CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Difelikefalin (Korsuva)

Indication: For the treatment of moderate to severe pruritus associated with chronic kidney disease in adult patients on hemodialysis.

Sponsor: Otsuka Canada Pharmaceutical Inc.

Recommendation: Do Not Reimburse

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that difelikefalin not be reimbursed for the treatment of moderate to severe pruritus associated with chronic kidney disease (CKD-aP) in adult patients on hemodialysis (HD).

Rationale for the Recommendation

Overall, CDEC concluded that the evidence considered did not demonstrate a clinically meaningful therapeutic benefit of difelikefalin over placebo for the treatment of patients with CKD-aP in Canada as the magnitude of the difference in pruritis observed in the trials is associated with considerable uncertainty. Two randomized controlled trials (RCTs) in patients with moderate to severe CKD-aP on HD (KALM-1, N = 378 and KALM-2, N = 471) evaluated the effect of difelikefalin on pruritis as measured by the Worst Itching Intensity Numerical Rating Scale (WI-NRS) score from baseline to week 12 versus placebo. In these trials, treatment with difelikefalin was associated with statistically significant improvements in pruritus based on an improvement by at least 3 points on the WI-NRS, with 50% to 52% of patients in the difelikefalin groups and 31% to 37% of patients in the placebo groups reporting at least a 3-point improvement on the WI-NRS at week 12. However, a 4-point improvement in the WI-NRS scale is considered a clinically meaningful measurement of improvement in pruritus in clinical practice. The proportion of patients with a 4-point improvement on the WI-NRS was 38% to 41% of patients in the difelikefalin groups and 21% to 25% in the placebo groups. The results of the assessments based on a 3-point improvement and the 4-point improvement were in favour of difelikefalin in both trials, but also associated with a high placebo response. The high placebo response observed in the trials may be due to optimization of HD and permitted use of concomitant therapies (including antihistamines, corticosteroids, and gabapentin), resulting in uncertainty of the magnitude of benefit that can be attributed to difelikefalin.

Patients identified a need for new treatments for moderate to severe CKD-aP to improve quality of life and treatment efficacy. It is unclear whether difelikefalin meets these needs as the magnitude of clinical benefit is uncertain. Further, it is uncertain whether difelikefalin improves health-related quality of life (HRQoL) due to conflicting results in the KALM trials. Patients also identified a need for treatments that would reduce hospital visits, the amount of overall medication required, sleep quality and disturbance, and side effects, though evidence to support a benefit of difelikefalin with regards to these needs was not identified.

Discussion Points

- CDEC acknowledged that pruritus is a common issue among patients with CKD on HD that impacts HRQoL as reflected in the patient group input. CDEC discussed the available data on the Skindex-10 total score and 5-D Itch Scale total score, which were both included as secondary endpoints included in the statistical testing hierarchy in the KALM trials. A benefit in HRQoL based on the Skindex-10 and 5-D Itch was demonstrated in KALM-1, but a benefit was not demonstrated based on these outcomes in KALM-2. The conflicting results between the trials lead to uncertainty regarding an improvement in HRQoL associated with difelikefalin.
- The efficacy results of the KALM trials were based on a 3-point improvement on the WI-NRS scale. Although this may be considered acceptable from a clinical trial perspective, clinical experts indicated that a 4-point improvement would be considered more appropriate and would be considered a meaningful improvement in pruritus in clinical practice; this is aligned with recommendations by the FDA.
- Concomitant medications were permitted in the trials, but a direct and systematic comparison to treatments used as part of usual care was not available and represents a gap in the evidence. CDEC discussed the definition of standard of care for the treatment of CKD-aP. Based on stakeholder feedback and input from clinical experts consulted by CADTH, patients currently manage CKD-aP with a variety of off-label options such as antihistamines, corticosteroids, opioids, gabapentin, and pregabalin, all of which were permitted concomitant medications in the trials. The clinical experts consulted by CADTH indicated that the use of these treatments varies between practices and noted gabapentin as an example of a commonly used treatment in Canadian clinical practice; however, there is uncertainty regarding whether difelikefalin offers a benefit over usual care treatments based on the available evidence.
- CDEC discussed whether the magnitude of benefit observed with difelikefalin compared to placebo would be meaningful to patients and generalizable to clinical practice. The clinical experts noted that patients with moderate to severe CKD-aP tend to align with a baseline WI-NRS score of at least 8; however, patients enrolled in the trials had a mean baseline WI-NRS score of 7 that may indicate a population with less severe disease than what would be expected in clinical practice. This was identified as a potential generalizability issue as patients enrolled in the trials may represent a population more likely to respond to treatment.

Background

Chronic kidney disease (CKD) is a progressive disease characterized by gradual loss of renal function and/or abnormalities of renal structure over 3 months. CKD constitutes a major health burden worldwide and is associated with high morbidity and mortality. Chronic kidney disease–associated pruritus (CKD-aP), also known as uremic pruritus, is a common, distressing, and underrecognized systemic itch CKD comorbidity that affects more than 60% of patients undergoing hemodialysis, with 20 to 40% of patients reporting moderate-to-severe pruritus. Intense and generalized systemic itching in these patients is associated with poor sleep quality, depression, reduced quality of life, increased risk of infection, and an increased risk of death. In Canada, the estimated overall prevalence of CKD-aP in adult hemodialysis patients is about 70% according to the international observational Dialysis Outcomes and Practice Patterns Study. Among CKD hemodialysis patients, over one third experience moderate to severe itch. There are currently no standardized lab or diagnostic testing for the diagnosis of CKD-aP available. A complaint of pruritus in someone with a diagnosis of CKD is presumed CKD-aP unless assessment determines a different diagnosis.

There is no approved therapy for CKD-aP in Canada. The standard of care for moderate to severe pruritus associated with chronic kidney disease includes administration of topical use of moisturizing agents, steroids in combination with menthol and camphor, calcineurin inhibitors, systemic use of gabapentin or pregabalin, naltrexone, and thalidomide, biologics (i.e., dupilumab or tralokinumab) and kappa-opioid receptor agonists (i.e., difelikefalin), and phototherapy to reduce itch intensity and improve sleep quality.

Difelikefalin, a selective kappa-opioid receptor agonist, has been approved by Health Canada for the treatment of moderate to severe pruritus associated with chronic kidney disease in adult patients on hemodialysis. It is available as 50 mcg/mL intravenous solutions and the dosage recommended in the product monograph is 0.5 mcg/kg dry body weight (i.e., the target post-dialysis weight).

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 2 of double-blind RCTs in adult patients with moderate to severe pruritus associated with chronic kidney disease who are on hemodialysis
- Patient perspectives gathered by 1 patient group: The Kidney Foundation of Canada.
- Input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with chronic kidney disease–associated pruritus
- Input from 3 clinician groups, including Saskatchewan Kidney Doctors; Hemodialysis Specialty Physician Group- Division of Nephrology, the Ottawa Hospital; and Division of Nephrology, Department of Medicine, Dalhousie University/Nova Scotia Health.
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

One patient advocacy group, The Kidney Foundation of Canada, provided input for the treatment of adult hemodialysis patients with CKD. Patient input was gathered from independent surveys among people living with chronic kidney disease and their caregivers across Canada in September 2022. Total 19 responses were gathered from the survey (10 fully completed and 9 partially completed).

More than 90% patients from the survey reported experiencing itchy skin as part of their kidney disease, with 50% respondents experiencing itchiness every day, 40% several times per week, and 10% occasionally. While 60% respondents reported living with pruritus for 1-2 years, 20% said they'd been living with it for 2-5 years, and 20% over 5 years. The itchiness was described as

moderate to severe by 80% respondents. While describing disease experience, several respondents reported developing scabs and/or sores because of their itchy skin. Many respondents also reported having trouble sleeping as a result of itchiness. 33% patients from this survey reported taking medication to treat their itchiness associated with kidney disease. While 33% respondents reported treatments being covered by their provincial drug plan, 67% reported paying out of pocket. Most respondents from this survey expressed satisfaction with their current medication/combination of treatments, with 33% being neither satisfied nor unsatisfied. On the other hand, over 66% respondents expressed uncertainty regarding the improvement of their skin appearance from currently available treatment.

While describing their expectations for CKD therapies in general, patients from the survey mentioned about improvement in their well-being or quality of life (QoL), with 90% respondents hoping for increased energy. In addition, fewer hospital visits, less medication overall, and side effects and efficacy were other important considerations. None of the respondents had experience with the drug under review.

Clinician input

Input from clinical experts consulted by CADTH

According to the clinical experts consulted by CADTH, treatment for moderate to severe pruritus associated with chronic kidney disease includes administration of topical use of moisturizing agents, steroids in combination with menthol and camphor, and calcineurin inhibitors, systemic use of gabapentin or pregabalin, naltrexone, and thalidomide, biologics (i.e., dupilumab or tralokinumab) and K-opioid receptor agonists (i.e., difelikefalin), and phototherapy to reduce itch intensity and improve sleep quality. The clinical experts stated that the goal of treatment is to reduce of itch intensity, improve QoL and sleep quality, and decrease itch-related depression and in some cases, suicidality. They also stated indicated that currently used off-label treatments do not adequately address these issues in all patients.

The clinical experts indicated that difelikefalin is a selective kappa-opioid receptor agonist which acts in the peripheral nervous system, and thus the drug has less neuromodulation effects compared with non-selective kappa-opioid receptor agonist. Difelikefalin is the first treatment approved in Canada for moderate to severe pruritus in patients on hemodialysis, although the clinical experts consulted by CADTH were uncertain about whether the drug would address the underlying disease process that causes pruritus as the etiology of CKD-aP is not yet fully understood. The clinical experts indicated that difelikefalin would be used in combination with other therapies in a later-line setting where existing therapies are intolerable or have failed to control symptoms or contraindicated. The clinical experts stated that the prior lines of therapy include menthol containing topical steroid and/or topical calcineurin inhibitor, systemic agent (gabapentin or naltrexone), and phototherapy. The clinical experts did not expect that difelikefalin would replace any treatments or cause a shift in the current treatment paradigm but instead be used after other more accessible topical and systemic treatment options have failed.

The clinical experts indicated that only patients with end-stage renal disease on hemodialysis with a moderate-severe pruritus who are not responsive to existing therapies would be candidates for treatment with difelikefalin. According to the clinical experts, the drug is not suitable for patients on peritoneal dialysis, with non-dialysis CKD or received kidney transplant.

The clinical experts stated that clinical evaluations, such as the itch numeric rating scale, can help identify pruritus severity at baseline and assess response to treatment but they are not typically used in clinical practice. The clinical expert indicated that it is important to consider other causes of pruritus in patients such as dermatologic conditions, chronic kidney disease mineral bone disease, hepatobiliary disorders, diabetes, and hematologic conditions, as patients with these conditions may not respond to difelikefalin. Further, the clinical experts mentioned that it is possible misdiagnosis of the cause of pruritus may occur in clinical practice due to various potential causes of pruritus as well as the lack of unique laboratory findings associated with CKD-aP.

The clinical experts consulted by CADTH indicated that in clinical practice, subjective patient-reported improvement in symptoms is the primary outcome used to determine whether a patient is responding to treatment. The clinical experts highlighted that reductions in the frequency and/or severity of symptoms would be considered when evaluating response to treatment along with other improvements in sleep quality, depression, adherence to dialysis, depression and suicidality, and overall QoL. The clinical experts consulted by CADTH stated that a patient may discontinue treatment if there is a lack of response and that this could be assessed at

12 weeks. The development of significant and persistent side effects such as diarrhea, dizziness and recalcitrant nausea/vomiting may also be cause for discontinuing treatment.

According to the clinical experts consulted by CADTH, difelikefalin would most be prescribed in dialysis units or clinics setting by nephrologists or other physicians.

Clinician group input

Clinician group input on the review of difelikefalin for the treatment of moderate to severe pruritus associated with CKD in adults on hemodialysis was received from 3 clinician groups: Saskatchewan Kidney Doctors; Hemodialysis Specialty Physician Group- Division of Nephrology, The Ottawa Hospital; and Division of Nephrology, Department of Medicine, Dalhousie University/Nova Scotia Health.

The clinician groups agreed that currently only “off-label” medications in Canada are available for treatment of pruritus in patients with kidney disease. There have been some unmet needs as current treatment options are unsatisfactory and not effective to help reduce the symptom burden. The debilitating symptoms in most severe cases may lead to deterioration in QoL. The clinician groups mentioned about the need for a new treatment option that may help relieve symptoms with a better tolerability, affordability, and ease to administer. One clinician group particularly indicated that the most important treatment goals would be to have a therapy that would reduce or maintain the severity of itch below a threshold of clinical importance that is known to be the level above which itch negatively impacts QoL and outcomes important to patients.

The clinician groups mentioned that difelikefalin may cause a paradigm shift in the treatment of itching, with data from RCTs and pooled analysis demonstrating objective effectiveness in reducing the severity of the symptoms of CKD associated (uremic) pruritus. Input from clinician groups suggested differing opinions about the place in therapy for difelikefalin. Some groups suggested it would likely be used as first-line therapy, while others recommended this as an add on or second-line treatment. Given the route of administration of difelikefalin, the clinician groups pointed out that hemodialysis patients with moderate to severe pruritus would benefit the most from this treatment. The clinician groups mentioned about the possibility of underreporting or underdiagnosis of CKD associated pruritus, which was also pointed out by the clinical experts consulted by CADTH. Regarding the diagnosis of this indication, the clinician groups indicated about the lack of diagnostic tests. While one group mentioned about using clinical history and exclusion criteria to identify patients, other groups pointed out that the identification of patients and severity of symptoms can be done through self-administered questionnaires and screening tools, e.g., 5-D itch scale, UP-Dial, Skindex-10 etc. The clinician groups stated that the reduction in itch severity measured on a numerical rating scale is used to evaluate symptom assessment. According to the clinician groups, lack of a clinical meaningful response as well as intolerable side effects should be considered as discontinuation criteria. The clinician groups added that a meaningful response to treatment for this disease would be symptom reduction leading to better sleep, improved QoL, improved mood, and return to activities of daily living.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for difelikefalin:

- Considerations for relevant comparator
- Considerations for initiation of therapy
- Considerations for prescribing of therapy
- Considerations for care provision issues
- Considerations for system and economic issues

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

KALM-1 and KALM-2 studies met the inclusion criteria for the CADTH systematic review. Both KALM trials were designed as multicenter, randomized, double-blind phase 3 clinical trials which compared difelikefalin to placebo in patients being treated with hemodialysis who were suffering from moderate to severe pruritus. The primary objective for both KALM trials was to evaluate the efficacy of difelikefalin at a dose of 0.5 mcg/kg compared with placebo in reducing the intensity of itch in patients undergoing hemodialysis and experiencing moderate-to-severe pruritus. The shared key secondary objectives for KALM-1 and KALM-2 were to evaluate the efficacy of difelikefalin at a dose of 0.5 mcg/kg compared with placebo in improving itch-related QoL and safety in hemodialysis patients experiencing moderate-to-severe pruritus. A total of 378 patients in KALM-1 and 473 patients in KALM-2 were randomized at a 1:1 ratio treatment to treatment with difelikefalin or placebo. KALM-1 was limited to study centres in the US and KALM-2 was conducted globally including 5 sites in Canada. For both KALM trials, the randomization was stratified based on the use of concomitant medications to treat their itch during the week before randomization (Yes/No), specific medical conditions such as history of fall or fracture or fall-related fracture, confusional state or mental status change or altered mental status or disorientation, and gait disturbance or movement disorder (Presence/ Absence).

The primary efficacy endpoint in KALM-1 and KALM-2 was the percentage of patients at week 12 who achieved a ≥3-point improvement from baseline in the weekly mean score on the daily WI-NRS. Key secondary efficacy endpoints for both trials were: mean change from baseline at week 12 in itch-related QoL (as measured by the 5-D itch scale total score), mean change from baseline at week 12 in itch-related QoL (as measured by the Skindex-10 scale total score), and the percentage of patients at week 12 achieving a ≥4-point improvement from baseline in the weekly mean score of the daily WI-NRS. In addition, the proportions of patients who achieved a ≥3-point improvement or ≥4-point improvement from baseline at week 4 and week 8 were considered as secondary endpoints for KALM-2.

The baseline patient characteristics were roughly balanced between treatment groups. The median age of all randomized patients was similar between the studies with 58.0 years (range 22 to 88 years) in KALM-1 and 60.0 years (range 23 to 87 years) in KALM-2. Most of the patients in each of the included studies were male (61.0% and 58.2%). The predominant races were White (48.8% and 70.3%) and black or African American (41.6% and 19.3% for KALM-1 and KALM-2). The median prescription dry body weight was 84.0 kg ranged from 42.0 to 135.0 kg in KALM-1 and 78.0 kg ranged from 42.0 to 135.0 kg in KALM-2. The median baseline WI-NRS score was 7.14 (range 4.1 to 10.0) in KALM-1 and 7.13 (range 4.5 to 10.0) in KALM-2. At baseline, 39.8% in KALM-1 and 36.5% in KALM-2 of patients were using anti-itch medications, and 14.1% and 16.6% reported at least 1 of the specified medical conditions (i.e., history of fall or fracture or fall-related fracture, confusional state or mental status change or altered mental status or disorientation, gait disturbance or movement disorder), respectively. The median duration of CKD-aP for all patients was 2.5 years (range 0.1 to 26.5 years) in KALM-1 and 2.3 years (range 0.0 to 58.4 years) in KALM-2.The median time intervals since the diagnosis of chronic kidney disease (CKD) and end-stage renal disease (ESRD) for all subjects were 5.45 years (range 0.3 to 42.9 years) and 3.92 years (range 0.3 to 28.7 years) in KALM-1, and 7.53 years (range 0.3 to 48.3 years) and 4.03 years (range 0.3 to 30.2 years) in KALM-2.

Efficacy Results

No evidence was identified in the KALM trials for mood, days of missed work, days of missed school, and days of missed dialysis, which were identified in the CADTH systematic review protocol and considered as important outcomes of interest by patients and clinicians.

Pruritus Severity

Worst Itching Intensity Numerical Rating Scale (WI-NRS)

The severity of pruritus was assessed in both KALM-1 and KALM-2 using the Worst Itching Intensity Numerical Rating Scale (WI-NRS).The primary and key secondary endpoint in both trials was the proportion of patients with at least a 3-point improvement in the

WI-NRS score from baseline to Week 12, and the proportion of patients with at least a 4-point improvement in the WI-NRS score from baseline to Week 12, respectively.

At Week 12, in KALM-1, 52% and 31% of patients randomized to difelikefalin and placebo, respectively, had a WI-NRS score that improved by at least 3 points from baseline to Week 12. This corresponded to an odds ratio of 2.72 [95% Confidence Interval (CI): 1.72 to 4.30; P < 0.001] in favour of difelikefalin. In KALM-2, 50% and 37% of patients randomized to difelikefalin and placebo, respectively, had a WI-NRS score that improved by at least 3 points from baseline to Week 12. This corresponded to an odds ratio of 1.61 (95% CI: 1.08 to 2.41; P = 0.02) in favour of difelikefalin. A 3-point improvement on WI-NRS has been validated as an appropriate threshold specifically for CKD-aP patients in an assessment of the psychometric properties published by the sponsor that was based on data from a phase II study (CR845-CLIN2101, NCT02858726) and KALM-1 and KALM-2. However, the FDA report states that, "in several communications to the sponsor the Agency recommended the primary efficacy endpoint to be the proportion of subjects achieving at least a 4-point improvement in WI-NRS score from baseline to Week 12." The clinical experts consulted by CADTH were aligned with the FDA guidance regarding a 4-point improvement, but input from clinician groups suggested preference for a 3-point improvement. In summary, there is uncertainty regarding the most appropriate MID for the WI-NRS score; therefore, results for an assessment of both outcomes have been presented. With regards to the proportion of patients achieving a ≥4-point improvement from baseline to Week 12 with respect to the weekly mean of the daily 24-hour WI-NRS, 41% and 21% of patients randomized to difelikefalin and placebo in KALM-1, and 38% and 25% of patients randomized to difelikefalin and placebo in KALM-2, respectively, had a WI-NRS score that improved by at least 4 points from baseline to Week 12. This corresponded to an odds ratio of 2.89 (95% CI: 1.75 to 4.76; P < 0.001) in KALM-1, and 1.77 (95% CI: 1.14 to 2.74; P = 0.01) in KALM-2 in favour of difelikefalin. Overall, difelikefalin demonstrated an improvement in the WI-NRS that was clinically meaningful based on both of the reported assessments of the 3- and 4- point improvement in the WI-NRS.

The supportive analyses performed for the primary endpoint in KALM-1 and KALM-2 was conducted using the Per Protocol (PP) population. The results were consistent with the primary analysis. Similarly, the sensitivity analyses for the primary endpoint conducted using the intention-to-treat (ITT) population showed efficacy with difelikefalin were consistent with the efficacy shown in the primary efficacy analysis.

The proportion of patients with at least a 3-point and 4-point improvement from baseline in the WI-NRS was also reported at Week 4 and Week 8 in both trials. In KALM-1, the proportion of patients with ≥3- and ≥4-point improvement from baseline in WI-NRS at Week 8 and Week 4 were considered exploratory but in KALM-2, they were included as key secondary endpoints. In KALM-2, a benefit from treatment with difelikefalin was also observed at Week 4 (35% vs.22% for difelikefalin vs. placebo) and Week 8 (45% vs. 33% for difelikefalin vs. placebo) for the proportion of patients with at least a 3-point improvement from baseline in the WI-NRS. Similar results were observed in KALM-1 (Week 4: 33% vs.18% for difelikefalin vs. placebo; Week 8: 43% vs.28% for difelikefalin vs. placebo). Similarly, with regards to the proportion of patients with at least a 4-point improvement from baseline, in KALM-2, a benefit from treatment with difelikefalin was observed at Week 4 (20% vs.13% for difelikefalin vs. placebo) and Week 8 (31% vs. 20% for difelikefalin vs. placebo). Similar results were observed in KALM-1 (Week 4: 18% vs. 8% for difelikefalin vs. placebo; Week 8: 31% vs.20% for difelikefalin vs. placebo). In the KALM trials, data for the primary and secondary/other outcomes were reported up to 12 weeks. According to the clinical experts consulted by CADTH, patients with CKD-aP would receive the difelikefalin treatment beyond 12 weeks for the desired treatment effect. A pooled analysis of 2 open-label extension studies of KALM-1 and KALM-2 assessed the 5-D Itch scale for 52 weeks following the 12-week pivotal trials and reported that the proportion of patients achieving a ≥5-point improvement (reduction) was maintained up to 64 weeks.[17] Due to the amount of missing data, the lack of reporting for other outcome measures (i.e., WI-NRS and Skindex-10), and the absence of a control group after Week 12, it is difficult to draw conclusion on whether the efficacy of difelikefalin beyond 12 weeks would be consistent with the result at Week 12.

Patient Global Impression of Change

Week 12, in KALM-1, [redacted] of patients randomized to difelikefalin and placebo, respectively, were complete responders. This corresponded to an odds ratio [redacted] In KALM-2, [redacted] of patients randomized to difelikefalin and placebo, respectively, were complete responders. This corresponded to an odds ratio of [redacted]. Of note, the P values were not adjusted for multiple testing.

Health-related quality of life (HRQoL)

Health-related quality of life was assessed in both KALM-1 and KALM-2 using the Skindex-10 Scale Score and 5-D Itch Scale Score. The change from baseline to week 12 in the Skindex-10 Scale total score and the 5-D Itch Scale score were included as key secondary endpoints in both of the trials.

Skindex-10 Scale total

Skindex-10 is a modified version containing 10 questions to evaluate CKD-associated pruritus and quality of life with relevant subdomains for patients in the hemodialysis setting with higher scores indicating more bothered and lower scores indicating less bothered. At the end of Week 12, the LS mean change(reduction) in total Skindex-10 Scale score was –17.2 vs. –12.0 for difelikefalin vs. placebo in KALM-1, –16.6 vs. –14.8 for difelikefalin vs. placebo in KALM-2. In KALM-1, the difference in LS mean change(reduction) from baseline to Week 12 for Skindex-10 Scale total score between the difelikefalin and placebo groups was –5.1 points (95% CI, –8.0 to –2.3 points, P <0.001). In KALM-2, the results for the change from baseline to Week 12 in the total Skindex-10 score indicated no difference between treatment groups (LS mean difference = –1.8 points; 95% CI, –4.3 to 0.8 points; P = 0.171). A 3- to 12-point change on the Skindex-10 was identified as a clinically meaningful change in patients on hemodialysis with moderate to severe CKD-aP. Therefore, the reported within-group differences in Skindex-10 were clinically meaningful as they met the MID identified by the literature search conducted by CADTH. With regards to the Skindex-10 domain scores, the results were in favour of difelikefalin, however, there was no adjustment for multiplicity, thus definitive conclusions could not be drawn with respect to the individual domains of Skindex-10 scale: disease total, mood/emotional distress total, and social functioning total. No long-term data reported in the KALM trials for the Skindex-10 Scale.

5-D Itch Scale Score total

5-D Itch Scale is a questionnaire assessing CKD-associated pruritus and quality of life with relevant subdomains for patients in the hemodialysis setting with higher scores indicating more bothered and lower scores indicating less bothered. At the end of Week 12, the LS mean change in total 5-D Itch Scale score was greater in the difelikefalin group than in the placebo group for both KALM trials (–5.0 vs. –3.7 for difelikefalin vs. placebo in KALM-1, –4.9 vs. –3.8 for difelikefalin vs. placebo in KALM-2), indicating the difelikefalin group had a greater improvement (reduction) than the placebo group. Overall, the difference in LS mean change from baseline to Week 12 for 5-D Itch Scale total score between the difelikefalin and placebo groups was –1.3 points (95% CI, –2.0 to –0.5 points, P <0.001) in KALM-1 and –1.1 points (95% CI, –1.7 to –0.4 points; P = 0.002) in KALM-2. Of note, the analysis of the difference in LS means for 5-D Itch at Week 12 for KALM-2 was at risk for type I error as the preceding in the testing hierarchy (i.e., difference in LS means for Skindex-10 at Week 12 for KALM-2) was not statistically significant. In addition, no published MID was identified for 5-D Itch in patients with CKD-aP. Therefore, it is unclear whether the reported within-group differences are clinically meaningful. No long-term data reported in the KALM trials for the 5-D Itch Scale.

Harms Results

The percentage of patients with any reported treatment-emergent adverse events (TEAE) in the difelikefalin group was comparable to the placebo group: 68.8% vs. 62.2% for difelikefalin vs. placebo in KALM-1, and 68.1% vs. 61.4% for difelikefalin vs. placebo in KALM-2. In KALM-1, the most common TEAEs reported for patients randomized to difelikefalin and placebo, respectively, were diarrhea (9.5% vs. 3.7%), dizziness (6.9% vs. 1.1%), vomiting(5.3% vs. 3.2%), and nasopharyngitis (3.2% vs. 5.3%). Diarrhea, dizziness, and vomiting were reported more commonly in the difelikefalin treatment group than the placebo treatment group in KALM-1. In KALM-2, the most common TEAEs reported for patients randomized to difelikefalin and placebo, respectively, were diarrhea (8.1% vs. 5.5%), vomiting(6.4% vs. 5.9%), fall(6.8% vs. 5.1%), dizziness(5.5% vs. 5.1%), and nausea (6.4% vs. 4.2% for), all of which were reported more frequently in the difelikefalin treatment group. Serious adverse events (SAEs) were reported in 25.9% of patients in the difelikefalin group and 21.8% of patients in the placebo group in KALM-1, and 24.7% for difelikefalin and 21.6% for placebo in KALM-2. The clinical experts stated that the proportion of patients reporting a SAE was consistent with what would be expected given the characteristics of patients that were enrolled in these studies. Specific SAEs reported in the trials included SAE due to hyperkalemia, sepsis, pneumonia, fluid overload, and chest pain, all of which were infrequently reported, having occurred in less than 4% of patients in any treatment group.

The proportion of patients who discontinued treatment due to TEAEs was 7.9% for difelikefalin and 4.8% for placebo in KALM-1, 5.5% for difelikefalin and 3.4% for placebo in KALM-2. Dizziness was the most frequently reported TEAE that caused discontinuation for both KALM trials. Deaths were reported in 1.1% of patients in the difelikefalin group and 1.6 % of patients in the placebo group in KALM-1, and 0.9% for difelikefalin and 0.8% for placebo for in KALM-2. In KALM-1, sepsis was the cause of death for 2 patients randomized to difelikefalin (0 patients randomized to placebo and 0 patients in KALM-2), and septic shock was the cause of death for 2 patients randomized to placebo (0 for difelikefalin and 0 patients in KALM-2). All other reported causes of death (dyspnoea/hypotension, cardiac arrest, unknown) were infrequently reported, with no more than 1 patient in any treatment group. No specific AE was identified to account for the majority of deaths in either group for KALM-2.

The following harms of particular interest were included in the CADTH systematic review protocol: diarrhea, nausea, vomiting, gait disturbance, fall, dizziness, headache, somnolence, seizures, syncope, mental status changes, mood changes, paresthesia (unusual feeling/sensation), hyperkalemia, back pain, tachycardia, and palpitation. The most common notable harms were diarrhea, dizziness, and vomiting for both KALM trials, as well as fall and nausea reported in KALM-2. Overall, during the 12-week treatment period of KALM-1 and KALM-2, patients who received difelikefalin reported notable harms at a similar or slightly higher frequency than patients who received placebo. There were imbalances in the proportion of patients reporting diarrhea (9.5% vs. 3.7% for difelikefalin vs. placebo) and dizziness (6.9% vs. 1.1% for difelikefalin vs. placebo) as an AE in KALM-1.

Critical Appraisal

The overall study design of KALM-1 and KALM-2 was appropriate for the objectives of the study. There was no particular concern with the methods of randomization and allocation concealment. According to the clinical experts consulted by CADTH, the frequency of hemodialysis (i.e., optimization of hemodialysis) is a potential effect modifier and prognostic factor that were not considered in both KALM trials. Patients with more frequent hemodialysis visits would have better control of the disease and more exposure to difelikefalin compared with patients who had less frequent hemodialysis visits. In addition, more frequent hemodialysis visits indicated better compliance to the difelikefalin treatment. Therefore, the frequency of hemodialysis may have potential impact on the validity of the study results for the treatment effect of difelikefalin, however, the magnitude of the impact is unknown as there were no data with regards to the treatment effect in patients with different frequencies of hemodialysis for both KALM trials. The 3-point reduction in WI-NRS scores was adopted in both KALM studies as the cutoff point to define improvement and response of treatment in pruritus intensity based on the results of a phase II study of difelikefalin (CR845-CLIN2101, NCT02858726) and 2 phase III trials (KALM-1 and KALM-2) conducted by the sponsor. The Food and Drug Administration (FDA) recommended the use of at least 4 points in improvement as the cutoff for primary efficacy endpoint (i.e., proportion of patients with a ≥4-point improvement in WI-NRS at Week 12). Overall, although odds ratios at Week 12 were similar based on the 3-point and 4-point cutoff, the proportion of patients in each treatment group that met the threshold was higher based on the 3-point threshold, which was used for the primary endpoint. It is worth mentioning that odds ratios were used throughout the KALM trials for the primary and key secondary endpoints and that odds ratios tend to give an inflated impression of the treatment effects compared with relative risks. Therefore, the results of the treatment effect of difelikefalin compared to placebo estimated using odds ratios should be interpreted with caution. While there were a large proportion of patients who had at least one major protocol deviation (around 30%) in both studies, the sensitivity and supplemental analyses were consistent with the primary estimand. In addition, a notable response was also observed in the placebo treatment groups in both KALM trials, albeit not as great as difelikefalin. According to the clinical experts consulted by CADTH, the placebo response may be due to optimized hemodialysis treatment associated with the trials as patients who were enrolled in the trials tend to attend their hemodialysis more frequently and regularly, which would provide a benefit to these patients. The CADTH review team considered the placebo effect is also a contributing factor for the response in the placebo group, however, the extent to which the placebo effect influenced the results is unclear.

In terms of generalizability of the pivotal KALM studies, pruritus severity was measured using WI-NRS and Patient Global Impression of Change and HRQoL was measured using Skindex-10 and 5-D Itch. However, the experts consulted by CADTH stated that these outcome measures are not routinely used in clinical practice to assess itch intensity and HRQoL in patients. Therefore, there is uncertainty about how the changes in pruritus severity measured by WI-NRS and Patient Global Impression of Change, and HRQoL measured by Skindex-10 and 5-D Itch translate to clinical practice. A limitation to note is that the studies included patients with better hemodialysis adherence and less pruritus severity compared to patients in clinical practice in Canada as per feedback from the clinical experts consulted by CADTH. The clinical experts for this review also indicated that the patients in KALM-1 and KALM-2 had better adherence to hemodialysis compared with Canadian clinical practice. As such, the generalizability of efficacy outcomes may

be overestimated and safety outcomes may be underestimated. In addition, the baseline median WI-NRS score was around 7 for both KALM trials (7.14 for KALM-1 and 7.13 for KALM-2), the clinical experts consulted by CADTH indicated the patients with CKA-aP would have a worse itch intensity (with a numerical rating scale greater than 8) in dermatology clinical practice in Canada. Overall, the selection of patients with better hemodialysis adherence and less severe pruritus (based on the WI-NRS scale) may limit the applicability of the study results to the patient population in Canada, and introduce selection bias, which may lead to uncertainty in the efficacy results. In the KALM trial, data for the primary and secondary/other outcomes were reported up to 12 weeks. According to the clinical expert, patients with CKD-ap would receive the difelikefalin treatment beyond 12 weeks for the desired treatment effect. While a reduction in symptoms of CKD-aP may be observed within 12 weeks of treatment, it is uncertain whether the treatment effect as well as safety of difelikefalin beyond 12 weeks would be consistent with the result at Week 12.

Indirect Comparisons

No indirect evidence was identified for this review.

Other Relevant Evidence

Additional safety data for an open-label, phase 3 CR845-CLIN3101 study for up to 52 weeks was summarized in this report.

Description of CR845-CLIN3101

One open-label, multicenter, phase 3 study (CR845-CLIN3101 study) that evaluated the long-term safety of difelikefalin at a dose of 0.5 mcg/kg administered for up to 52 weeks was included as other relevant evidence to address a gap in long-term safety of difelikefalin for this review.

The long-term safety study included patients received who participated in the phase 2 studies for difelikefalin (CR845-CLIN2005 or CR845-CLIN2101). The long-term safety study also included “de novo patients” with moderate-to-severe CKD-aP undergoing hemodialysis who had not been previously exposed to difelikefalin and had not participated in the phase 2 studies for difelikefalin. The open-label phase 3 study consisted of a screening visit, a 52-week treatment period, an end of treatment (EOT) visit, and a follow-up visit after 7-10 of EOT. Patients received difelikefalin at a dose of 0.5 mcg/kg after each dialysis session, 3 times per week for up to 52 weeks, meaning a total of approximately 156 doses of study drug. All scheduled study visits were conducted on dialysis days during the treatment period. The last dose was administered at the last dialysis visit on week 52, at or early termination (ET). The EOT visit was conducted at the dialysis visit following the last dose. A final safety follow-up was conducted 7-10 days after the EOT or ET visit. In the long-term safety study, AEs, SAEs, WDAEs, and deaths were reported descriptively for each of the three treatment groups.

Efficacy Results

No efficacy results were evaluated in the open-label phase 3 study.

Harms Results

In the open-label phase 3 study, 80.0%, 88.5% and 82.5% patients experienced at least 1 AE in the placebo and difelikefalin group in the previous study, and de novo group in the open-label study, respectively. The most common adverse events were (frequency ≥ 5%) were nausea, diarrhea, fall, vomiting, hypotension, non-cardiac chest pain, hyperkalaemia, dizziness, abdominal pain, fluid overload, pneumonia, dyspnoea, acute myocardial infarction, pain in extremity, arthralgia, and asthenia. Portion of patients with at least one serious AEs were 56.7%, 61.5% and 48.1% in the placebo and difelikefalin group in the previous study, and de novo group in the open-label study, respectively. The most common SAEs (>4%) among patients were acute myocardial infarction, angina pectoris, gastrointestinal haemorrhage, pneumonia, cellulitis, fluid overload, hyperkalaemia, respiratory failure, pulmonary oedema, and hypotension. A total of 35 patients discontinued study drug due to AEs, the proportion being 20.0%, 15.4% and 10.2% in the placebo and difelikefalin group in the previous study, and de novo group in the open-label study, respectively. Total 16 deaths occurred during the study, with the proportion of 6.7%, 7.7% and 4.9% in the placebo and difelikefalin group in the previous study, and de novo group in the open-label study, respectively.

Critical Appraisal

The objective of the open-label phase 3 study was to evaluate long-term safety of difelikefalin, administered intravenously after each dialysis session for up to 52 weeks. Since the results for the open-label phase 3 trial were only reported descriptively, the interpretation should be taken with caution. Discontinuation rates were high in all 3 treatment groups. One of the issues with discontinuation from an open-label study, particularly when patients discontinue due to AEs, is that the summary of harms may underestimate the frequency of AEs because those who remained in the study are more likely to have responded well to treatment. Overall, the high discontinuation rates as well as the descriptive nature of analysis introduce uncertainty in the long-term safety results. The lack of comparative evidence made it difficult to interpret the safety results.

Although the patient population in the open-label study is different than the KALM-1 and KALM-2 populations, the external validity points related to demographics factors from the main report could be applicable to this study population. While the 0.5 mcg/kg dose is consistent with HC approved dose, the duration of the open-label phase 3 trial (up to 52 weeks) is more than the pivotal KALM-1 and KALM-2 trials (12 weeks). Since it is expected that patients would receive this treatment beyond 12 weeks, the safety results of this open-label phase 3 study may be generalizable to this time frame to an extent, but not completely, as the rates of AEs are expected to increase with higher treatment time.

Summary of Pooled Analysis of OLE of KALM-1 and KALM-2 by Topf, et al. (2022)

A pooled analysis of 2 open-label extension studies of KALM-1 and KALM-2 assessed the 5-D Itch scale for 52 weeks following the 12-week pivotal trials.[17] The study reported the proportion of patients achieving a ≥5-point reduction in the 5-D Itch scale was maintained up to 52 weeks in the open-label phase of KALM-1 and KALM-2.However, there was some uncertainty in the reported long-term treatment effect due to the amount of missing data, with 26.5% (189 out of 712) of patients in the pooled analysis population contributing data at week 52 in the open-label extension phase. In addition, it is difficult to discern much about the long-term efficacy of difelikefalin due to a lack of reporting other outcomes (i.e., WI-NRS and Skindex-10) and the absence of a control group.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Moderate to severe pruritus associated with chronic kidney disease in adult patients on hemodialysis
Treatment	Difelikefalin added to Best Supportive Care (BSC)
Dose Regimen	0.5 mcg/kg dry bodyweight (i.e., target post-dialysis weight) 3 times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the hemodialysis treatment or after rinse-back
Submitted Price	Difelikefalin, 100 mcg vial (2 mL): $27.00 per single-use vial
Treatment Cost	Assuming a patient weight of 85.5 kg and no vial sharing, annual cost of treatment is expected to be $4,212 per patient
Comparators	BSC alone - includes topical therapies, antihistamines, gabapentinoids (i.e., gabapentin or pregabalin), antidepressants, and/or ultraviolet type B phototherapy
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life years (QALYs) and life years (LYs)
Time horizon	Lifetime (10 years)
Key data source	KALM-1 and KALM-2 trials
Key limitations	• The sponsor assumed a mortality benefit associated with pruritus improvement. There is no substantive evidence that treatment of pruritus results in a mortality benefit and this assumption runs counter to CADTH clinical expert opinion. • The model assumed that treatment that improves pruritus would reduce all cause hospitalization. There is no substantive evidence that treatment of pruritus results in reduced all cause hospitalization and this assumption runs counter to CADTH clinical expert opinion. • The model assumed greater frequency of primary care visits among patients with a higher severity of pruritus. The care of patients receiving hemodialysis in Canada is provided by nephrologists who manage kidney disease-related symptoms, including pruritus. As such, no change is expected with primary care visits. • The model assumed phototherapy would be part of BSC costs. However, phototherapy was not used in the KALM trials that informed comparative treatment efficacy within the model. The inclusion of phototherapy costs might overestimate BSC costs. • Mapping of WI-NRS to EQ-5D to derive preference-based utilities is uncertain and did not account for all confounders; modelled QALY benefits with difelikefalin are uncertain. • The model assumed difelikefalin would be discontinued at 12 weeks in patients who did not move to the 'mild' or 'no' pruritus health state (from a baseline of 'moderate' or 'severe' pruritus). The rating scale to classify pruritus within the trial is not used in clinical management. Clinicians may choose to continue treatment, according to clinical expert opinion obtained by CADTH, particularly in patients who achieve or remain with moderate disease.
CADTH reanalysis results	• Changes to derive a CADTH base case included: assuming no difference in mortality, hospitalization, or primary care visits by pruritus states and the exclusion of phototherapy from BSC costs.

Component	Description
	• In the CADTH base case, the ICER for difelikefalin + BSC compared to BSC alone was $582,515 per QALY (incremental costs = $16,500.82; incremental QALYs = 0.03). • Scenario analyses that considered smaller QoL gains with difelikefalin due to decreasing mapped pruritus related health-state utility values, or continuation of treatment with difelikefalin in patients who may have improvement but still have 'moderate' pruritus lead to ICERs of ~$1M per QALY • To achieve a mean ICER of $50,000 per QALY with the CADTH base case, a price reduction of at least 92% is required for difelikefalin. This is due to the small QALY gains with difelikefalin, and may be underestimated should the HRQoL increments between health states be smaller, or should more patients continue on difelikefalin than assumed in the base case.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life-year; QoL = quality of life.

Budget Impact

CADTH identified the following limitations with the sponsor's analysis: the market uptake of difelikefalin in the new drug scenario is likely underestimated; the estimated population size is uncertain as the proportion of patients assumed to have moderate to severe CKD-aP is unknown; there is uncertainty in the number of vials that need to be used per patient; discontinuation criteria could not be assessed in the sponsor's submission. CADTH estimated a revised based case by increasing the market shares to 10% in Year 1, 30% in Year 2, and 50% in Year 3. Based on the CADTH reanalyses, the estimated budget impact from the reimbursement of difelikefalin would be $2,607,678 in year 1, $5,336,460 in year 2, and $8,004,690 in year 3, for a total budget increase of $24,263,405 over a 3-year time horizon. This estimate is significantly different from the estimate derived using the sponsor's base case. The estimated budget impact also increases as the population size becomes larger based on the proportion of patients assumed to have moderate to severe pruritus, as well when a proportion of patients are assumed to require more than one vial of difelikefalin. Uncertainty remains with the potential impact of discontinuation criteria on the BIA results.

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting Date: February 22, 2023

Regrets

Two expert committee members did not attend.

Conflicts of Interest

None