease characteristics were comparable between the difelikefalin and placebo groups of the pivotal trials [12]. Patients had a mean age of 59 years and mean WI-NRS score of 7.2 [12]. Approximately 40% of patients were using medicinal products prescribed for pruritus relief (e.g. antihistamines, corticosteroids), while 14% (KALM-1) or 17% (KALM-2) reported at least one of the specific medical conditions used for stratification [17]. In both trials, the primary endpoint was the percentage of patients who achieved a ≥ 3-point improvement (i.e. reduction) from baseline in the weekly mean of the daily WI-NRS score at week 12 [18, 19].

Difelikefalin was effective in reducing itch intensity in KALM-1 and KALM-2, with a significantly ($p < 0.05$) higher proportion of difelikefalin recipients than placebo recipients achieving a ≥ 3-point improvement from baseline in WI-NRS score at week 12 of each trial (Table 2). In both trials, the proportion of patients achieving the more stringent ≥ 4-point improvement from baseline in WI-NRS score at week 12 was also significantly ($p \leq 0.01$) higher with difelikefalin than with placebo (Table 2). Significant ($p < 0.05$) improvements in ≥ 3-point and ≥ 4-point WI-NRS reduction rates with difelikefalin versus placebo were apparent by week 4 in KALM-2 (Table 2). In an analysis of pooled KALM-1 and KALM-2 data, significantly ($p < 0.05$) higher proportions of difelikefalin recipients than placebo recipients achieved ≥ 3-point WI-NRS improvements at all time points from week 1 to week 12 and WI-NRS complete responses (i.e. ≥ 80% of daily WI-NRS scores ≤ 1 for the preceding week) at all time points from week 3 to week 12 [23].

In subgroup analyses of the primary endpoint using pooled data from KALM-1 and KALM-2, difelikefalin was effective in both patients with moderate baseline itch (i.e. WI-NRS ≥ 4 to < 7) and severe baseline itch (WI-NRS ≥ 7; *p*-values not available), and in both the EU and other regions ($p < 0.05$ vs placebo) [post hoc analyses] [17]. The treatment effect was also directionally consistent across subgroups based on:

- age (< 65 or ≥ 65 years; $p < 0.05$ vs placebo for younger patients only);
- sex (male or female; both $p < 0.05$ vs placebo);
- race (white or black; both $p < 0.05$ vs placebo), except for in a smaller subgroup of patients of "other" race;
- geographical region (USA or non-USA; both $p < 0.05$ vs placebo); and
- randomization strata (anti-pruritus medication use or non-use, presence or absence of specific medical conditions; $p < 0.05$ vs placebo for all) [23].

Difelikefalin significantly improved measures of itch-related quality of life relative to placebo in KALM-1 but not KALM-2 (Table 2). At week 12 of KALM-1, improvements from baseline in the 5-D Itch Scale total score and Skindex-10 Scale total score were greater with difelikefalin than with placebo ($p < 0.001$) [18]. In KALM-2, the treatment difference in change from baseline in Skindex-10 Scale total score did not reach statistical significance and, due to the hierarchical testing procedure, the difference in change in 5-D Itch Scale total score was not formally assessed [12, 17]. In analyses of pooled data from KALM-1 and KALM-2, higher ($p < 0.05$) proportions of difelikefalin recipients than placebo recipients achieved clinically meaningful Skindex-10 responses (≥ 15-point improvements from baseline in Skindex-10 total score; 55.5% vs 40.5%) and 5-D Itch responses (≥ 5-point improvements in 5-D Itch total score; 52.1% vs 42.3%) at week 12 [23].

Improvements in mean 5-D Itch Scale scores were maintained over ≤ 52 weeks of open-label difelikefalin treatment, based on OLE data [17, 23]. At week 52 of the KALM-1 OLE, the least-squares mean change from baseline in 5-D Itch Scale total score was −6.9 in patients who had previously received placebo and were switched to difelikefalin ($n = 94$) and −7.8 in patients who received continuous difelikefalin treatment ($n = 90$) [17]. The KALM-2 OLE was terminated early, with only 5 patients completing 52 weeks of OLE treatment [17].

Results of KALM-1 and KALM-2 were supported by those of an open-label, multicentre phase 3 study of difelikefalin 0.5 μg/kg three times per week for up to 12 weeks in patients with moderate-to-severe CKD-associated pruritus undergoing haemodialysis in the USA and Europe ($n = 222$; mean baseline WI-NRS score 7.6) [22]. At week 12 of this study, the majority of patients achieved ≥ 3-point improvements from baseline in WI-NRS score (74%) and Sleep Quality Numerical Rating Scale (NRS) score (66%). Improvements of ≥ 4 points in WI-NRS score and Sleep Quality NRS score were achieved by 59% and 57%, respectively. Mean changes from baseline to week 12 in Skindex-10 Scale and 5-D Itch Scale total scores were −21.0 and −7.1, respectively (both $p < 0.001$); clinically meaningful Skindex-10 and 5-D Itch responses were achieved by 63% and 70% of patients [22].

Table 2 Efficacy of intravenous difelikefalin in the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing haemodialysis in pivotal phase 3 trials [17]

Trial (no. of pts receiving difelikefalin and placebo in ITT population)	Difelikefalin 0.5 µg/kg	Placebo	Odds ratio[a] or LSM difference (95% CI)
KALM-1 (n = 189 and 189)			
WI-NRS ≥ 3-point improvement from BL to wk 12[b,c] (% of pts)	51.0	27.6	2.72 (1.72 to 4.30)***
5-D Itch Scale total score LSM change from BL to wk 12	−5.0	−3.7	−1.3 (−2.0 to −0.5)***
Skindex-10 Scale total score LSM change from BL to wk 12	−17.2	−12.0	−5.1 (−8.0 to −2.3)***
WI-NRS ≥ 4-point improvement from BL to wk 12[c] (% of pts)	38.9	18.0	2.89 (1.75 to 4.76)***
KALM-2 (n = 237 and 236)			
WI-NRS ≥ 3-point improvement from BL to wk 12[b,c] (% of pts)	54.0	42.2	1.61 (1.08 to 2.41)*
WI-NRS ≥ 4-point improvement from BL to wk 12[c] (% of pts)	41.2	28.4	1.77 (1.14 to 2.74)**
WI-NRS ≥ 3-point improvement from BL to wk 8[c] (% of pts)	49.0	36.2	1.69 (1.13 to 2.53)**
WI-NRS ≥ 3-point improvement from BL to wk 4[c] (% of pts)	38.3	23.8	1.99 (1.29 to 3.06)**
WI-NRS ≥ 4-point improvement from BL to wk 8[c] (% of pts)	36.1	23.7	1.82 (1.16 to 2.86)**
WI-NRS ≥ 4-point improvement from BL to wk 4[c] (% of pts)	26.1	16.7	1.76 (1.04 to 2.98)*
Skindex-10 Scale total score LSM change from BL to wk 12	−16.6	−14.8	−1.8 (−4.3 to 0.8)
5-D Itch Scale total score LSM change from BL to wk 12	−4.9	−3.8	−1.1 (−1.7 to −0.4)[d]

Efficacy analyses were conducted in the ITT population, with endpoints assessed hierarchically in the order presented (to control for the family-wise error rate). For KALM-1, results are those of the prespecified analysis, which only included WI-NRS scores reported during receipt of difelikefalin or placebo.

BL baseline, *ITT* intention-to-treat, *LSM* least-squares mean, *pts* patients, *WI-NRS* Worst Itching Intensity-Numerical Rating Scale (scale of 0–10; higher scores indicate greater intensity), *wk* week

*$p < 0.05$, ** $p \leq 0.01$, ***$p < 0.001$ vs placebo

[a]Using Lawrence-Hung (odds ratios) and Cui-Hung-Wang (p-values) procedures

[b]Primary endpoint

[c]With respect to the weekly mean of the daily 24-h WI-NRS

[d]Nominal p-value 0.002 (previous endpoint in hierarchy did not reach statistical significance)

What is the tolerability profile of difelikefalin?

Intravenous difelikefalin is generally well tolerated in adults with moderate-to-severe CKD-associated pruritus undergoing haemodialysis, based on pooled safety data from phase 3 trials [24]. During the 12 weeks of placebo-controlled treatment in KALM-1 and KALM-2, treatment-emergent adverse events (TEAEs) were reported in 71.2% of difelikefalin recipients versus 65.3% of placebo recipients and were mostly of mild to moderate severity. The most common TEAEs in difelikefalin recipients (occurring in ≥ 2% and at an incidence ≥ 1% higher than with placebo) were diarrhoea, dizziness, gait disturbances, nausea, hyperkalaemia, headache, somnolence and mental status change (Fig. 1) [24]. In patients continuously exposed to difelikefalin over 6 and 12 months, the incidence and prevalence of diarrhoea, dizziness, somnolence, nausea and vomiting declined over time [17].

In the pooled KALM-1 and KALM-2 safety populations, TEAEs led to treatment discontinuation in 6.8% of difelikefalin recipients versus 4.0% of placebo recipients

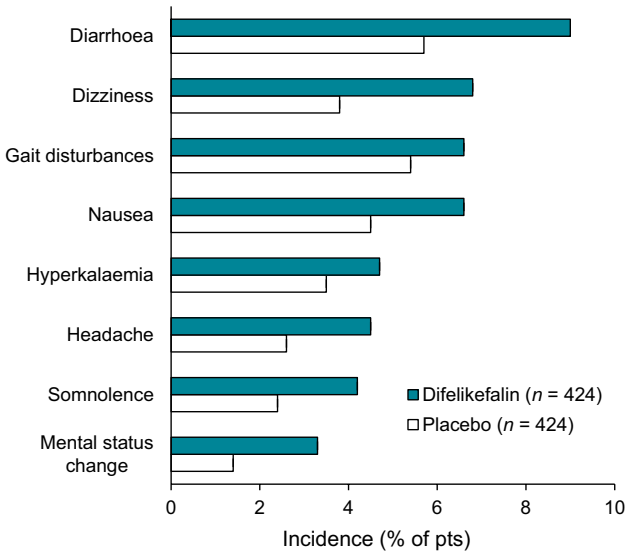

Fig. 1 Most common treatment-emergent adverse events with difelikefalin 0.5 µg/kg three times per week (occurring in ≥ 2% and at an incidence ≥ 1% higher than with placebo) in adults with moderate-to-severe pruritus associated with chronic kidney disease undergoing haemodialysis: pooled data from KALM-1 and KALM-2 [24]

[24]. Among the adverse reactions most commonly leading to discontinuation of difelikefalin were dizziness (0.9% vs 0.2% with placebo), mental status change (0.7% vs 0.2%), nausea (0.5% vs 0%) and headache (0.5% vs 0%) [13]. Serious but non-fatal TEAEs occurred in 25.2% of difelikefalin recipients versus 22.6% of placebo recipients, while adverse events led to death in three difelikefalin recipients (0.7%) versus five placebo recipients (1.2%) [24]. The most common serious TEAEs were hyperkalaemia (1.9% of difelikefalin recipients vs 1.9% of placebo recipients), chest pain (1.9% vs 0.9%), pneumonia (1.4% vs 1.7%), sepsis (1.2% vs 1.7%), mental status changes (1.2% vs 0.5%) and chronic obstructive pulmonary disease (1.2% vs 0.5%) [17]. Serious TEAEs of diarrhoea, dizziness and somnolence occurred at low rates (< 1% of patients receiving difelikefalin or placebo), while there were no serious TEAEs of nausea or headache. None of the fatal events were considered to be due to the study treatment [17]. During the two-week discontinuation period of KALM-1, during which patients were not administered difelikefalin or placebo, there were no potential signs of physical dependence or adverse events related to withdrawal [18].

Difelikefalin continued to be well tolerated over longer-term treatment (up to 64 weeks) in an analysis of pooled data from phase 3 trials and OLEs ($n = 1306$; 811.3 patient-years of exposure to the recommended dose of difelikefalin) [24]. The incidences of common TEAEs and serious TEAEs did not appear to increase over longer-term exposure. TEAEs were reported by 78.3% of difelikefalin recipients and non-fatal serious TEAEs were reported by 41.5%. TEAEs led to treatment discontinuation in 9.3% and death in 4.3%. The incidence rate of AEs leading to death was 69.0/1000 patient-years in difelikefalin recipients, which was less than the rate of death in patients undergoing haemodialysis reported by the US Renal Data System [24].

A small number of warnings and precautions pertain to the use of difelikefalin in the EU [12] and USA [13] (Table 3); consult local prescribing information for further details.

What is the role of difelikefalin in CKD-associated pruritus?

Difelikefalin is effective and well tolerated in the treatment of CKD-associated pruritus, representing a promising emerging option for patients undergoing haemodialysis. Difelikefalin administered intravenously at the end of each haemodialysis session produces clinically meaningful improvements in itch severity in patients with moderate-to-severe pruritus undergoing haemodialysis, based on results from the KALM-1 and KALM-2 clinical trials [18, 19]. The threshold for a clinically meaningful change in WI-NRS has been proposed to be either 3 points [25] or 4 points [26], and the benefit of difelikefalin over placebo for WI-NRS improvement rate was significant at each of these thresholds in KALM-1 and KALM-2 (Table 2). Based on the patient population evaluated in these pivotal trials, difelikefalin is

Table 3 Warnings and precautions relating to the use of difelikefalin in the EU [12] and USA [13]

Dizziness and somnolence (EU; USA), mental status changes, and gait disturbances (USA)	Have been reported with difelikefalin, but may improve over continued treatment
	Incidence of somnolence higher in recipients ≥ 65 y (7.0%) than in those < 65 y (2.8%)
	Exercise caution when co-administering with sedating antihistamines, opioid analgesics or other CNS depressants, due to potential for increased risk of these adverse reactions
Risk of driving and operating machinery	Caution pts about driving or operating dangerous machinery until it has been determined whether difelikefalin impacts their mental or physical ability to perform such tasks
Hyperkalaemia (EU)	Numerically higher incidence of hyperkalaemia adverse events in difelikefalin recipients (4.7%; 20/424) than placebo recipients (3.5%; 15/424) in clinical trials; no causality established
	Monitor potassium levels frequently
Cardiac failure and atrial fibrillation (EU)	Small imbalance between difelikefalin and placebo recipients in cardiac failure and atrial fibrillation events in pivotal clinical trials[a]; no causality established
	No data in pts with NYHA class IV heart failure
Use in pts with impaired blood-brain barrier (EU)	As blood-brain barrier integrity is crucial for minimizing CNS uptake of difelikefalin, difelikefalin may enter the CNS in pts with clinically relevant blood-brain barrier disruption (e.g. active MS, advanced AD, primary brain malignancies, CNS metastases or other inflammatory conditions)
	Prescribe with caution, considering benefit-risk ratios for individual pts; observe for possible CNS effects

Unless otherwise indicated, data are derived from the prescribing information for both the EU [12] and USA [13]

AD Alzheimer's disease, *CKD* chronic kidney disease, *MS* multiple sclerosis, *NYHA* New York Heart Association, *pts* patients

[a]Major adverse cardiovascular events (defined as non-fatal stroke or myocardial infarction, cardiovascular death, heart failure or revascularisation) occurred in 3.8% of difelikefalin recipients vs 2.4% of placebo recipients during placebo-controlled treatment [17]

specifically indicated for the treatment of moderate-to-severe pruritus (Table 1); a baseline WI-NRS score of > 4 can be considered to signify this severity of itch [17]. Data from OLEs, albeit limited, suggest that the clinical benefits of difelikefalin endure over long-term treatment [17, 23].

In clinical practice, CKD-associated pruritus remains under-recognised and under-treated [27, 28]. Proactively identifying patients with CKD who are experiencing pruritus is particularly important given the apparent detrimental impact of CKD-associated pruritus on health-related quality of life and medical outcomes. Symptoms such as sleep disturbance, fatigue, depression and pain tend to co-occur with pruritus in patients with CKD [27]. Alleviating one symptom may reduce the severity of other associated symptoms, thus reducing overall symptom burden and leading to improvements in health-related quality of life and other clinical outcomes [27]. While it remains to be confirmed, difelikefalin appears to have a favourable effect on itch-related quality of life [17–19]. Improvements in itch-related quality of life may be partially explained through the effects of alleviated itching on sleep.

Patients undergoing haemodialysis are often frail, with co-morbidities and receiving multiple medications [9, 28]. As such, it is important that their treatments for pruritus be safe with low potential for drug-drug interactions [28]. Difelikefalin is unlikely to interact with other medications (Table 1) and is generally well tolerated in patients with CKD-associated pruritus undergoing haemodialysis [24]. The most common TEAEs are gastrointestinal disorders (e.g. diarrhoea, nausea) and nervous system disorders (e.g. dizziness, headache) [24]. It is important to note that difelikefalin is specifically (and conveniently) intended for use at the end of in-centre haemodialysis sessions and should not be administered outside of this setting [12].

Difelikefalin represents the first drug to be specifically approved for the treatment of CKD-associated pruritus in the either the USA or Europe [9]. Off-label treatments typically have limited efficacy in these patients or substantial adverse effects that limit their use [9]. No direct comparisons between these agents and difelikefalin are available. Broad European guidelines on the treatment of chronic pruritus recommend various treatments (e.g. gabapentinoids) in patients with CKD [29]. These guidelines precede the approval of difelikefalin in the EU and updated treatment guidelines are awaited with interest. A recent US-based expert review specific to CKD-associated pruritus recommends that systemic therapies be utilized in patients with generalized, moderate-to-severe and/or refractory CKD-associated pruritus [30]. While gabapentinoids have historically been considered the first-line options, difelikefalin is proposed to be a safe and effective alternative to these [30].

Results from ongoing clinical trials of difelikefalin in patients with pruritus on haemodialysis, including a randomized, double-blind, phase 3 trial in Japan (NCT04711603) and its long-term OLE, will be useful in further establishing the position of difelikefalin in the treatment of CKD-associated pruritus.

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References

1. Verduzco HA, Shirazian S. CKD-associated pruritus: new insights into diagnosis, pathogenesis, and management. Kidney Int Rep. 2020;5:1387–402.
2. Shirazian S, Aina O, Park Y, et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. Int J Nephrol Renovasc Dis. 2017;10:11–26.
3. Kim D, Pollock C. Epidemiology and burden of chronic kidney disease-associated pruritus. Clin Kidney J. 2021;14(Suppl. 3):i1-7.

4. Combs SA, Teixeira JP, Germain MJ. Pruritus in kidney disease. Semin Nephrol. 2015;35:383–91.
5. Agarwal P, Garg V, Karagaiah P, et al. Chronic kidney disease-associated pruritus. Toxins. 2021;13(8):527.
6. Kremer AE. What are new treatment concepts in systemic itch? Exp Dermatol. 2019;28:1485–92.
7. Makar M, Smyth B, Brennan F. Chronic kidney disease-associated pruritus: a review. Kidney Blood Press Res. 2021;46:659–69.
8. Bergasa NV. Pruritus in primary biliary cirrhosis: pathogenesis and therapy. Clin Liver Dis. 2008;12(2):385–406.
9. Lipman ZM, Yosipovitch G. An evaluation of difelikefalin as a treatment option for moderate-to-severe pruritus in end stage renal disease. Expert Opin Pharmacother. 2021;22(5):549–55.
10. Martin CE, Clotet-Freixas S, Farragher JF, et al. Have we just scratched the surface? A narrative review of uremic pruritus in 2020. Can J Kidney Health Dis. 2020;7:1–14.
11. Albert-Vartanian A, Boyd MR, Hall AL, et al. Will peripherally restricted kappa-opioid receptor agonists (pKORAs) relieve pain with less opioid adverse effects and abuse potential? J Clin Pharm Ther. 2016;41(4):371–82.
12. European Medicines Agency. Kapruvia 50 micrograms/mL solution for injection: EU summary of product characteristics. 2022. https://www.ema.europa.eu/. Accessed 23 Aug 2022.
13. Vifor (International) Inc. KORSUVA™ (difelikefalin) injection, for intravenous use [US prescribing information]. 2021. https://dailymed.nlm.nih.gov/. Accessed 23 Aug 2022.
14. Gardell LR, Spencer R, Chalmers D, et al. Preclinical profile of CR845: a novel, long-acting peripheral kappa opioid receptor agonist [abstract no. PW-231 and poster]. In: International Association for the Study of Pain. 2008.
15. Viscusi ER, Torjman MC, Munera CL, et al. Effect of difelikefalin, a selective kappa opioid receptor agonist, on respiratory depression: a randomized, double-blind, placebo-controlled trial. Clin Transl Sci. 2021;14(5):1886–93.
16. Shram MJ, Spencer RH, Qian J, et al. Evaluation of the abuse potential of difelikefalin, a selective kappa-opioid receptor agonist, in recreational polydrug users. Clin Transl Sci. 2022;15:535–47.
17. European Medicines Agency. Kapruvia (international non-proprietary name: difelikefalin): public assessment report. 2022. https://www.ema.europa.eu/. Accessed 23 Aug 2022.
18. 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(3):222–32.
19. Wooldridge TD, McCafferty K, Schoemig M, et al. Efficacy and safety of difelikefalin for moderate-to-severe CKD-associated pruritus: a global phase 3 study in hemodialysis patients (KALM-2) [abstract no. FR-OR24]. J Am Soc Nephrol. 2020;31(Suppl.):22–3.
20. Fishbane S, Mathur V, Germain MJ, et al. Randomized controlled trial of difelikefalin for chronic pruritus in hemodialysis patients. Kidney Int Rep. 2020;5(5):600–10.
21. Narita I, Tsubakihara Y, Uchiyama T, et al. Efficacy and safety of difelikefalin in Japanese patients with moderate to severe pruritus receiving hemodialysis: a randomized clinical trial. JAMA Netw Open. 2022;5(5): e2210339.
22. Weiner DE, Vervloet MG, Walpen S, et al. Safety and effectiveness of difelikefalin in patients with moderate-to-severe pruritus undergoing hemodialysis: an open-label, multicenter study. Kidney Med. 2022. https://doi.org/10.1016/j.xkme.2022.100542.
23. 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. https://doi.org/10.1016/j.xkme.2022.100512.
24. 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. https://doi.org/10.1016/j.xkme.2022.100513.
25. Vernon M, Ständer S, Munera C, et al. Clinically meaningful change in itch intensity scores: an evaluation in patients with chronic kidney disease-associated pruritus. J Am Acad Dermatol. 2021;84(4):1132–4.
26. US Center for Drug Evaluation and Research. Risk asessment and risk mitigation review(s): application number 214916Orig1s000 (difelikefalin). 2021. http://www.accessdata.fda.gov/. Accessed 23 Aug 2022.
27. Ahdoot R, Kalantar-Zadeh K, Burton J, et al. Novel approach to unpleasant symptom clusters surrounding pruritus in patients with chronic kidney disease and on dialysis therapy. Curr Opin Nephrol Hypertens. 2022;31(1):63–71.
28. Santos-Alonso C, Maldonado Martín M, Sánchez Villanueva R, et al. Pruritus in dialysis patients. Literature review and new perspectives. Nefrologia (Engl Ed). 2021;42(1):15–21.
29. Weisshaar E, Szepietowski JC, Dalgard F, et al. European S2k guideline on chronic pruritus. Acta Derm Venereol. 2019;99:469–506.
30. Lipman ZM, Paramasivam V, Yosipovitch G, et al. Clinical management of chronic kidney disease-associated pruritus: current treatment options and future approaches. Clin Kidney J. 2021;14(Suppl. 3):i16-22.