NCPE Assessment

Technical Summary

Difelikefalin (Kapruvia®)

HTA ID:23001

February 2024

Applicant: Vifor Pharma UK Ltd

Difelikefalin (Kapruvia®) for the treatment of moderate to severe pruritis associated with chronic kidney disease in adult patients on haemodialysis

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of difelikefalin for the treatment of moderate to severe pruritis associated with chronic kidney disease in adult patients on haemodialysis

Following assessment of the Applicant's submission, the NCPE recommends that difelikefalin be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Vifor Pharma UK Ltd) Health Technology Assessment of difelikefalin (Kapruvia®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*

Summary

On the 12th September 2023 Vifor Pharma UK Ltd submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of difelikefalin (Kapruvia®) for the treatment of moderate to severe pruritis associated with chronic kidney disease in adult patients on haemodialysis. A common symptom experienced by patients undergoing dialysis is persistent and intense itchy skin which is referred to as chronic kidney disease – associated pruritis (CKD-aP) or uraemic pruritis (UP). It affects more than 60% of patients undergoing haemodialysis, with 20% to 40% of patients reporting moderate-to-severe pruritis. Intense and generalised systemic itching is associated with poor sleep quality, depression, reduced quality of life, increased risk of infection, hospitalisation and medication use and a poor prognosis. The pathogenesis of CKD-aP is incompletely understood and several hypothesis have been proposed including imbalances in the endogenous opioid system with mu-opioid receptor activity increasing itch and kappa-opioid activity supressing itch.

There are a wide range of unlicenced treatment options for CKD-aP including oral antihistamines, emollients, capsaicin cream, topical or systemic corticosteroids, antidepressants (paroxetine, mirtazapine, doxepin, amitriptyline), UV Phototherapy, gabapentin, pregabalin, mast cell stabilizers, cholestyramine, naltrexone and thalidomide. Ensuring adequate dialysis is also important in the management of CKD-aP.

Marketing authorisation for difelikefalin was granted by the European Medicines Agency (EMA) on the 25th April 2022. Difelikefalin is a selective kappa opioid receptor agonist and the activation of kappa opioid receptors on peripheral sensory neurons and immune cells by difelikefalin are considered the mechanism of action for its antipruritic and anti-inflammatory effects.

The pharmaceutical formulation is a clear, colourless solution for injection. It is presented in a pack size of 12 vials each containing 1 ml of solution for injection. Each 1 ml vial contains 50 µg of difelikefalin. The drug is administered three times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the haemodialysis

treatment. The recommended dose of difelikefalin is 0.5 µg/kg dry body weight. For patients with a dry body weight ≥ 195 kg the recommended dose is 100 µg (2 ml). If a fourth haemodialysis is performed in a week, difelikefalin is administered at the end of the haemodialysis as per the recommended dose. No more than four doses should be administered in a week. An effect of difelikefalin in reducing pruritis is expected after two to three weeks of treatment.

1. Comparative effectiveness

The primary evidence for the efficacy and safety of difelikefalin is based on two phase III, randomised, placebo controlled trials, KALM-1 and KALM-2. The findings from the KALM-2 study were not published in a peer reviewed journal but were published as a pooled analysis with the KALM-1 study. There were 52 week open label extension (OLE) studies for the KALM-1 and KALM-2 trials which were not published separately but are presented in a pooled analysis.

The KALM-1 study was a double-blind, placebo-controlled, phase 3 trial where 378 patients with moderate-to-severe pruritis undergoing haemodialysis were randomised to receive either difelikefalin (at a dose of 0.5 µg per kilogram of body weight) or placebo administered intravenously three times per week for 12 weeks. Eligible patients were adults (≥ 18 years of age) with end-stage kidney disease who had been undergoing haemodialysis at least three times per week for at least three months. Patients had moderate-to-severe pruritis defined as a weekly mean score of more than four points on the 24 hour Worst Itching Intensity Numerical Rating Scale (WI-NRS). The mean baseline WI-NRS was 7.3 in the placebo group and 7.1 in the difelikefalin group. During the 12 week intervention period patients reported their WI-NRS and itch related quality of life was measured with the use of two validated instruments, the 5-D itch and the Skindex-10 multidimensional questionnaires. Concomitant treatment with stable doses of antihistamines, glucocorticoids, opioids, gabapentin and pregabalin was permitted if used at the time of the screening visit.

The mean age of participants in the placebo group (n=188) was 56.8 years and 62.8% were male. In the difelikefalin group (n=189) the mean age was 58.2 years and 59.3% were male.

The time since the initiation of haemodialysis was 4.7 years in the placebo group and 4.4 years in the difelikefalin group. The most common causes of chronic kidney disease were diabetes mellitus (> 50% of participants in each group) and hypertension (38.8 % and 31.2% in the placebo and difelikefalin groups respectively). The most commonly used antipruritic medications at baseline included diphenhydramine, hydroxyzine and hydrocortisone.

The primary efficacy outcome was the percentage of patients who had an improvement (decrease) of at least three points from baseline at week 12 in the weekly mean score on the daily WI-NRS. The pre-specified secondary efficacy outcomes were the mean change from baseline at week 12 in the 5-D itch scale and the Skindex-10 scale total scores and the percentage of patients who had an improvement (decrease) of at least four points from baseline at week 12 in the weekly mean WI-NRS score. At week 12, the estimated percentage of patients who had an improvement (decrease) of at least 3 points from baseline on the WI-NRS was significantly greater in the difelikefalin group than in the placebo group (49.1% versus 27.9%; relative risk, 1.65; 95% confidence interval, 1.26 to 2.14; p<0.001). The treatment effect was evident at week one. In the pre-specified analysis, which included only scores during receipt of difelikefalin or placebo, 51% of patients receiving difelikefalin as compared with 27.6% of patients receiving placebo, had an improvement of at least 3 points from baseline in the WI-NRS score at week 12.

Difelikefalin also resulted in a significant improvement (decrease) from baseline to week 12 in itch-related quality of life as measured by the 5-D itch scale and the Skindex-10 scale. At week 12 the least-squares mean ± standard error (SE) change from baseline in the 5-D total score was -5.0 ± 0.3 in the difelikefalin group as compared with -3.7 ± 0.3 in the placebo group. The least-squares mean change from baseline at week 12 in the Skindex-10 total score was -17.2 ± 1.3 in the difelikefalin group and -12.0 ± 1.2 in the placebo group. A significantly higher percentage of patients in the difelikefalin group than in the placebo group had a decrease of at least four points from baseline at week 12 in the weekly mean WI-NRS score (37.1% versus 17.9%, p<0.001).

The KALM-2 study had similar inclusion and exclusion criteria as used in the KALM-1 trial and the primary endpoint was identical for both studies. The pre-specified secondary endpoints

differed and for KALM-2 included the proportion of subjects achieving (a) a ≥ 4 point improvement from baseline with respect to the weekly mean of the daily 24 hour WI-NRS at week 12 (b) a ≥ 3 point improvement from baseline with respect to the weekly mean of the daily 24 hour WI-NRS at week 8 and (c) a ≥ 3 point improvement from baseline with respect to the weekly mean of the daily 24 hour WI-NRS at week four of the double-blind treatment period. The results from the KALM-2 study were only published as a pooled analysis with the KALM-1 study. This analysis included 851 participants (difelikefalin, n=426; placebo, n=425) that were randomised to receive intravenous difelikefalin (at a dose of 0.5 µg/kg) or placebo for 12 weeks. The clinical outcomes in the published pooled analysis of the KALM-1 and KALM-2 studies included the WI-NRS and itch related quality of life measures Skindex-10 and 5-D itch questionnaires. The baseline characteristics for KALM-2 were similar to KALM-1 however there were some differences in terms of duration on chronic dialysis, mean prescription dry weight and hypertension.

In the pooled analysis 51.1% of participants in the difelikefalin group and 35.2% of participants in the placebo group achieved a ≥ 3 point reduction in the weekly mean of daily WI-NRS scores at week 12 ($p<0.001$). Corresponding figures from the KALM-2 study group were 53.4% in the difelikefalin group versus 42.6% in the placebo group ($p=0.03$). Achievement of a ≥ 4 point WI-NRS reduction was significantly greater with difelikefalin (38.7%) versus placebo (23.4%; $p<0.001$) in the pooled analysis which was similar to the results of the KALM-2 study group i.e 37.3% (difelikefalin) versus 26.4% in the placebo group ($p=0.02$).

In the pooled analysis, participants in the difelikefalin group achieved clinically meaningful improvements in itch-related quality of life versus the placebo group with a ≥ 15 point improvement in the Skindex-10 total scores (55.5% versus 40.5% respectively at week 12; $p<0.001$) and ≥ 5 point improvement in 5-D itch total scores (52.1% versus 42.3% respectively at week 12; $p=0.01$). Least squares mean changes from baseline to week 12 in Skindex-10 total scores were -16.9 (95% CI, -18.6 to -15.2) in the difelikefalin group and -13.5 (95% CI, -15.1 to -11.8) in the placebo group ($p=0.001$). Least squares mean changes from baseline to week 12 in 5-D itch scores were -4.9 (95% CI, -5.4 to -4.5) in the difelikefalin group and -3.7 (95% CI, -4.1 to -3.3) in the placebo group ($p<0.001$). Difelikefalin reduced

itch intensity in subgroups based on age, sex, anti-itch medication use, the presence of specific medical conditions and gabapentin or pregabalin use.

The results of the KALM-1 open-label extension study (OLE) are not published in a peer reviewed journal. Similarly, the KALM-2 OLE study is not published and was discontinued early. The results of both OLE studies are published as a pooled analysis in Topf et al. (2022). The 5-D itch scale was the only efficacy measure in the OLE phase. The change from baseline was maintained for both treatment sequence groups throughout the open-label treatment period. Least squares mean change from baseline was -6.9 and -7.8 at the end of open-label week 52 for the placebo/difelikefalin and difelikefalin/difelikefalin groups respectively.

2. Safety

A pooled safety analysis of intravenous difelikefalin in participants with moderate to severe chronic kidney disease–associated pruritus (CKD-aP) undergoing hemodialysis in four phase 3 clinical studies was referenced in the economic evaluation. This included the KALM-1 and KALM-2 randomized trials and CLIN3101 (52 weeks) and CLIN3105 (12 weeks) open-label studies. The safety analyses included 848 participants in the placebo-controlled cohort (424 participants each in the difelikefalin and placebo groups) and 1,306 participants in the all-difelikefalin-exposure cohort. In the placebo-controlled cohort, the most commonly reported treatment-emergent adverse events (TEAEs), occurring in ≥2% of participants receiving difelikefalin and with a ≥1% higher incidence than placebo, were diarrhoea (9.0% and 5.7%), dizziness (6.8% and 3.8%), nausea (6.6% and 4.5%), gait disturbances, including falls (6.6% and 5.4%), hyperkalemia (4.7% and 3.5%), headache (4.5% and 2.6%), somnolence (4.2% and 2.4%), and mental status changes (3.3% and 1.4%, respectively). These were mostly mild or moderate, with few leading to treatment discontinuation. Incidence rates of TEAEs, serious TEAEs, and discontinuations because of TEAEs did not increase with long-term exposure. Similar findings were noted in the KALM-1 study where adverse events led to discontinuation of treatment in 7.9% of patients in the difelikefalin group and 4.8% in the placebo group.

3. Cost effectiveness

The population considered in the base case analysis were adult patients with moderate-to-severe pruritis associated with chronic kidney disease undergoing haemodialysis. The baseline characteristics were weighted averages based on the pooled KALM trials and Irish/UK data. The intervention was difelikefalin 0.5 µg/kg dry body weight administered intravenously three times weekly after each haemodialysis session plus best supportive care. The comparator included in the economic evaluation was best supportive care (BSC). A Markov model was constructed to calculate lifetime costs and quality adjusted life years (QALYs) for treatment with difelikefalin plus best supportive care versus best supportive care.

The model comprises five core health states as defined by level of itch severity: none, mild, moderate, severe and very severe. For each of the five core health states it is possible to transition to either renal transplant or death. Renal transplant is assumed to be a definitive treatment for CKD-aP and all patients discontinue treatments for pruritis following transplantation. In the base case patients enter the model at the moderate-to-severe health states, consistent with the indication for difelikefalin. The model structure is designed to reflect the KALM-1 and KALM-2 trials for CKD-aP and includes an initial 12 week 'run-in' period which is followed by the long-term course of CKD-aP where those responding to treatment remain on same and non-responders (estimated at 45.3% in the model) discontinue difelikefalin and remain on best supportive care. Response to treatment is defined as a ≥ 5 point reduction from baseline in the total 5-D itch score.

A four week cycle length is used for the first three cycles (the 'run-in' period) and a 52 week cycle length is used from cycle four, continuing over the lifetime horizon (100 years). The starting age in the model is 60.6 years. The baseline distribution of patients at model entry reflects the pooled data from the KALM 1 and 2 trials as measured by the total score on the 5-D itch scale resulting in 55.28% in the moderate health state, 34.17% in the severe health state and 10.55% in the very severe health state. The efficacy estimates for difelikefalin and best supportive care were modelled using the 5-D itch scale. Transition probabilities were based on the 5-D itch total scores as they provided estimates of treatment efficacy up to 64

weeks. A simulated method was used in the base-case which used the mean change from baseline in the 5-D itch scores by CKD-aP severity to estimate transition probabilities. As no data was collected beyond the 52-week OLE phase, the base-case assumes that efficacy of difelikefalin remains unchanged after week 64 in the model. Another assumption in the model is that 45.3% of patients treated with difelikefalin will not achieve a clinically meaningful response and will discontinue treatment and progress through the model at the same rate as best supportive care. Probabilities of death and renal transplantation were provided. In the base-case it is assumed that difelikefalin reduces mortality as compared with best supportive care. Adverse events are considered in the model including diarrhoea, dizziness, nausea, gait disturbance, hyperkalaemia, headache and somnolence.

Patient outcomes were quantified as quality-adjusted life years (QALYs). The utility values used in this HTA submission are from Thokala et al. (2023) utilising a mapping algorithm of CKD-aP 5-D itch score to EQ-5D-3L and applying it to data from the KALM trial populations. Disutilities associated with adverse events were provided for the purpose of a scenario analysis but were not used in the base-case. Resource usage and costs considered in the model includes drug treatment costs, health state costs and adverse event costs. For the base case a discount rate of 4% was applied to both health outcomes and costs. The analysis was conducted from the perspective of the Health Service Executive (HSE).

A deterministic analysis of the cost-effectiveness of difelikefalin versus best supportive care was associated with incremental costs of €9,039 and an incremental quality adjusted life-year (QALY) of 0.15 resulting in a base case incremental cost-effectiveness ratio (ICER) of €60,151/QALY. Probabilistic analysis resulted in an ICER of €60,172/QALY which was similar to the deterministic ICER. The probability of difelikefalin being cost-effective at the €45,000/QALY threshold was 5.3%. A deterministic sensitivity analysis was also presented. The most important parameter that impacted the cost-effectiveness of difelikefalin versus best supportive care was the utility score for the 'none' CKD-aP health state.

4. Budget impact

The price to wholesaler for difelikefalin for a pack size of 12 is €498.59. When the Framework

Agreement rebate is included the total drug cost per pack is €456.21. The recommended dose of difelikefalin is 0.5 µg/kg dry body weight (the target weight post dialysis) and in calculating the annual cost of difelikefalin it is assumed that the average weight is 80.9 kg and one vial is administered three times weekly. The annual cost of difelikefalin was estimated at €5,930.73 per patient. The five year gross drug budget impact for difelikefalin, at list price, was estimated at €3,767,469. This was calculated taking into consideration the predicted market share and assuming that 45.3% of patients discontinue difelikefalin after 12 weeks of treatment. The NCPE Review Group consider this an underestimate. If all eligible patients were treated with difelikefalin (234 in year 1 increasing to 406 in year 5) the five year gross budget impact is estimated at €11,778,714.

5. Patient Organisation Submission. No patient organisation submissions were received during the course of the assessment.

6. Conclusion

This assessment demonstrates that difelikefalin is not cost-effective for the treatment of moderate to severe pruritis associated with chronic kidney disease in adult patients on haemodialysis. The NCPE recommends that difelikefalin be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.