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CADTH Reimbursement Recommendation

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.

Final recommendation: Do not reimburse

Note: This document was initially published on July 31, 2023, and subsequently revised on August 16, 2023, to correct an error in the reporting of the submitted price.

Summary

What Is the CADTH Reimbursement Recommendation for Korsuva?

CADTH recommends that difelikefalin should not be reimbursed by public drug plans for the treatment of moderate to severe pruritus associated with chronic kidney disease (CKD-aP) in adult patients on hemodialysis (HD).

Why Did CADTH Make This Recommendation?

- The CADTH Canadian Drug Expert Committee could not conclude whether treatment with difelikefalin resulted in clinically meaningful improvements. Evidence from 2 randomized controlled trials (KALM-1 and KALM-2) demonstrated that treatment with difelikefalin was associated with statistically significant improvements in itch; however, whether the improvement is clinically meaningful to patients is unclear due to a high placebo response and the trials measuring itch in a way that is inconsistent with clinical practice. As such, it is difficult to determine the actual treatment effect of difelikefalin.
- Patients living with moderate to severe CKD-aP on HD expressed a need for treatments that improve quality of life (QoL). Based on the available evidence, it is unclear if difelikefalin is associated with an improvement in QoL.
- There is a lack of evidence to show that difelikefalin would meet the needs identified by patients, such as reducing hospital visits and the amount of overall medication required, improving sleep quality and reducing sleep disturbance, and reducing side effects.

Additional Information

What Is CKD-aP?

CKD-aP, also known as uremic pruritus, is a common systemic itch that affects more than 60% of patients living with CKD who are undergoing HD. Approximately 20% to 40% of patients report moderate to severe itch associated with CKD. Intense and generalized systemic itching is often distressing to patients and is associated with poor sleep quality, depression, reduced quality of life, increased risk of infection, and an increased risk of death. In Canada, an estimated 70% of adult patients receiving dialysis experience itch associated with CKD, according to the international observational Dialysis Outcomes and Practice Patterns Study.

Unmet Needs in CKD-aP

Patients with moderate to severe CKD-aP who are undergoing HD have expressed a need for treatments that relieve itch, reduce hospital visits and

Summary

the amount of overall medication required, improve health-related quality of life (such as sleep quality and reducing sleep disturbance), and reduce side effects.

How Much Does Korsuva Cost?

Treatment with Korsuva is expected to cost approximately $4,212 per patient per year.

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 improvement in pruritus and health-related quality of life (HRQoL) observed in the trials is associated with 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 an improvement in the Worst Itching Intensity Numerical Rating Scale (WI-NRS) score from baseline to week 12 versus placebo. Although treatment with difelikefalin was associated with an improvement in pruritus that was statistically significant based on an improvement by at least 3 points on the WI-NRS as well as an improvement by at least 4 points on the WI-NRS, only about half of the patients in the difelikefalin treatment groups (50% to 52%) reported an improvement of 3 points or greater on the WI-NRS, and less than half (38% to 41%) reported an improvement of 4 points or greater. Most clinicians do not use pruritis scales in clinical practice, which raises uncertainty about measuring treatment effect. Further, the results of the assessments based on a 3-point improvement and 4-point improvement were also associated with a high placebo response, resulting in uncertainty of the magnitude of benefit that can be attributed to difelikefalin. CDEC acknowledged that pruritus is a common issue among patients with CKD on HD that has a notable impact on HRQoL, as reflected in the patient group input. Further, patients identified a need for new treatments for moderate to severe CKD-aP to improve quality of life (QoL) and treatment efficacy. However, conflicting results between the trials led to uncertainty regarding an improvement in HRQoL associated with difelikefalin. Patients also identified a need for treatments that would reduce hospital visits and the amount of overall medication required, improve sleep quality and reduce sleep disturbance, and reduce side effects, although evidence to support a benefit of difelikefalin with regard to these needs was not identified.

Discussion Points

- CDEC acknowledged that pruritus is a common issue among patients with CKD on HD that significantly 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 end points in the statistical testing hierarchy in the KALM trials. A benefit in HRQoL based on the Skindex-10 (treatment group difference of 5.1 points [95% confidence interval (CI), −8.0 points to −2.3 points, P < 0.001]) and 5-D Itch (treatment group difference of −1.3 points [95% CI, −2.0 points to −0.5 points, P < 0.001]) was demonstrated in the KALM-1 trial, but a benefit was not

demonstrated based on these outcomes in the KALM-2 trial. The conflicting results between the trials led to uncertainty regarding an improvement in HRQoL associated with difelikefalin. In addition, the committee discussed the between-groups difference in the least squares (LS) mean (95% CI) observed in the KALM-1 trial (i.e., a 5-point difference on a 60-point scale for the Skindex-10, and a 1-point difference on a 25-point scale for the 5-D Itch). As a between-groups minimal important difference (MID) for these outcomes was not identified in the literature, the clinical value of the difference between treatment groups was considered uncertain.

- 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. The committee rediscussed the use of the 3-point improvement on the WI-NRS scale as the primary end point instead of a 4-point improvement as part of the request for reconsideration. Upon reconsideration of the evidence, CDEC agreed that there is evidence to support the use of either a 3-point or 4-point WI-NRS threshold, although the 4-point change is more robust. In addition, the analysis based on a 3-point and a 4-point improvement were both statistically significant in favour of difelikefalin. However, an absolute difference of 22% (95% CI, 12% to 32%) in the KALM-1 trial and 11% (95% CI, 1% to 20%) in the KALM-2 trial based on the proportion of patients achieving a 3-point WI-NRS improvement, and an absolute difference of 16% (95% CI, 6% to 25%) in the KALM-1 trial and 11% (95% CI, 2% to 20%) in the KALM-2 trial based on the proportion of patients achieving a 4-point WI-NRS improvement, remained an area of uncertainty for the committee in terms of the magnitude of benefit attributable to difelikefalin.
- 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. This issue was discussed again as part of the sponsor's request for reconsideration. The committee acknowledged that conducting rigorous assessments of the efficacy and safety of difelikefalin compared to a single treatment in standard of care may have limitations but remains a reasonable option. Further, this would have provided evidence of comparative safety and tolerability between difelikefalin and standard of care, which has been highlighted as an issue by the sponsor despite the absence of safety signals identified in the KALM trials, even in patients receiving concomitant medications. As such, the lack of comparative data remains a limitation

of this review. In addition, long-term safety and efficacy of treatment with difelikefalin is unknown as the data are limited to 52 weeks of follow-up, with evidence beyond 12 weeks limited to a noncomparative, open-label assessment.

- 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, which might 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. This issue was considered by the committee again as part of the request for reconsideration. CDEC maintains that the median WI-NRS score at baseline is another area of uncertainty in the trial design. However, CDEC also noted that this issue factored into the discussion of the evidence for difelikefalin but was not a reason for recommendation.
- CDEC discussed each of the issues identified by the sponsor in their request for reconsideration. The issues indicate that the sponsor does not agree that the original recommendation is supported by the evidence due to the committee's interpretation that a clinically meaningful treatment effect was not demonstrated in the KALM-1 and KALM-2 trials. The committee discussed the 3-point improvement on the WI-NRS scale as the primary end point, the absence of comparative data as a limitation of the overall body of evidence, and the generalizability of the evidence to patients with moderate to severe CKD-aP based on the baseline median WI-NRS score. Due to the limitations of the available evidence from the KALM-1 and KALM-2 trials, CDEC remained uncertain whether difelikefalin meets important therapeutic needs for patients experiencing moderate to severe CKD-aP.

Background

Chronic kidney disease (CKD) is a progressive disease characterized by gradual loss of renal function and/or abnormalities of renal structure for a period of 3 months or longer. 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 HD, 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 patients undergoing HD is about 70%, according to the international observational Dialysis Outcomes and Practice Patterns Study. Among patients with CKD on HD, more than one-third experience moderate to severe itch. There is 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 to be 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 CKD-aP includes administration of topical 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 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 CKD-aP in adult patients on HD. It is available as 50 mcg/mL IV solutions and the dosage recommended in the product monograph is 0.5 mcg/kg dry body weight (i.e., the target postdialysis weight).

Sources of Information Used by the Committee

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

- a review of 2 double-blind RCTs in adult patients with moderate to severe CKD-aP who are on HD
- patient perspectives gathered by 1 patient group, the Kidney Foundation of Canada
- input from public drug plans that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with CKD-aP
- input from 3 clinician groups, including Saskatchewan Kidney Doctors; the Hemodialysis Specialty Physician Group – Division of Nephrology, the Ottawa Hospital; and the Division of Nephrology, Department of Medicine, Dalhousie University/Nova Scotia Health
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the request for reconsideration (described subsequently).

Stakeholder Perspectives

Patient Input

One patient advocacy group, the Kidney Foundation of Canada, provided input on the treatment of adult patients with CKD undergoing HD. Patient input was gathered from independent surveys among people living with CKD and their caregivers across Canada in September 2022. In total, 19 responses were gathered from the survey (10 fully completed and 9 partially completed).

More than 90% of patients from the survey reported experiencing itchy skin as part of their kidney disease, with 50% of respondents experiencing itchiness every day, 40% several times per week, and 10% occasionally. While 60% of respondents reported living with pruritus for 1 year to 2 years, 20% said they had been living with it for 2 years to 5 years, and 20% more than 5 years. The itchiness was described as moderate to severe by 80% of 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% of patients from this survey reported taking medication to treat their itchiness associated with kidney disease. While 33% of 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 or combination of treatments, with 33% being neither satisfied nor unsatisfied. On the other hand, more than 66% of 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 improvement in their well-being or QoL, with 90% of 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 CKD-aP includes administration of topical 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 itch intensity, improve QoL and sleep quality, and decrease itch-related depression and in some cases, suicidality. They also 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 that acts in the peripheral nervous system, and thus the drug has fewer neuromodulation effects compared with nonselective kappa-opioid receptor agonists. Difelikefalin is the first treatment approved in Canada for moderate to severe pruritus in patients on HD, 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, have failed to control symptoms, or are contraindicated. The clinical experts stated that the prior lines of therapy include menthol-containing topical steroids and/or topical calcineurin inhibitors, systemic drugs (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 would 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 HD with a moderate to 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 nondialysis CKD, or who have undergone 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, CKD 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 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 or vomiting, may also be cause for discontinuing treatment.

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

Clinician Group Input

Clinician group input on the review of difelikefalin for the treatment of moderate to severe CKD-aP in adults on HD was received from 3 clinician groups: Saskatchewan Kidney Doctors; the Hemodialysis Specialty Physician Group – Division of Nephrology, The Ottawa Hospital; and the 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 symptom burden. The debilitating symptoms in most severe cases may lead to deterioration in QoL. The clinician groups mentioned the need for a new treatment option that may help relieve symptoms with better tolerability, affordability, and ease of administration. One clinician group indicated in particular that the most important treatment goal 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 other 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-aP. 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 patients undergoing HD with moderate to severe pruritus would benefit the most from this treatment. The clinician groups mentioned 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 mentioned the lack of diagnostic tests. While 1 group mentioned 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, and Skindex-10). 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

The KALM-1 and KALM-2 studies met the inclusion criteria for the CADTH systematic review. Both KALM trials were designed as multicentre, randomized, double-blind, phase III clinical trials which compared difelikefalin to placebo in patients being treated with HD who were experiencing 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 HD and experiencing moderate to severe pruritus. The shared key secondary objectives for the KALM-1 and KALM-2 trials 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 patients undergoing HD experiencing moderate to severe pruritus. A total of 378 patients in the KALM-1 trial and 473 patients in the KALM-2 trial were randomized at a 1:1 treatment-to-treatment ratio with difelikefalin or placebo. The KALM-1 trial was limited to study centres in the US, and the KALM-2 trial 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 or no); specific medical conditions such as history of fall, fracture, or fall-related fracture; confusional state, mental status change, altered mental status, or disorientation; and gait disturbance or movement disorder (presence or absence).

The primary efficacy end point in the KALM-1 and KALM-2 trials was the percentage of patients at week 12 who achieved an improvement of at least3 points from baseline in the weekly mean score from the daily WI-NRS. Key secondary efficacy end points 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 an improvement of at least 4 points from baseline in the weekly mean score from the daily WI-NRS. In addition, the proportions of patients who achieved an improvement of at least 3 points or an improvement of at least 4 points from baseline at week 4 and week 8 were considered as secondary end points for the KALM-2 trial.

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

Efficacy Results

No evidence was identified in the KALM trials for mood, days of missed work, days of missed school, or 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

The severity of pruritus was assessed in both the KALM-1 and KALM-2 trials using the WI-NRS score. The primary and key secondary end points in both trials were the proportion of patients with an improvement of at least 3 points in the WI-NRS score from baseline to week 12, and the proportion of patients with an improvement of at least 4 -points in the WI-NRS score from baseline to week 12, respectively.

At week 12, in the KALM-1 trial, 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% CI, 1.72 to 4.30; P < 0.001) in favour of difelikefalin. In the KALM-2 trial, 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 the KALM-1 and KALM-2 trials. 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 regard to the proportion of patients achieving a ≥ 4-point improvement from baseline to week 12 in the weekly mean from the daily WI-NRS score, 41% and 21% of patients randomized to difelikefalin and placebo, respectively, in the KALM-1 trial, and 38% and 25% of patients randomized to difelikefalin and placebo, respectively, in the KALM-2 trial, 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 the KALM-1 trial, and 1.77 (95% CI, 1.14 to 2.74; P = 0.01) in the KALM-2 trial, in favour of difelikefalin. Overall, difelikefalin demonstrated an improvement in the WI-NRS score that was clinically meaningful, based on both of the reported assessments of the 3-point and 4-point improvement in the WI-NRS score.

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

The proportion of patients with at least a 3-point improvement or 4-point improvement from baseline on the WI-NRS was also reported at week 4 and week 8 in both trials. In the KALM-1 trial, the proportion of patients with an improvement of at least 3 points or 4 points from baseline on the WI-NRS at week 8 and week 4 was considered exploratory, but in the KALM-2 trial, they were included as key secondary end points. In the KALM-2 trial, a benefit from treatment with difelikefalin was also observed at week 4 (35% versus 22% for difelikefalin versus placebo) and week 8 (45% versus 33% for difelikefalin versus placebo) for the proportion of patients with at least a 3-point improvement from baseline on the WI-NRS. Similar results were observed in the KALM-1 trial (week 4: 33% versus 18% for difelikefalin versus placebo; week 8: 43% versus 28% for difelikefalin versus placebo). Similarly, with regard to the proportion of patients with at least a 4-point improvement from baseline, in the KALM-2 trial, a benefit from treatment with difelikefalin was observed at week 4 (20% versus 13% for difelikefalin versus placebo) and week 8 (31% versus 20% for difelikefalin versus placebo). Similar results were observed in the KALM-1 trial (week 4: 18% versus 8% for difelikefalin versus placebo; week 8: 31% versus 20% for difelikefalin versus placebo). In the KALM trials, data for the primary and secondary or 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 the KALM-1 and KALM-2 trials assessed the 5-D Itch Scale for 52 weeks following the 12-week pivotal trials and reported that the proportion of patients achieving at least 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

At week 12, in the KALM-1 trial, [redacted] of patients randomized to difelikefalin and placebo, respectively, were complete responders. This corresponded to an odds ratio of [redacted] In the KALM-2 trial, [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 was assessed in both the KALM-1 and KALM-2 trials 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 was included as a key secondary end point in both of the trials.

Skindex-10 Scale Total

Skindex-10 is a modified version containing 10 questions to evaluate CKD-aP and QoL with relevant subdomains for patients in the HD setting with higher scores indicating patients being more bothered and lower scores indicating being less bothered. At the end of week 12, the LS mean change (reduction) in total Skindex-10 Scale score was −17.2 versus −12.0 for difelikefalin versus placebo in the KALM-1 trial, and −16.6 versus −14.8 for difelikefalin versus placebo in the KALM-2 trial. In the KALM-1 trial, 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 points to −2.3 points; $P < 0.001$). In the KALM-2 trial, 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 points to 0.8 points; $P = 0.171$). A 3-point to 12-point change on the Skindex-10 was identified as a clinically meaningful change in patients on HD 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 regard 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 the Skindex-10 Scale: disease total, mood or emotional distress total, and social functioning total. No long-term data were reported in the KALM trials for the Skindex-10 Scale.

5-D Itch Scale Score Total

The 5-D Itch Scale is a questionnaire assessing CKD-aP and QoL with relevant subdomains for patients in the HD setting, with higher scores indicating being more bothered and lower scores indicating being 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 versus −3.7 for difelikefalin versus placebo in the KALM-1 trial, and −4.9 versus −3.8 for difelikefalin versus placebo in the KALM-2 trial), 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 points to −0.5 points; P < 0.001) in the KALM-1 trial and −1.1 points (95% CI, −1.7 points to −0.4 points; P = 0.002) in the KALM-2 trial. Of note, the analysis of the difference in LS means for 5-D Itch at week 12 for the KALM-2 trial was at risk for type I error, as the preceding test 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 score in patients with CKD-aP. Therefore, it is unclear whether the reported within-group differences are clinically meaningful. No long-term data were reported in the KALM trials for the 5-D Itch Scale.

Harms Results

The percentage of patients with any reported treatment-emergent adverse events (TEAEs) in the difelikefalin group was comparable to the placebo group: 68.8% versus 62.2% for difelikefalin versus placebo in the KALM-1 trial, and 68.1% versus 61.4% for difelikefalin versus placebo in the KALM-2 trial. In the KALM-1 trial, the most common TEAEs reported for patients randomized to difelikefalin and placebo, respectively, were diarrhea (9.5% versus 3.7%), dizziness (6.9% versus 1.1%), vomiting (5.3% versus 3.2%), and nasopharyngitis (3.2% versus 5.3%). Diarrhea, dizziness, and vomiting were reported more commonly in the difelikefalin treatment group than the placebo treatment group in the KALM-1 trial. In the KALM-2 trial, the most common TEAEs reported for patients randomized to difelikefalin and placebo, respectively, were diarrhea (8.1% versus 5.5%), vomiting (6.4% versus 5.9%), fall (6.8% versus 5.1%), dizziness (5.5% versus 5.1%), and nausea (6.4% versus 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 the KALM-1 trial, and 24.7% for difelikefalin and 21.6% for placebo in the KALM-2 trial. The clinical experts stated that the proportion of patients reporting an 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 SAEs 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 the KALM-1 trial, and 5.5% for difelikefalin and 3.4% for placebo in the KALM-2 trial. 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 the KALM-1 trial, and 0.9% for difelikefalin and 0.8% for placebo for in the KALM-2 trial. In the KALM-1 trial, sepsis was the cause of death for 2 patients randomized to difelikefalin (0 patients randomized to placebo and 0 patients in the KALM-2 trial), and septic shock was the cause of death for 2 patients randomized to placebo (0 for difelikefalin and 0 patients in the KALM-2 trial). All other reported causes of death (dyspnea or hypotension, cardiac arrest, unknown) were infrequently reported, with no more than 1 patient in any treatment group. No specific adverse event (AE) was identified to account for the majority of deaths in either group for the KALM-2 trial.

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 or 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 the KALM-2 trial. Overall, during the 12-week treatment period in the KALM-1 and KALM-2 trials, 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% versus 3.7% for difelikefalin versus placebo) and dizziness (6.9% versus 1.1% for difelikefalin versus placebo) as AEs in the KALM-1 trial.

Critical Appraisal

The overall study design of the KALM-1 and KALM-2 trials 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 HD (i.e., optimization of HD) is a potential effect modifier and prognostic factor that were not considered in both KALM trials. Patients with more frequent HD visits would have better control of the disease and more exposure to difelikefalin compared with patients who had less frequent HD visits. In addition, more frequent HD visits indicated better compliance with the difelikefalin treatment. Therefore, the frequency of HD may have a 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 regard to the treatment effect in patients with different frequencies of HD 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 FDA recommended the use of at least 4 points in improvement as the cutoff for the primary efficacy end point (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 end point. It is worth mentioning that odds ratios were used throughout the KALM trials for the primary and key secondary end points 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 was a large proportion of patients who had at least 1 major protocol deviation (approximately 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 in the difelikefalin groups. According to the clinical experts consulted by CADTH, the placebo response may be due to optimized HD treatment associated with the trials, as patients who were enrolled in the trials tend to attend their HD more frequently and regularly, which would provide a benefit to these patients. The CADTH review team considered the placebo effect to also be 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 the WI-NRS and Patient Global Impression of Change, and HRQoL was measured using Skindex-10 and 5-D Itch scores. 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 scores, translate to clinical practice. A limitation to note is that the studies included patients with better HD 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 the KALM-1 and KALM-2 trials had better adherence to HD 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 the KALM-1 trial and 7.13 for the KALM-2 trial); the clinical experts consulted by CADTH indicated that 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 HD 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 III CR845-CLIN3101 study for up to 52 weeks was summarized in this report.

Description of CR845-CLIN3101 Study

One open-label, multicentre, phase III study (CR845-CLIN3101) 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 II 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 HD who had not been previously exposed to difelikefalin and had not participated in the phase II studies for difelikefalin. The open-label phase III study consisted of a screening visit, a 52-week treatment period, an end of treatment (EOT) visit, and a follow-up visit after 7 to 10 days 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 to 10 days after the EOT or ET visit. In the long-term safety study, AEs, SAEs, withdrawals due to adverse events (WDAEs), and deaths were reported descriptively for each of the 3 treatment groups.

Efficacy Results

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

Harms Results

In the open-label phase III 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 AEs (frequency ≥ 5%) were nausea, diarrhea, fall, vomiting, hypotension, noncardiac chest pain, hyperkalemia, dizziness, abdominal pain, fluid overload, pneumonia, dyspnea, acute myocardial infarction, pain in extremity, arthralgia, and asthenia. The portions of patients with at least 1 serious AE 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 hemorrhage, pneumonia, cellulitis, fluid overload, hyperkalemia, respiratory failure, pulmonary edema, and hypotension. A total of 35 patients discontinued the study drug due to AEs, the proportions 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. In total, 16 deaths occurred during the study, with the proportions being 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 III study was to evaluate the long-term safety of difelikefalin, administered intravenously after each dialysis session for up to 52 weeks. Since the results for the open-label phase III 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 demographic factors from the main report could be applicable to this study population. While the 0.5 mcg/kg dose is consistent with the Health Canada–approved dose, the duration of the open-label phase III trial (up to 52 weeks) is longer 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 III study may be generalizable to this time frame to an extent, but not completely, as the rates of AEs are expected to increase with longer treatment time.

Summary of Pooled Analysis of Open-Label Extension of the KALM-1 and KALM-2 Trials by Topf et al. (2022)

A pooled analysis of 2 open-label extension studies of the KALM-1 and KALM-2 trials assessed the 5-D Itch Scale for 52 weeks following the 12-week pivotal trials.[17] The study reported the proportion of patients achieving at least a 5-point reduction in the 5-D Itch Scale was maintained up to 52 weeks in the open-label phase of the KALM-1 and KALM-2 trials. However, there was some uncertainty in the reported long-term treatment effect due to the amount of missing data, with 26.5% of patients (189 out of 712) 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 BSC
Dose regimen	0.5 mcg/kg dry body weight (i.e., target postdialysis weight) 3 times per week by IV bolus injection into the venous line of the dialysis circuit at the end of the hemodialysis treatment or after rinse-back
Submitted price	Difelikefalin, 50 mcg vial (1 mL): $27.00 per single-use vial
Treatment cost	Assuming a patient weight of 85.5 kg and no vial sharing, the 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 UV 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

Component	Description
	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. • 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 approximately $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; and discontinuation criteria could not be assessed in the sponsor's submission. CADTH estimated a revised base 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 1 vial of difelikefalin. Uncertainty remains with the potential impact of discontinuation criteria on the BIA results.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for difelikefalin for the treatment of moderate to severe pruritus associated with CKD-aP in adult patients on HD. In their request, the sponsor identified 4 issues:

- A clinically meaningful treatment effect was established by the KALM trials in spite of the concerns of CADTH regarding a high placebo response, optimization of HD, and the permitted use of concomitant medication.
- WI-NRS is an appropriate scale to assess meaningful clinical efficacy of treatments in CKD-aP using the validated 3-point minimal clinically important difference (MCID) for improvement, and evidence does not exist to support the CADTH experts' opinion of a 4-point change as being more appropriate.
- As there is currently no approved evidence-based treatment defined as the standard of care globally for CKD-aP resulting in a diverse range of antipruritic medications used, a direct and systematic comparison study of difelikefalin to a single treatment to assess its benefit would not address the current evidence required to identify effective and safe treatment.
- Despite the conclusion drawn from the CADTH expert opinion, the patient population enrolled in both KALM clinical trials is generalizable to the population of patients undergoing HD in HD centres across Canada with moderate to severe CKD-aP treated primarily by nephrologists.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered information from the initial submission relating to the issue identified by the sponsor, as well as feedback on the draft recommendation from:

- the sponsor
- 2 clinical specialists with expertise in the diagnosis and management of patients with CKD-aP
- 6 clinician groups: Scarborough Regional Health – Nephrologists; Scarborough Regional Health – Dermatologists; Nephrologists from the Division of Nephrology, Department of Medicine, Halifax, Nova Scotia, and a Nephrology Clinical Pharmacy Specialist who works with Nova Scotia Health; Hemodialysis Specialty Physician Group – Division of Nephrology, The Ottawa Hospital; Canadian Nephrologists; and Fraser Health, Division of Nephrology
- 1 patient group: the Kidney Foundation of Canada.

All stakeholder feedback that was received from clinician groups, patient groups, and the public drug programs in response to the draft recommendation is available on the CADTH website.

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.

Initial meeting date: February 22, 2023

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Reconsideration meeting date: June 28, 2023

Regrets: None

Conflicts of interest: None

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