Management of chronic kidney disease associated pruritus: it's time to ask 'do you itch?'

■ chronic kidney disease associated-pruritus ■ difelikefalin ▼ ■ haemodialysis ■ pruritus

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Abstract

Itchy skin is a common symptom for people with advanced chronic kidney disease (CKD), and it has a significant impact on outcomes of treatment. Due to a combination of patient and healthcare related factors, it remains under-reported, under-diagnosed and inadequately treated. Recently, the landscape for treatment has changed. Although the pathogenesis of CKD-associated pruritus (CKD-aP) is complex and multifactorial, the role of the endogenous opioid pathway is now much better understood. Difelikefalin is a peripherally acting kappa opioid receptor agonist indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on in-centre haemodialysis with a favourable safety profile; it does not produce typical opioid side-effects and is the first approved therapy for CKD-aP in Europe. People on dialysis should be asked 'do you itch?', and evidence-based management pathways should be used to treat this debilitating symptom much more effectively.

People undergoing haemodialysis (HD) have a very high burden of symptoms that can be intrusive and impact upon both quality and length of life. In fact, the median number of symptoms experienced by someone undertaking dialysis is estimated to be around nine symptoms (Weisbord et al, 2005), with up to half of people reporting at least one symptom that they described as severe or overwhelming (Moskovitch et al, 2020).

The symptom of itch associated with kidney disease, also known as chronic kidney disease associated-pruritus (CKD-aP), is a common symptom experienced by many individuals undergoing dialysis treatment for end-stage kidney disease. Data from the Dialysis Outcomes and Practice Patterns Survey (DOPPS) have consistently shown that CKD-aP is common, bothering around 67% of people receiving in-centre HD to some extent. The UK reports some of the highest figures of patients on HD experiencing pruritus, with the proportion of people who were at least moderately bothered by CKD-aP as high as 47% (Sukul et al, 2021).

For many healthcare practitioners, this may come as a surprise, as CKD-aP is consistently underreported by patients. In fact, DOPPS data from 6256 patients and 268 medical practitioners showed that almost two-thirds of nephrologists believed that the prevalence of CKD-aP experienced by patients was <5% in their dialysis units. Only 1% of nephrologists estimated the same prevalence that was reported by patients on the units that they managed (Rayner et al, 2017). The reason for this disconnect between the true and perceived prevalence is multifaceted, with key patient and healthcare related factors. Patient-related factors are those intrinsic to the patient, whereas healthcare provider factors relate specifically to knowledge and systems.

Patient-related factors

People perceive pruritus differently, and can describe it in different ways. This can lead to communication barriers between the patient and the healthcare provider due to the patient having difficulties in effectively describing the severity of their pruritus, especially as terms like numbness, burning, pain and restlessness often bring different underlying diagnoses or pathophysiological mechanisms to mind that could, in turn, lead practitioners down alternate treatment pathways (Menzaghi et al, 2023).

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This has the unfortunate consequence of leaving patients feeling misunderstood (Bathe et al, 2013), which on top of a perception that itch is not related to their kidney disease, means that the symptom often remains unreported. In fact, as many as 25% of people on regular HD who are bothered by itchy skin admit that they do not report the symptom to anyone (Rayner et al, 2017).

Healthcare-related factors

As described above, healthcare providers may not be fully aware of the prevalence and impact of itch in dialysis patients. Limited time during medical consultations may lead to itching being overlooked or under-reported, especially due to a lack of integration of symptom scores in routine clinical practice. Combined with a lack of consensus guidelines on CKD-aP management, this leaves healthcare practitioners perhaps prioritising others symptoms or health issues, partly because both patients and members of the kidney team assumed there were no effective treatments available (Aresi et al, 2019).

The impact of chronic, untreated CKD-aP extends beyond the discomfort of the symptom itself, as CKD-aP is associated with reduced quality of life (QoL), poor sleep quality and depression (Pisoni et al, 2006; Mathur et al, 2010). Scratching and broken skin can lead to increased infections and antibiotic use, and patients with severe pruritus are also more likely to miss dialysis sessions (Sukul et al, 2021). This in turn leads to worse clinical outcomes, including increased medication use (e.g. erythropoiesis-stimulating agents, iron supplementation) hospitalisations and mortality (Figure 1). All of this highlights the importance of renewed strategies to focus on CKD-aP as a symptom of importance to people on dialysis, that if treated correctly, can improve outcomes for patients, including quality of life.

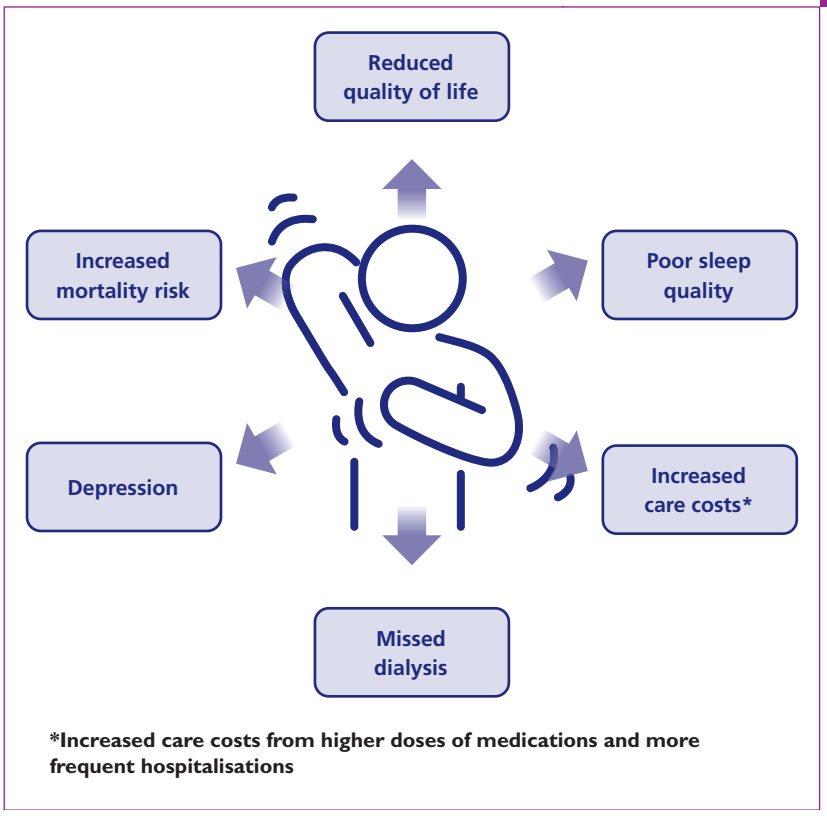

Figure 1: Impact of chronic, untreated chronic kidney disease associated pruritis on health outcomes

Pathophysiology of CKD-associated pruritus

The precise pathophysiology of CKD-associated pruritus is not fully understood, although several mechanisms have been proposed and, in most people, it is likely multi-factorial (Figure 2). Chronic itch occurs after the activation of special receptors called pruriceptors upon exposure to mediators of itch and inflammation. This activation subsequently

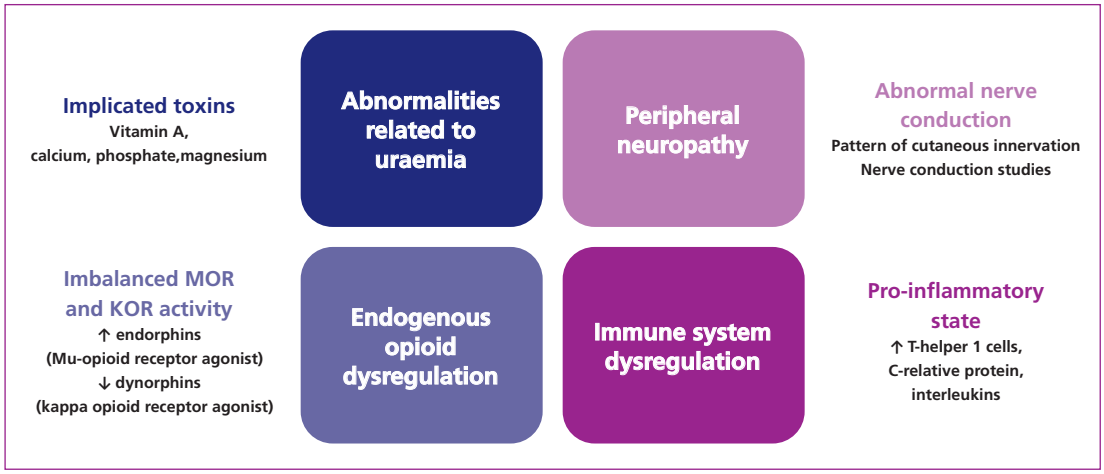

Figure 2: The multifactorial nature of chronic kidney disease associated pruritis (Mettang and Kremer, 2015)

enhances the responsiveness of sensitive nerve fibres. In addition, alterations to an individual's immune system result in further interactions with sensory nerve fibres, transmitting signals that ultimately result in the patient experiencing itching.

Nevertheless, some factors are likely to contribute more than others. Although some observational studies have described elevated uraemic toxin levels in people experiencing CKD-aP (Hiroshige et al, 1995), large scale observational data from DOPPS reported no association between laboratory values and CKD-aP (Rayner et al, 2017). This may mean that undue importance is placed on strategies like phosphate control, that are neither likely to be a significant contributing factor, nor an effective treatment strategy. This can subsequently cause delays in initiating more effective treatments and adds to patients' experience that this is an under-prioritised symptom without effective treatments.

Current evidence for the treatment of CKD-aP

The lack of any clear single pathway underlying the symptom of itch is made clear in the British Association of Dermatologists' guidelines for the investigation and management of generalised pruritus in adults without an underlying dermatosis (Millington et al, 2018), published in 2018, which states that the only definitive treatment for CKD-aP is renal transplantation. In practice, some healthcare professionals have found that topical creams and antihistamines provided some benefit, however, the guidelines highlighted that 'no single topical or systemic treatment is effective' and that 'sedative antihistamines long term may predispose to dementia and should be avoided, except in palliative care' (Millington et al, 2018).

Off-label treatment with gabapentin and pregabalin has shown some benefit in small clinical trials (Rayner et al, 2012), as well as meta-analysis (Burton et al, 2023). However, data from over 140 000 patients from the US Renal Data System showed that gabapentin was associated with 50%, 55%, and 38% higher hazards of altered mental status, fall, and fracture, respectively, in the highest dose category of >300 mg, but even lower dosing was associated with a higher hazard of altered mental status (31%–41%) and fall (26%–30%) (Eusebio-Alpapara et al, 2020). Similar results were seen for pregabalin. This clearly explains the low level of physician satisfaction with therapies for the management of CKD-aP (Burton et al, 2023).

A combination of the mechanisms in Figure 2 contributes to the phenomenon of opioid imbalance and, more recently, evidence has emerged on the role of the opioid receptors in the pathophysiology of CKD-aP. A cross-sectional study of mu- and kappa-receptor (MOR, KOR) expression from the skin biopsies in 40 HD patients with (n=21) and without (n=19) CKD-aP showed that KOR expression was significantly decreased in patients with CKD-aP versus those without, with MOR expression being similar in both groups (Wieczorek et al, 2020). KOR expression negatively correlated with CKD-aP severity, highlighting that this imbalance between KOR and MOR expression may contribute to CKD-aP pathophysiology (Mettang and Kremer, 2015).

Difelikefalin is a kappa-opioid receptor agonist, which acts mainly on peripheral neurons and cells of the immune system. Its structure also differs from other KOR that act primarily on the central nervous system; difelikefalin was designed to activate KORs located in the peripheral nervous system without producing typical opioid side-effects (e.g. respiratory depression, dysphoria, sedation, constipation and diarrhoea) (Albert-Vartanian et al, 2016). Additionally, difelikefalin has limited membrane permeability, thereby limiting the ability of the drug to cross the blood-brain barrier into the central nervous system (Cowan et al, 2015). Consequently, difelikefalin is expected to have no meaningful abuse potential and no physical dependence.

Clinical trials of difelikefalin

The use of difelikefalin in haemodialysis patients was evaluated in the KALM-1 and KALM-2 trials (Fishbane et al, 2020). KALM-1 recruited 378 HD patients from 56 dialysis centres in the US with moderate-to-severe CKD-aP who were then randomly assigned to receive either IV difelikefalin (0.5 µg/kg) (n=158) or a placebo 3 times per week (n=165), with an additional open-label follow-up extension of 1 year. The primary outcome was the proportion of patients with a clinically meaningful improvement of at least 3 points in the Worst Itch Numerical Rating Score (WI-NRS) over 12 weeks. The overall conclusion of the trial was that HD patients with moderate-to-severe itch treated with difelikefalin had a significant and clinically meaningful reduction in itch intensity and improved itch-related quality of life compared with those patients who received the placebo. The KALM-2 study was conducted in 471 participants across 75 sites in North America, Europe and Asia-Pacific region with very similar inclusion criteria; the pooled data from the two studies has shown that the results are consistent across a wide range of HD patient subgroups, demonstrating an acceptable safety profile and good tolerability with long-term use (Fishbane et al, 2022; Topf et al, 2022).

Here in the UK, difelikefalin is the only licensed medication for treating moderate to severe pruritus in adults with chronic kidney disease receiving in-

centre haemodialysis, and is recommended by the National Institute of Health and Care Excellence (2023). Difelikefalin is directly commissioned by NHS England with no impact on the existing dialysis tariff and administered intravenously at a dose of 0.5 µg/kg dry body weight, 3 times per week, identical to that in the clinical studies. Causes of pruritus other than chronic kidney disease should be excluded before initiating treatment with difelikefalin. Scottish Medicines Consortium has also accepted difelikefalin for restricted use within NHSScotland for the treatment of moderate-to-severe pruritus associated with CKD in adult patients on haemodialysis (Scottish Medicines Consortium, 2024).

An approach to the assessment and management of CKD-aP

Given that the symptom of itch is under-recognised, the key to a successful management strategy must be to regularly ask patients 'do you itch?'. As mentioned above, for a number of reasons a high proportion of people on dialysis do not report their symptoms to anybody, so it is the responsibility of healthcare providers to proactively ask about the symptom of CKD-aP. Moreover, it is not just the responsibility of the doctor to ask this question, as for those patients who do mention the symptom of CKD-aP to a member of the healthcare team, around a third of the time it is to a nurse or other member of staff (Rayner et al, 2017).

Once the symptom has been identified, the next step is to identify a tool that can assess the severity of itching and allow tracking of the symptom over time in response to a therapy. One such patient reported outcome measure is the Worst Itching Intensity Numerical Rating Scale (WI-NRS), used in the KALM-1 and KALM-2 studies (Fishbane et al, 2020). The WI-NRS is a single-question tool, and therefore quick and simple to complete, which can rapidly assess the severity of itch. It consists of a validated 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable), and patients rate the intensity of their worst itching during the previous 24-hour period. A score of ≥4 is classified as moderate-to-severe and a 3-point improvement on the scale validated as clinically meaningful. As such, this can act not just as an effective screening tool, but also a way to track whether there is a clinically meaningful response to therapy.

A systematic approach to the management of CKD-aP is key. Skin moisturisation and barrier therapy with emollients, moisturisers and bath oils remain a universal approach to the management of dry skin related to CKD-aP, as well as dialysis optimisation including control of calcium, phosphate and parathyroid hormone levels.

However, for those individuals with moderate-to-severe CKD-aP, use of an itch-specific therapy would be appropriate earlier in the pathway.

Individualisation of therapy is important, and it may be that for individuals with more than one symptom, synergistic prescribing could be effective and prevent polypharmacy. For example, someone living with diabetes and also requiring dialysis suffering from neuropathic pain and CKD-aP may derive benefit for both with the prescription of a gabapentinoid, although their use for CKD-aP is off-label. As difelikefalin is the only licensed treatment of CKD-aP in the US and Europe (including the UK), it has been proposed in a number of treatment algorithms as a first-line treatment for patients with moderate-to-severe pruritus (WI-NRS ≥4) (Wieczorek et al, 2020; Rastogi et al, 2023). Other treatments, such as phototherapy and selective serotonin reuptake inhibitors are also recommended, but similar to gabapentinoids, their use is off-label and may be more appropriate in synergistic prescribing or as third-line therapies.

The importance of symptom clusters in the management of CKD-aP

For under-reported symptoms, like CKD-aP, a greater understanding of the surrounding symptoms may improve overall symptom control, and in turn, health-related quality of life (Ahdoot et al, 2022). As discussed above, people on HD suffer from multiple symptoms, and these can often cluster together to generate a symptom cluster; the co-existence of two or more connected symptoms. Principle component

Figure 3: Components of the skin cluster within the haemodialysis population (Moore et al, 2022)

analyses identified three clusters of symptoms in the HD population: lack of energy and mobility, gastrointestinal and skin. Within the skin cluster of symptoms, the components were itch, changes in skin, restless legs and difficulty sleeping (Figure 3) (Moore et al, 2022).

Furthermore, CKD-aP is the predominant symptom in predicting the persistence and exacerbation of the entire skin symptom cluster and often co-exists with fatigue (Hull et al, 2023). Knowledge of these associated and inter-dependent symptoms is actually the key to a more efficient cluster-based approach to symptom assessment. If a person volunteers a symptom, healthcare professionals must pro-actively ask about the other symptoms in the cluster to which that symptom pertains as they frequently co-occur. Given that individuals often perceive and report the symptom of CKD-aP in different ways, specifically asking about itching, and subsequently commencing treatment for CKD-aP for those people reporting restless legs or difficulty in sleeping could have a profound impact on their health-related outcomes and quality of life.

Real world case study

Mr AB is a 75-year-old gentleman with a history of hypertension, thought to be the cause of his kidney disease. He was referred to the advanced kidney disease clinic with an estimated glomerular filtration rate of 8 ml/min/1.73m2 (stage 5 chronic kidney disease (CKD)) where he was followed up for 6 months before he started haemodialysis last year. After assessment he was deemed too frail for kidney transplantation.

He has been managing well on dialysis via arteriovenous fistula. During a routine dialysis review he revealed that over the past month his mild itching has become much more severe. It is generalised on both arms, as well as his back and chest. He explained that the itching has now started to affect his sleep, particularly over the last three nights, and he has only had a few hours of sleep each night and is exhausted. When asked to rate the severity of itch, using the Worst Itch- Numerical Rating Scale (WI-NRS), he scored 7 which is classed as severe itching. Reviewing Mr AB's results found his phosphate was 1.17 mmol/L, normal liver function tests and he was achieving good blood flows on dialysis that resulted in adequate clearances. He was not taking any opioid medication or other medications that could contribute to itch. His last echocardiogram showed preserved left ventricular function. After examination of the skin there was no evidence of a dermatological condition or a rash, but there were visible marks from where he had been scratching.

Mr AB was still using an emollient, Balneum plus, that had been started when he was in the advanced kidney disease clinic along with loratadine 10 mg daily. To treat the itch, it was decided to initiate gabapentin 100 mg three times weekly. After 3 weeks, there had been no improvement in Mr AB's itching with no adverse effects, so the gabapentin was increased to 100 mg each night. After a further 3 weeks, response was minimal, and Mr AB was struggling due to lack of sleep which was affecting his mood leading to tension with his family. He also had visible scratch lesions on his arms. It was decided to stop the gabapentin and initiate difelikefalin based on the National Institute of Health and Care Excellence's Technology appraisal guidance (NICE, 2023). The dose was calculated on his dry weight of 80 kilograms and 40 microgram each dialysis session was prescribed, to be administered in the washback. At this time the loratadine was also stopped to minimise risk of adverse effects and due to lack of benefit. Within 3 weeks, the itching had started to improve and he had started sleeping better. At 3 months, he was re-assessed using the WI-NRS and his score had now reduced to three, deemed as mild itching, and his skin lesions had fully healed. Mr AB was getting more sleep and was feeling happier overall. He commented that receiving the treatment via dialysis also meant that he didn't have to take more tablets as he 'had plenty of tablets'.

Key points

- People undergoing haemodialysis (HD) have a very high burden of symptoms that can be intrusive and impact upon both quality and length of life
- Chronic kidney disease associated-pruritus (CKD-aP) is a common symptom experienced by many individuals undergoing dialysis treatment for end-stage kidney disease
- Given that individuals often perceive and report the symptom of CKD-aP in different ways, specifically asking about itching, and subsequently commencing treatment for CKD-aP for people reporting restless legs or difficulty in sleeping could have a profound impact on their health-related outcomes and quality of life
- Difelikefalin is a kappa-opioid receptor agonist, which acts mainly on peripheral neurons and cells of the immune system. Consequently, difelikefalin is expected to have no meaningful abuse potential and no physical dependence
- Difelikefalin is the only licensed medication for treating moderate to severe pruritus in adults with CKD receiving in-centre haemodialysis and is recommended by National Institute for Health and Care Excellence.

CPD reflective questions

- How often do you ask someone with chronic kidney disease about pruritus?
- What impact does pruritus have on someone's life?
- What measures can be taken to improve the severity of itching experienced by someone with chronic kidney disease?

Conclusion

CKD-aP is a common, under-reported and distressing symptom that significantly impacts the physical, psychological, and social well-being of affected individuals. Although the pathophysiology of pruritus in CKD remains incompletely understood, various mechanisms, including uraemic toxin accumulation, inflammatory cytokine dysregulation, and neuroendocrine abnormalities, are believed to contribute to its development. Management of CKD-associated pruritus requires a comprehensive and individualised approach, starting with the question 'do you itch?' and finishing with the goal of adequate and sustained symptomatic relief. Difelikefalin is the only licensed treatment for the relief of moderate to severe CKD-aP in adult in-centre haemodialysis patients; other treatments are used off-label, have varying levels of effectiveness, and may present an increased risk of toxicity in patients with CKD. Clearer clinical guidelines on the detection, reporting and management of CKD-aP (and other related symptoms) have the potential to improve health-related outcomes and quality of life for people on HD experiencing this debilitating symptom. JKC

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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

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