CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

difelikefalin (Korsuva)

(Otsuka Canada Pharmaceutical Inc.)

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

March 31, 2023

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752-000
Brand name (generic)	difelikefalin
Indication(s)	Moderate to severe pruritus associated with CKD in adults on hemodialysis.
Organization	Scarborough Regional Health - Nephrologists
Contact informationa	Dr. Robert Ting, Nephrologist, Scarborough Regional Health

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with thecommittee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

CDEC did not think a 3 point improvement in the Worst Itching Intensity Numerical Rating Scale (WI-NRS) was clinically significant. It was felt a 4 point improvement would be necessary to demonstrate clinical significance.

The 4 point improvement is based on specific skin disorders and not generalized uremic pruritis. It has been shown using anchor-based analysis that a reduction of 3 points from baseline score represents an appropriate clinically meaningful within-patient change on the WI-NRS. In exit interviews, all patients with a reduction of at least 3 points considered the change meaningful. (1) Uremic pruritis consistently ranks in the top two concerns patients have on dialysis and is an orphan disease for which we have no good therapies. Patients are often prescribed antihisthamines(2-5) and topical steroids (6) which studies have shown are completely useless. We also use pregabalin and gabapentin but these drugs are quite dangerous in our patients because they cause ataxia and at higher doses are associated with a several fold increase risk of falls and fractures (7). CKD associated pruritus is a disease with very little in the way of therapeutics and our patients are desperate for something to help them with a condition which affects all aspects of their life. Please see the following video which illustrates the magnitude of this problem.

https://app.frame.io/presentations/54c23445-95ea-41c1-886d-9c672ea73d70

This is a video of one of my patients describing the way uremic pruritis affects all aspects of their life.

(1) Psychometric validation and meaningful change thresholds of the Worst Itching Intensity Numerical Rating Scale for assiting itch in patients with chronic kidney disease-associated pruritis, Margaret K Vernon et al, J Patient Rep Outcomes, 2021.
(2) Combs SA, et al. Semin Nephrol 2015;35:383–91
(3) Martin CE, et al. Can J Kidney Health Dis 2020;7: 2054358120954024
(4) Hercz D, et al. Cochrane Database Syst Rev 2020;12:CD011393;
(5) Weisshaar E, et al. Acta Dermatol Venereol 2019;99:469–506
(6) Hercz D, et al. Cochrane Database Syst Rev 2020;12:CD011393
(7) Ishida H. I. J Am Soc Nephrol 29: 1970–1978, 2018

There was also a comment that the improvement in the placebo group means that there may have been optimization of dialysis or use of concomitant medications that improved outcomes thereby reducing the benefit of Difelikefalin.

High placebo response in clinical trial is a well-known phenomenon. To get into the study, the patients all had to be well dialyzed and meet the cutoff KT/V. To suggest that the patients once in a study showed up for dialysis more regularly and that this might be the reason why they have less pruritis is erroneous. We in fact try to switch patients to nocturnal hemodialysis for severe uremic pruritis in order to lengthen their dialysis time from 4 to 6 hours but do not see any improvement in uremic prurutis. For the 11 month period ending Feb 28, 2023, at Scarborough Regional Health, there were a total of 135,740 dialysis treatments. 134,149 treatments were completed and there was a total of 1,591 no shows. This means that 98.9% of treatments were completed as prescribed. To suggest increased dialysis optimization was a possible reason for the improvement in pruritis when the habitual no-show patients were already screened out because they would not have passed the KT/V cutoff is really a stretch. Furthermore there have been at least 4 studies showing no benefit with antihisthamines. Topical steroids provide fleeting or no relief and clinical trials have failed to show efficacy. The only drugs that have marginal benefit are gabapentin and pregabalin but we are limited to the very lowest doses because of the higher risk of ataxia and falls.

CDEC felt that a baseline score of 7 was not high enough for the WI-NRS score and that 8 should have been used as the cutoff.

This is a random statement and to say a patient went from a 7 to a 4 does not have a significant improvement is also not correct. Uremic pruritis affects patients ability to sleep, causes depression and is associated with increased CV mortality so any drop from 7 to 4 would be highly welcomed by patients.

There was a suggestion that the patients enrolled in the trials may represent a population more likely to respond to treatment.

We have demonstrated in our own dialysis unit that consistently 15-20% of the patients will have a WI-NRS score of 7-10. The population studied is representative of what we routinely see in Scarborough. In reality, we would probably only consider Difelikefalin in the patients in this group because their symptoms are the most severe and debilitating as you can see from the video above.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that thecommittee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐

Clarity of the draft recommendation		
3. Are the reasons for therecommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

The CDEC draft recommendation is based primarily two expert witnesses, presumably one nephrologist and one dermatologist. Most dermatologists do not see a lot of cases of uremic pruritis. This is because their practices are not closely affiliated with regional dialysis programs. Most dermatologists do not do consults inside the hospital and only a handful really have a lot of

experience dealing with uremic pruritis. In Scarborough, we work closely with our one hospital dermatologist. Dr..MorvaridHessami has tried a variety of treatments in our patients including the use of strong immunosuppression such as mycophenolate mofetil but up to now we really have not been able to find anything that works well in the most severely affected patients. Our patients are desperate to try something that will help them live their lives. We have had patients consider stopping dialysis because their uremic pruritis was so debilitating. I think the results of two randomized clinical trials should have more weighting than the opinions of two expert witnesses.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside yourclinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed:		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr Robert Ting, MD, FRCP(C), FACP*
Position	*SHN Nephrologist, DMC Markham Medical Director*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.	
Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca	☐	☐	☒	☐
Otsuka	☐	☒	☐	☐
GSK	☐	☒	☐	☐
Bayer	☐	☒	☐	☐
Boehringer	☐	☒	☐	☐
Janssen	☒	☐	☐	☐
Novo Nordisk	☒	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr Paul Tam, MD, FRCP (C), FACP*
Position	*SHN Nephrologist, SHN Nephrology Chief & Medical Director-Scarborough Regional Dialysis Program*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Dr Janet Roscoe, MD, FRCP (C), FACP*
Position	*Associate Professor Toronto*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**

Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Dr Gordon Nagai, MD, FRCP(C)*
Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Dr Jason Fung, MD, FRCP(C)*
Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	*Dr Andy Zhang, MD*

Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 7	
Name	*Dr Tabo Sikaneta, MD*
Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 8	
Name	*Dr Denise Tam, MD*
Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 9	
Name	*Dr Simon Tsui, MD*
Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 10	
Name	*Dr Andrew Wong, MD*
Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 11	
Name	*Dr Ryan Pratt, MD*
Position	*SHN Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 12	
Name	*Dr Hitesh Mehta, MD, FRCP(C)*
Position	*William Osler Hospital Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 13	
Name	*Dr Eliot Beaubien, MD, FRCP(C)*
Position	*Peterborough Regional Health Nephrologist, DMC Peterborough Medical Director*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 14	
Name	*Dr Danny Sapir, MD, FRCP(C)*
Position	*Oakville Trafalgar Hospital Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Otsuka	☒	☐	☐	☐
Boehringer	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 15	
Name	*Dr Nancy Barrese, MD, FRCP(C)*
Position	*Lakeridge Nephrologist, DMC Pickering Medical Director*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 16	
Name	*Dr Laura Berall, MD, FRCP(C)*
Position	*Humber River Hosptial Nephrologist*
Date	*30-03-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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AstraZeneca	☒	☐	☐	☐
GSK	☐	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752-000
Brand name (generic)	Difelikefalin
Indication(s)	Moderate to severe pruritus associated with CKD in adults on hemodialysis.
Organization	Nephrologists from the Division of Nephrology, Department of Medicine, Halifax, Nova Scotia, and a Nephrology Clinical Pharmacy Specialist who works with Nova Scotia Health
Contact information	Name: Dr. Karthik Tennankore, MD SM FRCPC, Consultant Nephrologist (Nova Scotia Health) and Associate Professor of Medicine (Dalhousie University). Interim Co-Division Head (Division of Nephrology, Department of Medicine, Dalhousie University, Halifax, NS Canada

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

We feel that the draft recommendation did not accurately capture the strength of the data in support of difelikefalin. In addition, to our knowledge, the evidence review of CDEC did not include a key recent systematic review in the decision (that should be evaluated) which provides further support of the importance of Kappa opioid receptor agonists (driven by difelikefalin) in the management of Chronic Kidney Disease Associated Pruritus (CKD-aP). Our specific responses to each of the provided rationales for the CDEC recommendation are provided below.

Statement: "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…However, a 4-point improvement in the WI-NRS scale is considered a clinically meaningful measurement of improvement in pruritus in clinical practice."

Response: *We strongly disagree with this statement. In a recent psychometric validation of the WI-NRS for assessing itch in patients with chronic kidney disease-associated pruritus, anchor-based analysis showed that a reduction of >=3 points from baseline score represented an appropriate clinically meaningful within-patient change on the WI-NRS. [1] Furthermore, 100% of patients interviewed deemed a reduction of >=3 points as a meaningful change. Therefore, based on the CDEC observation that both trials demonstrated a statistically significant improvement using this threshold at a level that is clinically meaningful to patients, these trials demonstrate efficacy of difelikefalin. This trial used the FDA's Patient-Focused Drug Development Guidance of incorporating quantitative and qualitative methods to define meaningful within-patient change thresholds. Thus, rejecting this threshold as the one of importance to patient's would effectively be ignoring their perceptions and voice of what is clinically important.*

Reference:

[1] Vernon et al. Journal of Patient-Reported Outcomes, 134(2021).

Statement: 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 eight; 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.

Response: *It is unclear why the demonstration of benefit in a population with less severe disease would be identified as a generalizability issue. This seems counter-intuitive; wouldn't the demonstration of benefit to a broader population than those with more severe disease be demonstration of generalizability? Furthermore, ignoring a therapy that achieves clinically significant improvements in itch on the basis that the mean itch scores were at the lower threshold of the highest category of severity (often defined as >=7) as opposed to 1 point higher seems overly restrictive.*

Statement: 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.

Response: *High placebo responses are well-known to occur in multiple trials and are not unique to this area. Placebo responses may be high with subjective outcome measures, however, replacing subjective outcomes with objective ones will not necessarily lead to better results. [1] In CKD, identifying therapies to mitigate itch was identified as the second MOST important priority for nephrology patients in a recent Canadian survey study. [2] Importantly, in the open-label extension phase, there was a rapid, consistent and sustained improvement when those randomized to placebo were given access to difelikefalin.[3] Even if we assumed that these patients were receiving a variety of other therapies to try to treat itch, it seems surprising that the impact of a placebo effect would be given so much consideration when those on placebo experienced a significant improvement in itch (N=141) after being provided the medication. In addition, it is important to understand the limited therapeutic options for CKD-aP, even if there may have been a variety of off-label treatments that were used. Moderate to Severe CKD-aP was estimated to be present in 40% of Canadian patients in the large Dialysis Outcomes and Practice Patterns Survey. [4] CKD-aP is underestimated; in one study, 65% of dialysis directors identified <5% of patients experienced it when the true prevalence was 20%, and 20% were on no treatment. [4] The most commonly used therapy was antihistamines, which has LOW quality evidence for use based on a recent Cochrane review.[5] We feel it is highly unlikely that optimization of other therapies would have led to a benefit leading to a reduction in attribution of efficacy to difelikefalin. Further, head-to-head comparisons would not be feasible, even with gabapentin. This is because there are adverse effects of gabapentin including somnolence, falls and general harm. In fact, there are concerted efforts to deprescribe this therapy for this reason.*

Reference:

[1] Vollert et al. JAMA Network Open, 3(9), 2020. [2] Manns et al. CJASN, 9(10), 2014. [3] Topf et al. Kidney Medicine, 2022. [4] Rayner et al. CJASN 12(12), 2017. [5] Hercz et al. Cochrane, 2020

Statement: 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. 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.

Response: *It is unclear why individual trial results would be used as opposed to evaluating the combined effects when multiple studies are present? In this regard, a recent systematic review demonstrated difelikefalin was effective at reducing itch and showed improvement in quality of life using the Skindex and 5-D itch scale.[1] We feel the combined effect needs to be looked at when more than one trial is present. In addition, in a recently conducted systematic review of medications that are Kappa Opioid Receptor Agonists (KORAs), it was shown that this class of medications (primarily driven by difelikefalin) led to moderate improvements in*

itch scores at 2 and 8 weeks (GRADE recommendation: high), and moderate improvements on sleep scores and the Skindex-10 (GRADE recommendation: high). Thus, there is even further support regarding the efficacy of these therapies.

Reference:

[1] Wala et al. Pharmaceuticals, 15(8), 2022. [2] Bailey et al. Br J Dermatol, 186(3), 2022.

As a final comment, there are large implications for this decision when it comes to treatment access for dialysis patients in the face of a new medication with demonstrated clinical benefit. It is well established that dialysis patients have limited financial resources, a 2018 report on the financial burden of dialysis demonstrated that 50% of respondents experienced a decrease in income after starting dialysis, and 41% are below the Canadian Low-Income Cut-Off (LICO). It is a reasonable assumption that many of those individuals belong to a racial minority group. If this medication is not recommended by CADTH, it will become only accessible to those with private coverage and or those with financial resources. Therefore, it will result in health inequity to some of the already most vulnerable populations we serve.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

Response: *Several points in our original submission were not read. The side effects and harms of gabapentin were not discussed in this CADTH review, i.e., these alternative treatments are not without their risks which we mentioned in our original feedback. Furthermore, we identified that the NRS scale score change of 3 was clinically important, yet the threshold of 4 was used in this submission.*

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

Response: *As noted, the choice of using a 4 vs 3 threshold is not clear. The rationale for looking at individual trials as opposed to combined efficacy data from KALM-1 and 2 is not supported either, as the combined data would reflect a larger population. The concern about a lack of generalizability because the study enrolled patients with slightly lower itch scores than suggested by clinical experts (although this is not the experience we have found at our site) is also not clear.*

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

N/A

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

N/A

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
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  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Steven Soroka, Professor, MD FRCPC, Department of Medicine, Division of Nephrology, Dalhousie University, Medical Director, Nova Scotia Health Renal Program and Pharmacy Services. Interim Co-Division Head. • Dr. David Clark, Assistant Professor, MD FRCPC, Department of Medicine, Division of Nephrology, Dalhousie University • Dr. Neil Finkle, MD FRCPC, Associate Professor, Department of Medicine, Division of Nephrology, Dalhousie University • Dr. Jo-Anne Wilson, BSc. Pharm, ACPR, MEd (student), PharmD, Associate Professor of Pharmacy, Faculty of Health, Dalhousie University and Clinical Pharmacy Specialist, Nova Scotia Health (Renal Program)		

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752-000
Brand name (generic)	difelikefalin
Indication(s)	Moderate to severe pruritus associated with CKD in adults on hemodialysis.
Organization	Hemodialysis Specialty Physician Group- Division of Nephrology, The Ottawa Hospital.
Contact informationa	Name:Dr. Pierre Antoine Brown, Medical Director, Hemodialysis Program, The Ottawa Hospital Associate Professor, Faculty of Medicine, University of Ottawa

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

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 ***Our clinical group does not understand the rationale of selecting a 4-point improvement to be considered meaningful. This appears to be entirely opinion based, as no evidence to support this assertion is presented here. We are perplexed as to the experts clinical practice selected to consider that a 4-point improvement is necessary, specifically, did the expert's recommendation come from a patient population afflicted by CKD associated pruritus (CKD-aP) or from a patient population with pruritus in general. CKD-aP is a unique pathology (1,2) with a unique pathophysiology and "lumping" this disease with other pruritic conditions with regards to treatment and meaningful response to treatment would not present an appropriate comparison. In short, the decision to use a cut off of 4 points (effectively negating the positive results seen in the RCTs) appears arbitrary and solely based on opinion.***

1. ***Kidney Int 2015 Apr;87(4):685-91***
2. ***Clin Kidney J 2021 Oct 14;14(Suppl 3):i1-i7.***

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
High placebo response in clinical trial is a well-known phenomenon (3,4) that is seen in numerous RCTs across a multitude of specialities (5). As a salient example, almost 1 in 6 patients with

fistulizing Crohn's disease will see closure of their fistulae when receiving placebo alone (6). The CDCE seems to dismiss the well established and documented response to placebo alone see in the RCTs of difelikefalin for CKD-aP. Rather, it suggests the findings of placebo response here are attributable to the permitted used of concomitant therapies, something that may be plausible yet entirely hypothetical.

3. ***Trials2021 Jul 26;22(1):493.***
4. ***Handb Exp Pharmacol 2019;260:399-431.***
5. ***Philos Trans R Soc Lond B Biol Sci 2011 Jun 27;366(1572):1889-95***
6. ***Clin Gastroenterol Hepatol 2014 Dec;12(12):1981-90***

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

The committee suggests that data comparing the efficacy of off label gabapentin to on label difelikefalin would be required evidence to determine efficacy. First, we respectfully submit that high level evidence (i.e. RCT data) is impossible to obtain in the Canadian context as it is extremely unlikely that any Institutional Research Ethic Board would approve such a trial design. Retrospective case control studies would be fraught with confounding. Briefly, it would be impossible to obtain reliable data to address this uncertainty. The committee also seems to make abstraction of the need for an orphan drug framework in Canada (7,8). We submit that CKD-aP in hemodialysis patient is an orphan disease (given that ESKD afflicts 0.12% of the overall Canadian population) (9).

7. CMAJ October 16, 2017 189 (41) E1274-E1275

8. https://sencanada.ca/content/sen/Committee/412/soci/rep/rep05jan14-e.pdf

9. *https://www.cihi.ca/en/annual-statistics-on-organ-replacement-in-canada-2012-to-2021#:~:text=In%202021%2C%20more%20than%2048%2C000,kidney%20transplant%20(excludes%20Quebec).*

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 appears to be opinion based, as no evidence to support this assertion is presented here. The draft CDEC recommendations does not identify the clinical experts who provided this opinion, nor whether they have expertise in CKD-aP and/or nephrology practice. The CDEC recommendations does not document on what evidence (if any) the above is based. The chosen cut-off seems based on extrapolation alone ("moderate to severe CKD-aP tend to align with a baseline WI-NRS score of at least 8") from a non-CKD-aP patient population. This makes abstraction of the unique disease process and unique patient population afflicted by CKD-aP.(1,2)

This was identified as a potential generalizability issue as patients enrolled in the trials may represent a population more likely to respond to treatment.

The patient population in both KALM trials is quite representative of the patient population receiving hemodialysis in Canada as can be seen by comparing the baseline demographics in the trial to the baseline characteristics of patient receiving hemodialysis in Canada (https://www.cihi.ca/sites/default/files/document/end-stage-kidney-disease-transplants-2012-2021-data-tables-en.xlsx). It is therefore extremely probable that hemodialysis patients in Canada would exhibit CKD-aP disease severity and response rates very similar to those seen in the KALM trials. No data or evidence is presented above to support the assertion above that the

patients enrolled would be more likely to respond to treatment than those in Canada. Again, this appears to be entirely opinion based and unsupported by any data elements.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

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.
All current alternatives for CKD-aP in hemodialysis patients require a combination of oral and topical medications that are dose multiple times daily. UVB therapy requires daily standalone appointments. All current available therapies thus significantly increase the "pill burden" and "disease burden "on patients. Difelikefalin is administered 3x weekly as part of routine treatments and thus clearly reduces additional visits and the amount of overall medication required.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.
The CDEC draft recommendation appears heavily based on the opinion of two clinical experts and often seems to dismiss concrete RCT evidence of safety and efficacy for difelikefalin to rather favor clinical expert input and opinion on how these concrete data do not apply to patients in Canada afflicted by CKD-aP. For this recommendation the CDCE puts greater emphasis on expert opinion than on objective RCT data. This is contrary to the principles of evidence-based medicine.(10)
10. Lancet. 2017 Jul 22;390(10092):415-423.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

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  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Peter Magner, Associate Professor, Department of Medicine, Division of Nephrology, University of Ottawa • Dr. Swapnil Hiremath, Associate Professor, Department of Medicine, Division of Nephrology, University of Ottawa • Dr. Edward Clark, Associate Professor, Department of Medicine, Division of Nephrology, University of Ottawa • Dr. Brendan McCormick, Associate Professor, Department of Medicine, Division of Nephrology, University of Ottawa • Dr. Marcel Ruzicka, Professor, Department of Medicine, Division of Nephrology, University of Ottawa		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*

Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3

Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752-000
Brand name (generic)	Korsuva (difelikefalin)
Indication(s)	For the treatment of moderate to severe pruritus associated with chronic kidney disease in adult patients on hemodialysis.
Organization	Canadian Nephrologists
Contact information[a]	Name: Claudio Rigatto crigatto@sbgh.mb.ca

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Dear colleagues,

We respectfully disagree with the recommendation 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)".

We write to you as a pan-Canadian group of concerned clinical nephrologists, researchers, renal program administrators, and renal society leaders representing programs and practices coast to coast, regarding a recent decision by CADTH about reimbursement for a new product to treat CKD-aP in people on dialysis.

Specifically, we are concerned that there has been a recent CADTH decision not to reimburse the drug Difelikefalin under any circumstances for the treatment of CKD-aP in patients with moderate to severe symptoms.

As clinicians and researchers, we believe this decision does not adequately reflect the totality of the evidence available and ignores the current clinical context in which there is a dearth of safe and effective therapies available to patients, with many patients continuing to suffer significant symptoms despite treatment (8). Most importantly, this ruling ignores the social context of dialysis patients, most of whom belong to vulnerable, impoverished, and racialized groups who have no private insurance or means to pay out of pocket. In this context, the recommendation not to reimburse will amplify existing structural inequalities in access to therapies: those with means will pay privately, whereas those without means will have to do without.

CKD-aP is an important but under-recognized symptom adversely impacting function and quality of life (1-2). Development of new therapies for itch has been identified as a major priority by patients themselves (3-4). Currently there are no greatly effective therapies. Antihistamines are not effective and are not recommended for chronic CKD-aP (5-6). Many centres are now actively deprescribing antihistamine use for chronic itch in ESRD. Gabapentin/Pregabalin has been used off-label for CKD-aP, usually as a 2nd or 3rd line agent (2). Systematic reviews of several small RCT's (5-6) have suggested good efficacy for treatment of CKD-aP, but it is important to point out that the total number of patients in these included trials is less than the number of patients enrolled in the KALM trials of Difelikefalin. Moreover, gabapentin/pregabalin are challenging drugs to titrate because of the long half-life in dialysis, and recent data suggest severe adverse effects such as delirium, ataxia, falls, and

fractures are common and harmful (5). Finally, even with Gaba analogues, 15-40% of treated patients will have insufficient control of symptoms (8).

We believe that the totality of the randomized clinical trial data on Difelikefalin supports its efficacy and safety for treating moderate to severe itch in CKD-aP (9-11). As in other studies of a subjective symptom (e.g. pain, anxiety, depression), placebo response was high in both trials. Both KALM1 and 2 showed similar response to active treatment with Difelikefalin, with ~50% showing a 3 point or greater reduction in the WI-NRS itch score. This 3-point difference has been validated as a clinically important change for patients (12), so we disagree with the Recommendation's assertion that this magnitude of change is unimportant, as this seems contrary to the available evidence. The placebo response was stronger in KALM 2, diminishing effect size and power of that trial in comparison to KALM 1. Because the trials were nearly identical in design, pooling the results is methodologically reasonable and will give the most powerful, accurate, and generalizable estimate of the true treatment effect. The pooled results confirm the significant effect of Difelikafalin not only on itch severity (WI-NRS), but on important QOL domains as measured by the Skindex-10 and 5D scales (10). Finally, this efficacy is achieved with high tolerability and a low frequency of adverse effects (11), in contrast to emerging data on Gaba analogues (7).

We acknowledge the importance of CADTH's focus on cost effectiveness, and we acknowledge that this medication will be expensive. We worry, however, that CADTH may be undervaluing the enormous amount of human and financial resources that go into managing people with intractable pruritis (e.g. referrals to dermatology; prescription of expensive and unproven therapies such as UV therapy, medicated creams, antihistamines; pharmacy/nursing and MD time), as well as to the ongoing burden of symptoms in people afflicted with severe itch.

Finally, we believe CADTH should also take into consideration the societal implications of their recommendation not to reimburse Difelikefalin under any circumstances. Dialysis patients for the most part have very limited income, and very few have private insurance. The minority of patients with generous income or private insurance would still have access to this therapy, but the large majority would not, thus exacerbating and amplifying the structural, socioeconomic and race-based inequalities in access to therapies that unfortunately persist in our health care system.

Thus, we respectfully ask you, our colleagues at CADTH, to reconsider your recommendation. At minimum we ask that Difelikefalin be reimbursed for individuals with severe symptoms despite treatment trial with available anti-pruritic therapies, including Gaba analogues. This strikes us as a reasonable and responsible approach which better balances patient needs, fairness in access, and fiscal stewardship.

References:

1. Sukul N, et al. Self-reported Pruritus and Clinical, Dialysis-Related, and Patient-Reported Outcomes in Hemodialysis Patients. Kidney Med. 3(1):42-532021
2. Rayner HC, et al. International Comparisons of Prevalence, Awareness, and Treatment of Pruritus in People on Haemodialysis. Clin J Am Soc Nephrol 2017; 12:2000–07.
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4. Jun M, et al. Assessing the extent to which current clinical research is consistent with patient priorities: a scoping review using a case study in patients on or nearing dialysis. Can J Kidney Health Dis. 2015 Oct 1; 2:35. doi: 10.1186/s40697-015-0070-9.
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8. Rayner H, et al. Uraemic pruritus: relief of itching by gabapentin and pregabalin. Nephron Clin. Pract 2012; 122:75-9. 3.
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11. Fishbane S, et al. Safety and tolerability of difelikefalin for the treatment of moderate-to-severe pruritus in hemodialysis patients: pooled analysis from the phase 3 clinical trial program. Kidney Medicine, 2022. 4(8):100513
12. Vernon K, et al. Psychometric validation and meaningful change thresholds of the Worst Itching Intensity Numerical Rating Scale for assessing itch in patients with chronic kidney disease-associated pruritus. Journal of Patient-Reported Outcomes, 2021. 5:134

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
If not, what aspects are missing from the draft recommendation? Please see above		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. See above		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. See above		

[a] CADTH may contact this person if comments require clarification.

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- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)* •		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Claudio Rigatto*
Position	*President, Canadian Society of Nephrology* *Nephrologist, Seven Oaks General Hospital, Winnipeg, Manitoba, Canada* *Professor of Medicine, University of Manitoba*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐
Bayer	☒	☐	☐	☐
Boehringer Ingelheim	☒	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Alexandre Granger*
Position	*Néphrologue - Hémodiafiltration - Hémodialyse à domicile Centre Hospitalier de l'Université de Montréal* *Professeur adjoint de clinique - département de médecine Université de Montréal* *Chercheur investigateur - Centre de Recherche du CHUM*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Bharat Nathoo*
Position	*Nephrologist, CKD Program, Mackenzie Health Hospital, Richmond Hill Hospital and Southlake Regional Health Centre, Ontario*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration	
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.	
Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Otsuka	☒	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Dana Baran*
Position	*Associate Professor, Division of Nephrology, McGill University Health Care Centre*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Alexion	☒	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Daniel Muruve*
Position	*Nephrologist, Foothills Hospital* *Professor, Department of Medicine at the University of Calgary* *Chief Science Officer (CSO), Arch Biopartners*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	*David Mendelssohn*
Position	*Medical Director, Nephrology, Humber River Hospital* *Professor of Medicine, University of Toronto*
Date	*30-03-2023*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 7	
Name	*Edward Clark*
Position	*Nephrologist, The Ottawa Hospital* *Associate Professor, University of Ottawa*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 8	
Name	*Emilie Trinh*
Position	*Nephrologist, McGill University Health Centre, Montreal, Quebec*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 9	
Name	*Faisal Rehman*
Position	*Professor of Medicine, Clerkship Director of Medicine* *Schulich School of Medicine and Dentistry, Western University, London Health Sciences Centre*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Janssen	☐	☒	☐	☐
Pfizer	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐

New or Updated Declaration for Clinician 10	
Name	*Gaylene Hargrove*
Position	*Nephrologist, Victoria Nephrology Associates', Victoria BC* *Chair, BC Renal Palliative Care Committee*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka Pharmaceuticals	☒	☐	☐	☐

New or Updated Declaration for Clinician 11	
Name	*Gerald da Roza*
Position	*UBC Clinical Professor* *Division Head, Fraser Health Nephrology* *Director, Royal Columbian Hospital Clinical Teaching Unit, Postgraduate* *Head of Medicine, Royal Columbian Hospital*

	Associate Site Medical Director, Royal Columbian Hospital
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 12	
Name	*Gershon Frisch*
Position	*Nephrologist, McGill University, Jewish General Hospital, Montreal QC*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 13	
Name	*Jean Maxime Côté*
Position	*Consultant Nephrologist, Centre hospitalier de l'Université de Montréal* *Clinical Investigator, CRCHUM*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 14	
Name	*Jolanta Karpinski*
Position	*Nephrologist, Division of Nephrology, The Ottawa Hospital, University of Ottawa*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 15	
Name	*Karthik Tennankore*
Position	*Associate Professor of Medicine, Dalhousie University, Halifax, NS, Canada* *Consultant Nephrologist, Nova Scotia Health*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka	☐	☒	☐	☐

New or Updated Declaration for Clinician 16	
Name	*Louise Moist*
Position	*Professor of Medicine Epidemiology and Biostatistics* *Clinician Researcher, Western University* *Deputy Chair Division of Nephrology, Schulich School of Medicine & Dentistry, Western University* *London Health Sciences Centre*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
GSK Advisory Board	☒	☐	☐	☐

New or Updated Declaration for Clinician 17	
Name	*Manish Sood*
Position	*Nephrologist, Associate Professor, University of Ottawa* *Secretary-Treasurer, Canadian Society of Nephrology* *Deputy Editor- in- Chief/ Founder of the Canadian Journal of Kidney Health and Disease* *Jindal Research Chair for the Prevention of Kidney Disease*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐
Servier	☒	☐	☐	☐
GlaxoSmithKline	☒	☐	☐	☐

New or Updated Declaration for Clinician 18	
Name	*Melissa Schorr*
Position	*Nephrologist and Ph.D. candidate Department of Nephrology, Western University and Department of Health Research Methodology, Evidence and Impact, McMaster University.*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**

None	☐	☐	☐	☐

New or Updated Declaration for Clinician 19	
Name	*Nicola Matthews*
Position	*Nephrologist, Mackenzie Health, Richmond Hill Hospital, Ontario*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Baxter International	☐	☐	☒	☐

New or Updated Declaration for Clinician 20	
Name	*Paul Komenda*
Position	*Nephrologist, Seven Oaks General Hospital* *Professor of Medicine, University of Manitoba*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 21	
Name	*Paul Sohi*
Position	*Clinical Nephrologist, Saint John Regional Hospital, Horizon Health Network, New Brunswick* *Assistant Professor of Medicine, Department of Medicine at Dalhousie University* *Assistant Professor of Medicine, Department of Medicine at Memorial Universities*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 22	
Name	*Pierre Antoine Brown*
Position	*Associate Professor* *Medical Director, Hemodialysis* *Medical Director, Cystic Kidney Diseases Clinic Division of Nephrology* *The Ottawa Hospital & uOttawa*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka	☐	☒	☐	☐
AstraZeneca	☐	☒	☐	☐
Amgen	☐	☒	☐	☐

New or Updated Declaration for Clinician 23	
Name	*Robert Pauly*
Position	*University of Alberta Hospital*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 24	
Name	*Ron Wald*
Position	*Staff Physician, Division of Nephrology, St. Michael's Hospital* *Medical Director, Hemodialysis, St. Michael's Hospital* *Scientist, Li Ka Shing Knowledge Institute of St. Michael's Hospital* *Professor, Department of Medicine and Institute of Health Policy, Management and Evaluation, University of Toronto*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Baxter	☒	☐	☐	☐
Lilly	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐

New or Updated Declaration for Clinician 25	
Name	*Samuel Silver*
Position	*Chair-CSN QI and Implementation Science Committee* *Assistant Professor, Division of Nephrology, Department of Medicine, Queen's University*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☐	☐	☒	☐
Baxter Canada	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐
Novo Nordisk	☒	☐	☐	☐

New or Updated Declaration for Clinician 26	
Name	*Sara Dunsmore*

Position	*Nephrologist, Seven Oaks General Hospital* *Assistant Professor, University of Manitoba*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 27	
Name	*Sheldon Tobe*
Position	*University of Toronto Postgraduate Fellowship Director - Nephrology* *Professor of Medicine, University of Toronto and Northern Ontario School of Medicine*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Boehringer Ingelheim	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Bayer	☒	☐	☐	☐

New or Updated Declaration for Clinician 28	
Name	*Tamara Glavinovic*
Position	*CSN Quality Improvement & Implementation Science Committee Member* *Assistant Professor, University of Ottawa*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 29	
Name	*Tomoko Takano*
Position	*Professor of Medicine, McGill University* *President (elect), Canadian Society of Nephrology*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 30	
Name	*Veronica Silva*
Position	*Nephrologist* *Trillium Health Partners*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 31	
Name	*William Beaubien-Souligny*
Position	*Centre Hospitalier de l'Université de Montréal*
Date	*30-03-2023*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
GSK	☒	☐	☐	☐
Bayer	☐	☐	☒	☐
AstraZeneca	☐	☐	☒	☐

New or Updated Declaration for Clinician 32	
Name	*Caroline Stigant*
Position	*Nephrologist, Assistant Professor of Medicine, Division of Nephrology, Department of Medicine, University of British Columbia and Island Health Authority*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 33	
Name	*Adeera Levin*
Position	*Professor of Medicine, University of British Columbia* *Head Division of Nephrology* *Executive Director BC Renal* *Consulting Nephrologist St Paul's Hospital*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐

New or Updated Declaration for Clinician 34	
Name	*Louis Girard*
Position	*Medical Director of Apheresis* *Medical Director of Glomerulonephritis* *Glomerulonephritis Fellowship Program Director* *Nephrologist & Clinical Professor of Medicine, Cumming School of Medicine, University of Calgary*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Otsuka	☐	☐	☒	☐

New or Updated Declaration for Clinician 35	
Name	*Normand Proulx*
Position	*Staff Nephrologist CISSS de l'Outaouais*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Otsuka	☐	☒	☐	☐

New or Updated Declaration for Clinician 36	
Name	*Ann Young*
Position	*Unity Health Toronto*

Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
none	☐	☐	☐	☐

New or Updated Declaration for Clinician 37	
Name	*Yasin Parpia*
Position	*Nephrologist, Seven Oaks General Hospital*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 38	
Name	*Navdeep Tangri*
Position	*Nephrologist, Seven Oaks General Hospital* *Professor of Medicine, University of Manitoba*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka	☒	☐	☐	☐

New or Updated Declaration for Clinician 39	
Name	*Ronald Hons*
Position	*Retired (45 years experience in below positions)* *Nephrologist, Foothills Hospital* *Associate Clinical Professor and Medical Director of Dialysis Services, University of Calgary*
Date	*30-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 40	
Name	*Andrea Mazurat*
Position	*Nephrologist, Seven Oaks General Hospital* *Assistant Professor, University of Manitoba*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 41	
Name	*Bhanu Prasad*
Position	*Professor of Medicine, University of Saskatchewan* *Consultant Nephrologist, Regina, SKHA*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Medtronic	☐	☐	☐	☒
Astra Zeneca	☐	☐	☒	☐

New or Updated Declaration for Clinician 42	
Name	*Sara MacDonald*
Position	*Nephrologist CISSSO, Hôpital de Hull, Gatineau, QC*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 43	
Name	*Sandra Dumanski*
Position	*Nephrologist, Assistant Professor, Cumming School of Medicine, University of Calgary*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 44	
Name	*Daniel Schwartz*
Position	*Director, Home Peritoneal Dialysis Program, Fraser Health* *Clinical Assistant Professor, Faculty of Medicine, University of British Columbia*
Date	*31-03-2023*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka	☒	☐	☐	☐

New or Updated Declaration for Clinician 45	
Name	*Jay Hingwala*
Position	*Nephrologist, Health Sciences Centre Winnipeg, Manitoba Renal Program* *Assistant Professor of Medicine, Section of Nephrology, University of Manitoba*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka Advisory Board	☐	☒	☐	☐

New or Updated Declaration for Clinician 46	
Name	*Alissa Chehade*
Position	*Nephrologist, Hull Hospital (CISSSO)*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 47	
Name	*Daniel Samaha*
Position	*Nephrologist, Hull Hospital, Gatineau Quebec*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 48	
Name	*Paul Ayoub*
Position	*Chief of Nephrology, Nephrologist, Verdun Hospital*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐

New or Updated Declaration for Clinician 49	
Name	*Phil McFarlane*
Position	*Division of Nephrology, St. Michael's, Toronto*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**

Otsuka	☐	☐	☒	☐

New or Updated Declaration for Clinician 50	
Name	*Jordan Weinstein*
Position	*Associate Professor of Medicine, University of Toronto* *Nephrologist, St. Michael's Hospital*
Date	*31-03-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
OCPI	☒	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752-000
Brand name (generic)	Korsuva (difelikefalin)
Indication(s)	Uremic pruritus
Organization	Fraser Health, Division of Nephrology
Contact information[a]	Name:

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We do not agree with the recommendation to not fund this therapy.

The recommendation indicates that the studies "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."

In fact, the KALM-1 and KALM-2 studies both showed statistically and clinically significant improvement in the primary outcome of percentage of patients with improved WI-NRS (Worst Itching Intensity Numerical Rating Scale) of at least 3 points.

While all studies have some degree of uncertainty, this is addressed by the statistical analysis of the outcome data. In the KALM clinical trial program, the differences in outcomes between placebo and intervention arm were statistically significant with acceptable 95% confidence intervals.

We do not agree there is "considerable uncertainty".

The CADTH recommendations suggest that the KALM trials should have used a threshold of 4 points on the WI-NRSS rather than 3 points. We are not aware that there is strong evidence to support the 4 point threshold over the 3 point threshold. Moreover, even if one were to use the 4 point threshold, both KALM-1 and KALM-2 showed a statistically significant improvement based on that measure.

The recommendations indicate that "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."

There are several points in this statement that we disagree with.

First, the fact that there is a placebo response is not unique to these trials. In fact, this is a known phenomenon in countless clinical trials. The burden on the investigators is to show benefit beyond placebo, which was done. A high placebo rate has no impact on the validity of the magnitude of benefit reported.

Moreover, even with a placebo response rate, there is still a very high burden of symptoms that is unaddressed. The data available clearly indicates that difelikefalin provides clear and meaningful added benefit beyond placebo.

Even if the placebo rate was an important determinant of the quality of the trials, we do not agree that the optimization of HD and permitted use of concomitant therapies impacted the validity of the trials.

The trials were careful to ensure that patients enrolled were well-dialyzed with adequate Kt/V. Most clinicians will first ensure adequate dialysis when faced with a patient with uremic pruritus. Had the patients been under-dialyzed at enrollment, the papers would have rightfully been criticized for not first optimizing dialytic clearance. You can't have it both ways – you can't criticize an RCT in uremic pruritis if dialytic adherence is good and also criticize it if it isn't good. Overall, if one had to choose, you would clearly want a trial that made efforts to ensure both arms were on good background therapy.

With regards to background therapy with pharmaceutical agents, this is a more challenging question as there are currently no medications with an indication to treat uremic pruritus. It seems reasonable to have allowed patients to be enrolled on whatever background therapy their doctors had prescribed and ensure the Table 1 showed no significant imbalance between groups. It would have been impossible to design a study that required all patients to be on specific background therapy given the absence of a clear standard of care. It is encouraging to see that the efficacy of difelikefalin appears to be independent of the use of antipruritic medications as per Topf J et al. Kidney Med. 2022 Jun 28;4(8):100512. doi: 10.1016/j.xkme.2022.100512.

Even if there was some impact on the trial participants based on the patients' Kt/V and background anti-pruritic therapy, the purpose of randomization is to ensure that these confounders are applied equally to both placebo and intervention arm. So we do not agree that that there is "uncertainty of the magnitude of benefit that can be attributed to difelikefalin." If these were a set of observational trials, then yes, confounders would be a concern.

It should also be recalled that difelikefalin is the first drug we have in nephrology that is specifically made available to address symptom burden. We are used to using drugs that reduce future events such as kidney failure, MI, stroke or hospitalization for heart failure, etc. In those sorts of trials, we need to treat all patients indefinitely, recognizing that only some will benefit, but we will never know which ones (hence the concept of the number needed to treat).

With a drug such as difelikefalin that is designed to improve symptoms, we can simply ask patients (using a validated scoring system) if the drug is helping. If not, we can stop it (de-prescribe). Unlike in a clinical trial, we have no obligation to continue a therapy that isn't helping. This will allow us to focus resources on those patients who are seeing a benefit, which in turn should improve the cost effectiveness of the drug.

The CADTH recommendations point out that "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." We would completely agree that those goals are universal among dialysis patients.

However, pruritus is one of the most common symptoms we face that we struggle to treat. It seems unlikely that patients would decline a therapy that addresses bothersome pruritus simply because it doesn't also address other desires. For example, while we would love it if SGLT2 inhibitors prevented lower extremity amputation, we will still prescribe this class even if it only prevents progression of CKD.

For now, we'll take what we can get. A new option for a symptom that is often debilitating remains exciting, even if it can't solve other problems.

The CADTH report criticizes difelikefalin as there was uncertainty "...about whether the drug would address the underlying disease process that causes pruritus." Like many therapies that address symptom burden, we agree that difelikefalin does not treat the underlying disease. However, the goal for patients and clinicians is to reduce symptom burden even if the underlying disease cannot be cured. Again, we'll take what we can get for now. While a cure is the long term goal, we'll accept a successful treatment while waiting for a cure to be discovered.

We do agree with the report that a therapy such as difelikefalin would likely be used after first-line options are not tolerated or fail to control symptoms. We imagine most patients would receive an emollient, gabapentin and perhaps other interventions before difelikefalin is offered. This pattern of practice may also mitigate excess cost associated with usage of this therapy.

Overall, we find the data in support of difelikefalin persuasive enough to want to offer it to our patients with an unaddressed pruritus symptom burden despite best efforts otherwise. The rationale for recommending against coverage does not seem clearly supported by the data available, and the arguments used are not persuasive.

As frontline clinicians caring for these patients, we'd ask you how we should respond to patients who are suffering, knowing there is a Health Canada approved therapy but an absence of funding. The Canadian nephrology community has a strong track record of responsible use of scarce resources. We believe we are in the ideal position to identify patients who can be offered this therapy when other options have failed, and also de-prescribe it in the absence of efficacy.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐

If not, what aspects are missing from the draft recommendation?

Not applicable

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

While the reasons are clear, we disagree with many of the reasons, as described above.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Gerald Da Roza*

Position	Nephrology & Internal Medicine, Fraser Health UBC Clinical Professor Division Head, Fraser Health Nephrology Director, Royal Columbian Hospital Clinical Teaching Unit, Postgraduate Head of Medicine, Royal Columbian Hospital Associate Site Medical Director, Royal Columbian Hospital Nephrology & Internal Medicine, Fraser Health
Date	*March 26, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Daniel Schwartz*
Position	Director, Home Peritoneal Dialysis Program, Fraser Health Clinical Assistant Professor, Faculty of Medicine University of British Columbia
Date	*March 26, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Otsuka	☒	☐	☐	☐
Fraser Health	☐	☒	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Aleisha Hatakka*
Position	*Nephrologist, Fraser Health*
Date	*March 26, 2023*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Gerardo Carpenito*
Position	*Nephrologist, Fraser Health*
Date	*March 26, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Shaoyee Yao*
Position	Nephrologist, Division of Nephrology, Fraser Health Medical Director, Fraser Health Hemodialysis Program Clinical Instructor, University of British Columbia
Date	*March 26, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Mike Bevilacqua*
Position	Nephrologist, Division of Nephrology, Fraser Health Medical Director, Fraser Health Home Hemodialysis Program Clinical Assistant Professor, University of British Columbia
Date	*March 26, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company
None

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752-000
Brand name (generic)	difelikefalin
Indication(s)	Moderate to severe pruritus associated with CKD in adults on hemodialysis.
Organization	Scarborough Regional Health - Dermatologist
Contact informationa	Dr. Morvarid Hessami, Dermatologist, Scarborough Regional Health

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

CDEC did not think a 3 point improvement in the Worst Itching Intensity Numerical Rating Scale (WI-NRS) was clinically significant. It was felt a 4 point improvement would be necessary to demonstrate clinical significance.

The 4 point improvement is based on recent experiences with atopic dermatitis and use of biologics[1]. **It has been demonstrated that the minimally clinically important difference(MCID) is ≥ 2 -3 point reduction in the baseline NRS in atopic dermatitis[3]. In addition, the Worst Intensity-NRS scale is validated for assessing itch in pts with chronic kidney disease associated pruritus and ≥ 3 points from baseline score represents an appropriate clinically meaningful within-patient change on the WI-NRS.[4] The *NRS is not a practical score on everyday dermatology practice.***

Uremic pruritis consistently ranks in the top two concerns patients have on dialysis[5]. It affects quality of life significantly, mood sleep and recovery from dialysis[6].

(1) This is not a common disease for general dermatologists to manage unless there is affiliation with a hospital and dialysis clinic. Taking care of these patients and not having any effective treatment is frustrating.

(2) Patients with uremic pruritus are treated with gabapentin, pregabalin, Myfortic, Cellcept, Prednisone and recently off lable with Dupilumab[7]. Dupilumab could be effective; however, it does not have an indication for the treatment of CKD-aP and currently only case reports are reported. Moreover, it is much more expensive than difelikefalin.

(3) As a dermatologist dealing with dialysis patients and facing the challenges and frustrations, I was hoping to have another option to improve this orphan disease! The comparison in my practice is Hidradenitis suppurativa a severe disease with the only on label option in advanced forms to be Humira which would be 30% effective but still improves their quality of life so widely used despite the cost.

(4) Real world experience in USA based on the recent talks in American Academy of Dermatology meeting and Fall clinical states the significant improvement on quality of life of these patients on Difelikefalin

Note: We do not have any financial interest in this company nor this drug and never received any honorarium nor attended any adboards. Our statements above are based on vast experience with these patients and hoping to improve their quality of life. Even 30-40% improvement makes a huge difference in their quality of life.

1) Beck L. A. ***Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis*** N Engl J Med **2014;371:130.**
2) **Shi V. Y. *et al.*** *Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND)* J AM ACAD DERMATOL VOLUME 87, NUMBER 2
3) **Reich A. *et al.*** *Itch Assessment with Visual Analogue Scale and Numerical Rating Scale: Determination of Minimal Clinically Important Difference in Chronic Itch Acta Derm Venereol 2016; 96: 978–980*
4) **Vernon *et al.* Psychometric validation and meaningful change thresholds of the Worst Itching Intensity Numerical Rating Scale for assessing itch in patients with chronic kidney disease-associated pruritus. Journal of Patient-Reported Outcomes (2021) 5:134**
5) **Manns B. *et al.* Setting research priorities for patients on or nearing dialysis. Clin J Am Soc Nephrol. 2014 Oct 7;9(10):1813-21.**
6) **Mettang T., Kremer A. E.** Uremic pruritus. Kidney International (2015) 87, 685–691
7) Hercz D. *et al.* Interventions for Itch in people with advanced chronic kidney disease (review)Cochran database of systematic reviews. 2020.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Morvarid Hessami-Booshehri
Position	*Head of dermatology at Scarborough General Hospital , UofT lectrurer*
Date	*Please add the date form was completed (31-03-2023)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.	
Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No conflicts of interest to declare	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Scott Walsh
Position	*Associate Professor, Division of Dermatology* *Department of Medicine* *Sunnybrook Health Sciences Centre and Women's College Hospital*
Date	*Please add the date form was completed (31-03-2023)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No conflicts of interest to declare	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*FIROUZEH NIAKOSARI*
Position	*Dermatologist, Consultant of North York General Hospital*
Date	*Please add the date form was completed (31-03-2023)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No conflicts of interest to declare	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752
Name of the drug and Indication(s)	Difelikefalin (Korsuva) for severe pruritus associated with chronic kidney disease
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0752-000
Brand name (generic)	difelikefalin
Indication(s)	Moderate to severe pruritis associated with chronic kidney disease in adult patients on hemodialysis
Organization	The Kidney Foundation of Canada
Contact information[a]	Name: Carrie Thibodeau

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation?	Yes	☐
	No	☒

The Kidney Foundation of Canada does not agree with the recommendation that difelikefalin should not be reimbursed for the treatment of moderate to severe pruritis in hemodialysis patients on these grounds:

- Pruritis is a very common symptom experienced by people undergoing dialysis, and many report that it has a negative effect on their quality of life, including their ability to sleep and their mental health. Severe pruritis can lead to scratches, bleeding, and scabs, and as reported in the Foundation's patient input submission, the detrimental effect on patients' appearance can sometimes mean that they withdraw and limit their interactions with others.
- Any increase to quality of life is relevant to people on dialysis, whose daily lives are structured around their illness. In-centre hemodialysis generally requires three treatments a week of approximately 4 hours each, and those receiving this treatment also face dietary restrictions, the need for multiple medications per day, and treatment for co-morbid conditions.
- People who are receiving dialysis treatment already face significant out-of-pocket costs. Pruritis is a symptom that can be expensive to alleviate for patients, because the main treatments available are over-the-counter and often not covered by provincial/territorial or private drug plans. These treatments include antihistamines, corticosteroid creams or ointments, and moisturizing creams and ointments.
- The stated outcomes for the evaluation of the cost and cost-effectiveness of difelikefalin are QALYs and LYs. By this measure, people with chronic conditions such as kidney disease may be disadvantaged, because while their quality of life may increase with a particular medication, the effect on the length of their lives may be difficult to quantify.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

The Kidney Foundation of Canada is requesting a more fulsome consideration of the following information provided in our original patient input submission:

- Over 90% of the respondents to the Kidney Foundation's survey reported having experienced itching, and 80% described the itching as severe.
- Sleep disturbance, an important quality of life issue, was reported by many survey respondents.
- People with kidney failure and their caregivers often face significant out-of-pocket costs, which may be compounded by reduced income due to absence from or inability to work. A medication that reduces pruritis could decrease out-of-pocket costs for over-the-counter treatments in a population already grappling with financial burdens.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

A. Patient Group Information	
Name	*Carrie Thibodeau*
Position	*Manager of Health Policy and Government Relations*
Date	*Please add the date form was completed (30-03-2023)*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Chinook	☐	☒	☐	☐
Astellas	☒	☐	☐	☐