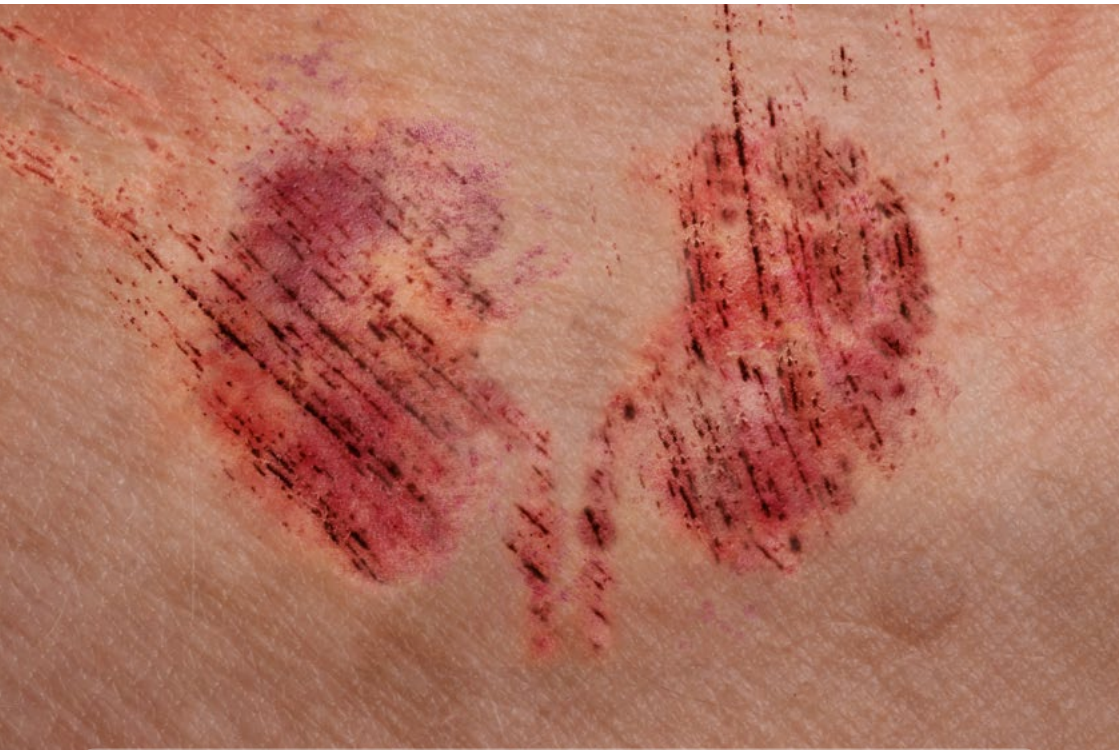
KAPRUVIA®▼
(difelikefalin) Injection



TARGET PRURITUS WITH KAPRUVIA®▼ (difelikefalin)

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

Prescribing information and adverse event reporting can be found on the back page of this document.

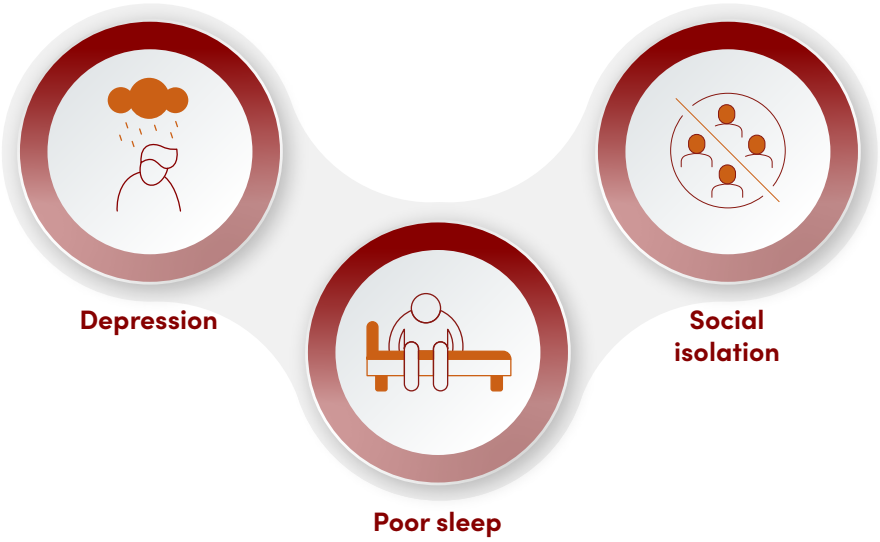
VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

UK-DFK-2400095 | June 2024

CSL Vifor

CKD-ASSOCIATED PRURITUS (CKD-aP): MUCH MORE THAN JUST AN ITCH

48% of all UK patients (n=654/1,363) in DOPPS* were **moderately-to-severely**† bothered by itch[2]



The burden your patients experience with itch can affect them both physically and emotionally. They may be struggling with symptoms of **depression** and **poor sleep**, which can lead to **social isolation**[2-5]

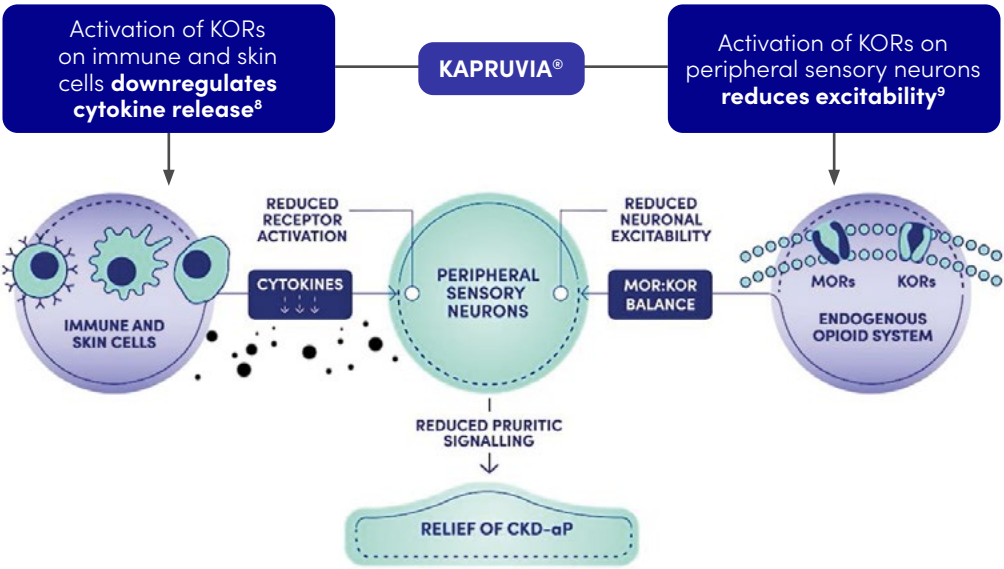
*DOPPS was a multinational, prospective cohort study including data from 23,264 haemodialysis patients (≥18 years) across 21 countries in the DOPPS phases 4 to 6 (2009-2018).[2]

†Severity of itch was established from a single question of the KDQoL-36 questionnaire: In the past 4 weeks to what extent were you bothered by itchy skin?[2]

DOPPS, Dialysis Outcomes and Practice Patterns Study;
KDQoL-36, Kidney Disease Quality of Life 36-item short form survey.

KAPRUVIA® AND MECHANISM OF ACTION (MOA)

KAPRUVIA® is a selective KOR agonist that acts on two underlying mechanisms of CKD-aP[6,7]



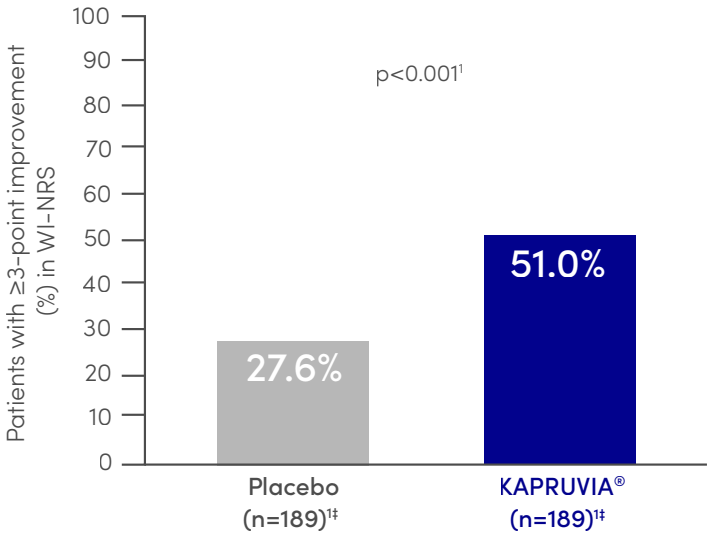
KAPRUVIA® is the **ONLY treatment** indicated for moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis. It should be restricted for in-centre haemodialysis use only[1,10]

KORs, kappa-opioid receptors; **MORs**, mu-opioid receptors.

KAPRUVIA® EFFICACY & GUIDELINES

KALM-1:* More patients treated with KAPRUVIA® achieved a clinically meaningful (≥3-point)† improvement in WI-NRS vs placebo at Week 12 (primary endpoint)[1]

ITCH INTENSITY WI-NRS



Graph adapted from KAPRUVIA® SmPC

KALM-2:* More patients treated with KAPRUVIA® achieved a clinically meaningful (≥3-point)† improvement in WI-NRS vs placebo at Week 12 (54% vs 42%, p=0.02, primary endpoint)[1]

NICE RECOMMENDED TREATMENT

NICE recommends KAPRUVIA®, within its marketing authorisation, for treating moderate-to-severe CKD-associated pruritus in adults receiving in-centre haemodialysis[11]

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[12]

*KALM-1 and KALM-2 were two independent studies of similar design: randomised, double-blind, multicentre, placebo controlled, Phase 3 trials. There were 378 randomised patients in KALM-1 and 473 in KALM-2.[13–16]

†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.[13]

‡95% CI are not available in the source reference for these data.[1]

CI, confidence interval; **SmPC**, Summary of Product Characteristics; **WI-NRS**, Worst Itch Intensity-Numerical Rating Scale; **NICE**, National Institute for Health and Care Excellence; **SMC**, Scottish Medicines Consortium.

KAPRUVIA® SAFETY AND TOLERABILITY

System Class	Adverse reaction	Frequency
Psychiatric disorders	Mental status changes[1]*	Uncommon
Nervous system disorders	Somnolence Paraesthesia† Dizziness Headache	Common Common Uncommon Uncommon
Gastrointestinal disorders	Nausea Diarrhoea Vomiting	Uncommon Uncommon Uncommon

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

Please refer to the full SmPC for further information on safety and tolerability

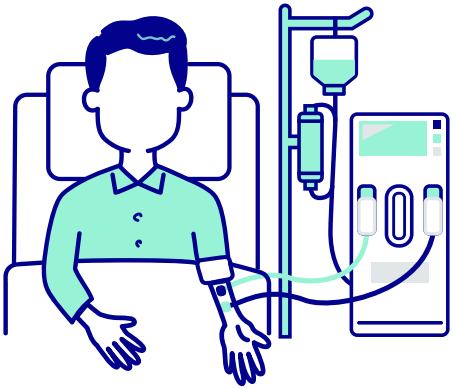
In placebo controlled and uncontrolled phase 3 clinical studies, approximately 6.6% of the patients experienced at least one adverse reaction during KAPRUVIA® treatment. The most common adverse reactions were **somnolence (1.1%), dizziness (0.9%), paraesthesia (including hypoesthesia, paraesthesia oral 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]

*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]

MedDRA, Medical Dictionary for Regulatory Activities; **SmPC**, Summary of Product Characteristics.

KAPRUVIA® DOSING AND ADMINISTRATION



KAPRUVIA® is administered **as an IV bolus injection** 3 times per week into the venous line of the dialysis circuit during rinse-back or after rinse-back[1]

An effect of KAPRUVIA® in reducing pruritus is expected after 2-3 weeks of treatment. The recommended dose is **0.5 micrograms/kg dry body weight** (i.e., the post-dialysis target weight)[1]

KAPRUVIA® administration should be restricted for in-centre HD only and is intended for use by HCPs experienced in the diagnosis and treatment of moderate-to-severe CKD-aP. Causes of pruritus other than CKD should be excluded before initiating treatment with KAPRUVIA®[1]

Please refer to the full SmPC before prescribing and administration

IV, intravenous; **SmPC**, Summary of Product Characteristics; **HCP,** healthcare professional; **HD**, haemodialysis; **CKD-aP**, chronic kidney disease associated pruritis.

TARGET PRURITUS WITH KAPRUVIA®

NICE RECOMMENDED TREATMENT

SMC ACCEPTED TREATMENT

Despite its **high prevalence**, CKD-aP still remains **under-recognised and under-reported**[17]

KAPRUVIA® is the **ONLY treatment** indicated for moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis. It should be restricted for in-centre haemodialysis use only[1,10]

Significantly more patients treated with KAPRUVIA® **achieved clinically meaningful improvements** in itch intensity from baseline vs placebo at Week 12[1]*

The most common (≥1/100 to <1/10) adverse events attributed to KAPRUVIA® are **somnolence and paraesthesia**[1]

KAPRUVIA® is delivered as an IV bolus **3 times per week** at the end of the dialysis session[1]

*≥3-point improvement in WI-NRS (KALM-1, p<0.001 vs placebo; KALM-2, p=0.02 vs placebo).[1]

IV, intravenous; **NICE**, National Institute for Health and Care Excellence; **SMC**, Scottish Medicines Consortium.

References: 1. KAPRUVIA® Summary of Product Characteristics. Available at: www.medicines.org.uk. **2.** Sukul, N, et al. *Kidney Med.* 2020;3(1):42–53. **3.** Pisoni RL, et al. *Nephrol Dial Transplant.* 2006;21:3495–3505 **4.** Silverberg J, et al. *Am J Clin Dermatol.* 2018;19(5):759–769. **5.** Ibrahim M, et al. *J Clin Diagn Res.* 2016;10(3):WC01–WC05. **6.** Verduzco HA & Shirazian S. *Kidney Int Res.* 2020;5:1387–1402. **7.** Finley MJ, et al. *Cell Immunol.* 2008;252(1–2). **8.** Albert-Vartanian A, et al. *Journal of Clinical Pharmacy and Therapeutics.* 2016;41:371–382. **9.** Beck TC, et al. *Pharmaceuticals.* 2019;12:95. **10.** Lipman ZM & Yosipovitch G. *Expert Opin. Pharmacother.* 2021;22(5):549–555. **11.** NICE (2023). Difelikefalin for treating pruritus in people having haemodialysis. Available at: https://www.nice.org.uk/guidance/TA890. Date accessed: June 2024. **12.** SMC (2024). Available at: https://www.scottishmedicines.org.uk/medicines-advice/difelikefalin-kapruvia-full-smc2623/ Date accessed: June 2024. **13.** Fishbane S, et al. *New Engl J Med.* 2020;382:222-232. **14.** Wooldridge T, et al. Efficacy and safety of difelikefalin for moderate-to-severe chronic kidney disease-associated pruritus: a global Phase 3 study in hemodialysis patients (KALM-2) (FR-OR24). Presented at Kidney Week 2020; October 19–25, 2020. Virtual Congress. Available at: https://www.caratherapeutics.com/wp-content/uploads/2022/05/Woolridge-T-et-al.-Presented-at-the-American-Society-of-Nephrology-Kidney-Week-2020-1.pdf. Date accessed: June 2024. **15.** Topf J, et al. *Kidney Med.* 2022;4(8):100512. Published online June 28, 2022. **16.** Topf J, et al. *Kidney Med.* 2022;4(8):100512. Supplementary appendix. Published online June 28, 2022. **17.** Rayner HC, et al. *Clin J Am Soc Nephrol.* 2017;12:2000–2007.

PRESCRIBING INFORMATION

Kapruvia® ▼ (Difelikefalin)
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 breast-feeding 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: PLGB 50784/0009, EU/1/22/1643/001, EU/1/22/1643/002
Date of Authorisation: 29/04/2022
MA Holder: Vifor Fresenius Medical Care Renal Pharma France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France

Kapruvia® is a registered trademark

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Date of preparation: October 2023

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.
Tel: +44 1276 853633.
E-mail: MedicalInfo_UK@viforpharma.com