

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final draft guidance

# Difelikefalin for treating pruritus in people having haemodialysis

## 1 Recommendations

- 1.1 Difelikefalin is recommended, within its marketing authorisation, for treating moderate to severe pruritus in adults with chronic kidney disease having in-centre haemodialysis. Difelikefalin is only recommended if the company provides it according to the commercial arrangement (see [section 2](#)).

### Why the committee made these recommendations

Usual treatment for pruritus (itching) in people with chronic kidney disease having haemodialysis includes creams and emollients, antihistamines and gabapentin. Difelikefalin would be offered if usual treatments do not work well enough.

Evidence from clinical trials shows that difelikefalin reduces itching compared with usual treatment, despite some uncertainty about how long it works for and whether it improves people's quality of life.

The cost-effectiveness estimates for difelikefalin are within the range that NICE usually considers an acceptable use of NHS resources. So it is recommended.

## 2 Information about difelikefalin

### Marketing authorisation indication

- 2.1 Difelikefalin (Kapruvia, Vifor Pharma) is indicated for 'the treatment of moderate-to-severe pruritus associated with chronic kidney disease in

adult patients on haemodialysis'. Difelikefalin should be restricted to in-centre haemodialysis use only.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in [the summary of product characteristics for difelikefalin](#).

## Price

2.4 The list price of 50-microgram 1-ml vials of difelikefalin is £420 for 12 vials (excluding VAT; BNF online accessed February 2023)

2.5 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. It is the company's responsibility to let relevant NHS organisations know details of the discount.

## 3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Vifor Pharma, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

## The condition

### Details of the condition

3.1 Chronic kidney disease (CKD) is a common and progressive disease. It is characterised by abnormalities of kidney function or structure for more than 3 months. CKD-associated pruritus (CKD-aP) is a systemic itch that occurs in people with CKD, especially those having dialysis. The itch can affect the skin over the entire body, or only specific areas such as the scalp, face, upper back, arms or buttocks. Severity can change over time but can affect quality of life, and cause sleep disturbance, anxiety and depression. The patient experts explained people with CKD-aP will often have an additional treatment burden that can be physically and

emotionally exhausting. They can have increased risks of infection, hospitalisation and mortality compared with people with normal renal function. CKD-aP can affect daily activities, and people may have visible signs of scratching, which can have a negative emotional impact. The committee agreed there is an unmet need for treatment in people with moderate to severe CKD-aP having haemodialysis.

## Clinical management

### Treatment pathway

3.2 There is no established standard care for CKD-aP. The company stated that treatment would only be started when dialysis has normalised the calcium–phosphate balance and controlled parathyroid hormones to acceptable levels. Best supportive care could include anti-itch medicines such as creams and emollients, antihistamines and gabapentin. But these are currently unlicensed for this condition. If a person still has pruritus after having best supportive care, difelikefalin would then be offered. But the clinical experts explained that difelikefalin may be used earlier in the treatment pathway. It would be an intravenous in-centre treatment at the same time as having dialysis. It would continue for the duration of dialysis, as long as there is a sufficient reduction in itch score in the first 12 weeks of treatment. The committee agreed that the positioning of difelikefalin in the treatment pathway was appropriate.

### Comparators

3.3 The company's submission compared difelikefalin plus anti-itch medicines used in established clinical practice with placebo plus anti-itch medicines used in established clinical practice. The EAG noted that this comparison was different from that in the NICE scope, which only listed difelikefalin compared with placebo. At technical engagement, the company clarified that the key clinical evidence considered the effect of difelikefalin compared with placebo including people that were both having and not having additional anti-itch medication. Considering the vast array of anti-

itch medicines used in established clinical practice, the EAG thought that it would be hard to identify whether there was a possible interaction between difelikefalin and specific anti-itch treatments when taken together. Any interaction might increase the benefit of difelikefalin compared with the benefits from anti-itch treatments being used alongside placebo. A clinical expert stated that there is a lack of empirical evidence on the efficacy of commonly used anti-itch treatments for pruritus, so the magnitude of any interactive effect is unknown. Pruritus treatment varies across the UK because there is no established standard care. Difelikefalin would be given at the same time as in-centre dialysis. So it was not unreasonable to expect that people would also be using other anti-itch medicines at the same time. The patient experts explained that people with CKD-aP might be having multiple treatments to relieve their itch, as well as controlling their CKD symptoms. The committee agreed that difelikefalin would be used in addition to other anti-itch medicines to treat pruritus, so the comparison presented by the company was appropriate. It also acknowledged that the impact of these other treatments on the efficacy of difelikefalin is unknown.

## **Clinical effectiveness**

### **KALM trials**

3.4 The main clinical evidence came from 2 phase 3, randomised, multicentre, double-blind, placebo-controlled studies: KALM-1 (n=378) and KALM-2 (n= 474). These investigated the safety and efficacy of difelikefalin in adults with end-stage renal disease who had been having haemodialysis at least 3 times per week for at least 3 months, and who had moderate to severe CKD-aP. Difelikefalin was administered after each haemodialysis session (usually 3 times per week). Both studies included a 12-week double-blind phase in which people were randomised to have intravenous difelikefalin (0.5 microgram/kg) or placebo. Each trial had a 7-day run-in period during the week before randomisation, to identify the baseline itch intensity and whether the pruritus was moderate

to severe. Treatment with other anti-itch medicines and presence of other medical conditions were recorded in the run-in period. A 52-week open-label extension period followed, in which difelikefalin was provided. In KALM-1, there was a 2-week discontinuation period at 12 weeks, between the double-blind and open-label phases, in which participants were evaluated for signs of physical dependence. The committee considered that this might influence the efficacy results, but this was unknown. It concluded that the trials were appropriate for evaluating the efficacy of difelikefalin in people with moderate to severe pruritus, but that some aspects of the trial design might influence results.

### Itch severity

3.5 The primary efficacy outcome in both KALM trials was the percentage of people who had an improvement of at least 3 points from baseline at week 12 in the weekly mean score on the daily worst itching intensity numerical rating scale (WI-NRS). In KALM-1, the mean percentage of people with at least a 3-point improvement from baseline in the WI-NRS was 51% in the difelikefalin group and 27.6% in the placebo group. The estimated odds ratio for an improvement of at least 3 points from baseline with difelikefalin compared with placebo was 2.72 (95% confidence interval [CI] 1.72 to 4.30;  $p < 0.001$ ). In KALM-2, the mean percentage of people with at least a 3-point improvement from baseline in the WI-NRS was 54% in the difelikefalin group and 42.2% in the placebo group. The estimated odds ratio for an improvement of at least 3 points from baseline with difelikefalin compared with placebo was in favour of difelikefalin at 1.61 (95% CI 1.08 to 2.41). The company provided further evidence on the efficacy of difelikefalin from a pooled analysis of results from the KALM trials ([Topf et al., 2022](#)). The odds of having at least a 3-point reduction in WI-NRS score at week 12 with difelikefalin compared with placebo was 1.93 (95% CI 1.44, 2.57). The EAG was concerned about the company's method of doing the pooled analysis. It had included all randomised participants from the pooled KALM-1 and KALM-2 studies.

The EAG suggested that the individual patient data from both trials was

simply added together rather than doing a meta-analysis. It considered that pooling data in this way might lead to over-precise results and might bias the results. It did its own meta-analysis of the results from the KALM studies. This resulted in the odds of at least a 3-point reduction in WI-NRS score at week 12 with difelikefalin compared with placebo was 2.07 (95% CI 1.24 to 3.45). The committee concluded that the evidence suggested that difelikefalin reduces itch severity compared with placebo, but that there was uncertainty in the pooled data.

### **Measures of itch intensity**

3.6 In the KALM trials, itch severity was measured using the WI-NRS and the 5-D itch scale. The WI-NRS is a single-item patient-reported outcome that assesses the intensity of the worst itching experienced in the past 24 hours. The company considered that the WI-NRS was a reliable, reproducible and valid measure of itch intensity in people with moderate to severe CKD-aP. The 5-D itch score is a multidimensional questionnaire that assesses itch severity and itch-related quality of life in the previous 2 weeks. The dimensions of itch assessed are degree, duration, direction, disability and distribution. Each domain is scored from 1 to 5 (1 suggesting no pruritus, and 5 for the most severe pruritus) and has a total score range of 5 to 25. A 5-point change is considered clinically significant. The committee considered how appropriate the WI-NRS and 5-D itch scores are for measuring itch intensity in CKD-aP. The clinical expert explained that a multidimensional scale is less likely to be used in clinical practice, because it is time consuming and relies on people retaining information over a longer time than a daily single-item scale. In practice, healthcare professionals are unlikely to use a questionnaire and would usually rely simply on people verbally reporting their itch severity. The committee accepted that both scales would inform itch severity, but in clinical practice neither is likely to be used.

## Generalisability

### Concomitant medicines

3.7 The company clarified that the participants in the KALM trials were allowed anti-itch medicines other than difelikefalin throughout the trial. This was restricted to the medicine they were taking before the trial and changes in dosage were not allowed. The EAG considered whether the overall array of anti-itch medicines allowed in the KALM trials was comparable to UK standard care. The company had provided data from KALM-1 and KALM-2, grouped by 5 key anti-itch medicines. This showed that, based on WI-NRS improvement, there was a trend for greater benefits with difelikefalin compared with placebo when used with anti-itch medicines, antihistamines, opioids or steroids. Used with gabapentin or pregabalin, the benefits of difelikefalin compared with placebo were reduced. Whether the anti-itch medicines used in the KALM trials were applicable to UK practice was unclear. The committee recalled that there is variation in practice across the UK (see sections 3.2 and 3.6). One clinical expert said that it is difficult to compare UK practice to the anti-itch medicines used in the KALM trials, but that topical therapies, antihistamines (mainly non-sedating medicines like cetirizine) and gabapentin are likely to be the most commonly used. Differences between the anti-itch medicines included in the trials and those used in UK clinical practice could limit the generalisability of the clinical-effectiveness evidence from the trials. The committee concluded that the impact of the various anti-itch medicines used in the KALM trials could affect the efficacy of difelikefalin. But there is currently no established standard care, and there is too little evidence for commonly used anti-itch medicines to allow the interaction of these medicines with difelikefalin to be explored.

### Family background

3.8 The company considered that the KALM trial data was representative of a UK population with CKD-aP. It provided data from the UK Renal Register which showed that the data from UK participants in the KALM trials

aligned reasonably well with the UK population. But the EAG noted that the overall population in the KALM trials and the UK target population were not comparable. The KALM trials had recruited a larger proportion of Black participants (29.2%) than is seen in the UK target population (12.8%). The company provided subgroup analyses of family background, sex and age for the primary efficacy results of each trial. The results suggested that people reported as being Black or African American in the trial had better outcomes with difelikefalin than people from other family backgrounds. The EAG questioned whether family background may be an effect modifier, which meant the overall efficacy from the KALM trials would overestimate the efficacy in the UK population. The company said that the KALM trials had been carried out in 5 treatment centres in the UK, and included 20 UK participants. It considered that this represented the UK population well. The company stated that the effect of difelikefalin was not statistically significantly different in Black participants compared with people from other family backgrounds in the KALM trials. The committee noted that the trials were not powered to detect statistically significant differences in treatment effect by family background. One clinical expert explained that because the KALM trials had recruited participants in a large number of UK clinical centres, the populations were broadly generalisable to the UK population. There are large health inequalities in CKD. People from Black and Asian family backgrounds may have faster progression to renal failure and have haemodialysis for longer, so there would be a high proportion of people with CKD from Black and Asian family backgrounds in UK clinical practice. The committee concluded that the KALM data was representative of the UK clinical population.

### **Handling missing data in the KALM trials**

- 3.9 The company used multiple imputation to handle missing data in the double-blind phases of KALM-1 and KALM-2. At technical engagement, the company clarified that it had chosen this approach because single imputation methods would have overestimated a treatment effect but underestimated the variability caused by the missing data. The company



stated that it had done 20 imputations, but the EAG was not clear how all of the transition matrices were identified based on the company's methods of accounting for the missing data. It was unsure whether the company's transition probabilities were based on averages over the 20 different probabilities, or if each came from a different complete dataset to create an overall estimated dataset. The company had not directly tested the variability of the between-arm datasets. It had used several covariates in KALM-1 and KALM-2. These were baseline WI-NRS score, use of anti-itch medication during the week before randomisation, presence of a specific medical condition, and the patient-reported numerical rating scale scores for each week. It also considered region to be a covariate, for KALM-2 only, but had not considered all regions that had participated in the trial. The variables used in the logistic regression model were trial group, baseline WI-NRS score, baseline use of antipruritic medication, and history of prespecified medical conditions. The EAG explained that, when imputing data, it is important to explore how uncertainty was estimated. This should account for both within-dataset and between-dataset variation. So, it is usual to include as many variables as possible rather than only exploring covariates that might influence effectiveness. The EAG queried the company's rationale for choosing specific covariates over other potential prognostic variables that may be correlated with the outcome of interest. Because there were 279 missing observations throughout the KALM trials, the committee considered that using an imputed approach to missing clinical data in the KALM trials was more appropriate than relying on direct observations. But it noted that the company had provided insufficient information about the methodology of the multiple imputation.

## **Economic model**

### **Company's model**

3.10 The company developed a Markov model to assess the cost effectiveness of difelikefalin for adults with moderate to severe CKD-aP who are having

haemodialysis. The model had 5 core health states, which were defined by itch severity (none, mild, moderate, severe, and very severe). It had 2 additional health states of renal transplant and death. The 5 core health states used in the model were defined using the outcome measures of WI-NRS and 5-D itch scale scores, as these were collected in the KALM trials. The committee had some concerns about the company's modelling of treatment efficacy, and the fact that the 'severe' and 'very severe' health states had identical costs and utility values. The company used the 5-D itch scores to model treatment efficacy in its base-case analysis, but the WI-NRS had been the primary outcome in KALM-1 and KALM-2. The company explained that the 5-D itch scale had been used for up to 64 weeks in the KALM open-label phases, whereas the WI-NRS was only used for the first 12 weeks. The EAG felt that the model structure adequately reflected clinical issues for people with moderate to severe CKD-aP who are having haemodialysis. The committee accepted this, but considered there was still some uncertainty in using the 5-D itch scores to model treatment efficacy.

## **Assumptions in the economic model**

### **Waning of treatment effect**

3.11 In the company's original base case, the comparator arm was modelled as having a 5% waning of treatment effect per year. The company assumed no waning in the difelikefalin arm. It did not provide evidence to support these waning assumptions, so the EAG considered that they were uncertain. At technical engagement, the company presented evidence based on an economic literature review that identified 3 NICE highly specialised technology appraisals in which itching was important, and treatment waning had been accepted in the comparator arm. Based on this, the company carried out 2 scenario analyses to explore the impact of a waning effect in the comparator arm of its model. This showed that waning rates were much higher than the 5% waning per year that was assumed in its original base case. So the company increased the waning

for the comparator arm in its revised base case to 10%. The EAG considered this to be a reasonable approach and accepted 10% waning per year in the comparator arm, and updated its base case in line with this. One clinical expert explained that in people having established standard care, there is likely to be a placebo effect and so waning would occur. The committee recognised that the 10% waning applied in the comparator arm was a conservative estimate, and accepted this. It was less certain that that no waning would occur in the difelikefalin group, and considered it plausible that there would be a waning of treatment effect for difelikefalin. The committee welcomed the scenarios exploring the impact of different waning assumptions for difelikefalin. It considered that the scenario analysis assuming 5% waning in the treatment arm and 10% waning in the control arm was useful.

### **Health state utility values**

3.12 No generic health state measures of quality of life were collected in the KALM trials. So the company carried out a separate primary data collection study across UK dialysis centres to map the WI-NRS and 5-D itch scale to the EQ-5D-3L. These utility values were used to reflect the CKD-aP health states in its base case. In the mapping study, the severe and very severe populations were merged, so the utility scores for these populations were equal and had the same measures of utility, quality of life and costs. The company explained that the populations were merged because of the small numbers of observations in each group. The committee noted that most observations were populated by the severe health state, and queried whether it was appropriate to include the very severe health state in the model. The company stated that the model had been developed to represent the 5 core health states of CKD-aP severity and it considered this was appropriate. One clinical expert stated that in practice, severe CKD-aP would be different to very severe CKD-aP. The committee agreed the mapping study was robust and accepted that the model should include all 5 health states of CKD-aP severity.

## Transition probabilities

3.13 To account for the missing data in the KALM trials, the company used multiple imputation (see section 3.9). In its base case, transition probabilities were estimated using a simulated approach that considered the mean change from baseline in itch scores by CKD-aP severity for the moderate, severe and very severe health states at baseline. The simulated approach only allowed for a person's condition to improve, whereas the observed data showed people's conditions could improve or deteriorate up to 3 health states at time. One clinical expert explained that in clinical practice, people's conditions would likely improve or deteriorate, rather than only improving. The EAG preferred to estimate transition probabilities from directly observed data. The committee agreed that the observed data better reflected clinical practice. It considered that the company had provided little justification for how, in its base case, it had estimated and simulated the transition probabilities from aggregate data. It preferred the EAG's approach of estimating transitions using observed patient-level data, as this better reflected transitions in clinical practice. The committee was aware of the uncertainties in using this simulated approach (see section 3.9). The company provided a histogram plot showing the frequency of observations for each 5-D itch scale total score at week 12 using the observed patient-level data set and simulated data set. The committee felt that a longer-term exploration of the observed data, compared with data drawn from the simulated data set, might address these uncertainties. A comparison showing the health state occupancy from the simulated data used in the company's model against the directly observed health state occupancy from the KALM trials would have been helpful to the committee's decision making.

## Cost-effectiveness estimates

### Acceptable ICER

3.14 The [NICE health technology evaluations manual](#) notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per

quality-adjusted life year (QALY) gained, decisions about the acceptability of the technology as an effective use of NHS resources will specifically consider:

- the degree of certainty and uncertainty around the ICER
- uncaptured benefits and non-health factors.

The committee noted several points when it considered the uncertainty around the cost-effectiveness estimates, specifically:

- waning of treatment effect of difelikefalin in the economic model (see section 3.11)
- estimation of transition probabilities from the observed patient data (see section 3.13)
- modelling of itch severity using the 5-D itch scale (see section 3.10.)

The committee concluded that these uncertainties would have to be reflected in the maximum ICER it would be willing to accept, which would need to be well below £30,000 per QALY gained.

### **The committee's preferred cost-effectiveness estimate**

3.15 The committee recalled its preference to use transition probabilities directly from the trial, and that the ERG's base case more closely matched its preferred assumptions. The committee noted that when taking into account the confidential discount for difelikefalin, the ERG's base-case ICER was £22,000 per QALY gained for difelikefalin compared with established standard care. The committee was satisfied that the most likely cost-effectiveness estimates were within what NICE considers an acceptable use of NHS resources.

### **Other factors**

#### **Uncaptured benefits**

3.16 One clinical expert pointed out that in clinical practice, difelikefalin would be administered at the same time as having dialysis. The committee

recognised this would reduce the treatment burden for people with CKD-aP. It noted that this benefit had not been captured in the cost-effectiveness analysis.

## Equality issues

3.17 The company submission noted several groups of people that are at greater risk of developing CKD-aP and having symptoms for longer while on dialysis. These include:

- people with lower socioeconomic status, who are more likely to develop CKD, whose condition is more likely to progress towards kidney failure, and who die earlier because of CKD
- people from Black, Asian and other minority ethnic family backgrounds, whose condition is more likely to progress to kidney failure faster, and who are less likely to receive a transplant
- women, who are more likely to be diagnosed with CKD, but less likely to start dialysis
- older people with CKD, who are less likely to have a kidney transplant than younger people.

The company noted that difelikefalin is restricted for in-centre haemodialysis use, which may be considered a barrier for people that find in-centre haemodialysis less accessible. The committee recalled the treatment burden of having CKD-aP (see section 3.1). It considered that 1 advantage of difelikefalin might be to lessen that burden and therefore help reduce health inequalities. The committee further concluded that a recommendation for difelikefalin would be unlikely to result in any direct or indirect discrimination.

3.18 NICE's advice about conditions with a high degree of severity did not apply.

## Innovation

- 3.19 The committee considered if difelikefalin was an innovative treatment for CKD-aP. It recalled that the reduced treatment burden had not been captured in the modelling, and that it would take this into account in its decision making.

## Conclusion

### Recommendation

- 3.20 The committee noted its preference for the EAG's base-case results, the uncaptured benefits, and the need for uncertainty to be taken into account in its decision. The committee concluded that difelikefalin would be a cost-effective use of NHS resources. So it recommended difelikefalin, within its marketing authorisation, for treating moderate to severe pruritus in adults with CKD having in-centre haemodialysis.

## 4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has moderate to severe pruritus with chronic

kidney disease and the doctor responsible for their care thinks that difelikefalin is the right treatment, it should be available for use, in line with NICE's recommendations.

## **5 Evaluation committee members and NICE project team**

### **Evaluation committee members**

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The [minutes of each evaluation committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **Chair**

#### **Baljit Singh**

Vice Chair, technology appraisal committee

### **NICE project team**

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

#### **Victoria Gillis-Elliott**

Technical lead

#### **Rufaro Kausi**

Technical adviser



**Jeremy Powell**

Project manager

ISBN: [to be added at publication]