

**7.02 DIFELIKEFALIN,
Solution for I.V. injection 50 micrograms in 1 mL vial,
Korsuva[®],
Vifor Pharma Pty Limited.**

1 Purpose of submission

- 1.1 The Standard Re-entry submission requested a Section 100 (Highly Specialised Drugs Program (HSD)), Authority Required (Telephone/Online) listing for the treatment of moderate to severe pruritus associated with chronic kidney disease (CKD) in adult patients on haemodialysis.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of difelikefalin versus best supportive care.

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Adult patients on haemodialysis with moderate to severe pruritus associated with chronic kidney disease, who have inadequate response to best supportive care
Intervention	Difelikefalin in addition to best supportive care
Comparator	Best supportive care
Outcomes	Improvements in disease-related symptoms leading to improved quality of life
Clinical claim	Superior efficacy and inferior safety compared to best supportive care

Source: Table 1, p18 of the resubmission

2 Background

Registration status

- 2.1 Difelikefalin was approved by the TGA on 10 November 2022 for the treatment of moderate to severe pruritus associated with CKD in adult patients on haemodialysis.

Previous PBAC consideration

- 2.2 Table 2 summarises the key matters of concern identified at the March 2023 PBAC meeting and how these were addressed in the resubmission.

Table 2: Summary of key matters of concern

Matter of concern (March 2023 meeting)	Addressed in the resubmission
Context and intended use	
<p>The PBAC considered the proposal to limit treatment to patients receiving in-centre haemodialysis inappropriately excluded patients undergoing haemodialysis at home (para 7.3, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The requested restriction was revised, allowing any patient on haemodialysis (in-centre or at-home) access to treatment with difelikefalin.</p>
<p>The PBAC noted the proposed restriction did not include formal criteria for assessing baseline pruritus severity or treatment response for continuing therapy. The PBAC considered that use of the Worst Itching Intensity Numerical Rating Scale (WI-NRS) would be feasible, with baseline severity and response criteria based upon trial-based thresholds (i.e. severity: a WI-NRS score > 4; response criteria: at least a 3-point improvement in WI-NRS) (para 7.3, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The revised restriction includes formal initial and continuing treatment criteria based on the WI-NRS instrument. Definitions of baseline severity and treatment response were based on thresholds used in the clinical trials, consistent with PBAC's consideration.</p>
<p>The PBAC considered the quantities and repeats needed to allow for variability in dosing regimens, as dosing of difelikefalin was weight based and some patients receive more dialysis sessions per week (para 7.3, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The revised restriction includes prescribing instructions that allow applications for increased vials according to weight-based dosing requirements but not additional doses associated with unplanned dialysis sessions.</p>
<p>Given changing haemodialysis regimens, the PBAC considered the restriction should be silent on the frequency of haemodialysis (para 7.3, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The requested restriction is silent on the frequency of haemodialysis.</p>
Economic evaluation	
<p>The PBAC noted the reliability of the economic evaluation for decision-making was contingent on acceptance of the modelled utility decrements for pruritus. The PBAC noted concerns regarding the reliability of the approach used to map 5D-Itch scores to utility values, yielding utility decrements that were implausibly large (mild 0.0676, moderate 0.1544 and severe 0.2606) (para 7.8, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The resubmission provided additional justification to address PBAC's concerns with the large utility decrements in the previous submission based on an updated literature review and comparisons with other sources of utilities.</p> <p>The resubmission used an alternative set of utilities from a mapping function developed by the University of Sheffield that converted trial-based 5D-Itch scores to utility values. The resubmission argued that the updated estimates have greater plausibility than the estimates previously considered by the PBAC, as the utility values were lower at baseline and yielded smaller utility decrements for pruritus.</p>
<p>The PBAC noted the economic model assumed an attenuating placebo effect for patients on best supportive care (BSC) with no matching adjustments to difelikefalin treated patients who also continued to improve up to Week 64. The PBAC noted this differential approach to extrapolating the effects of difelikefalin and placebo led to an increase in the incremental treatment benefit between Weeks 12 and 64 of the model. The PBAC considered the approach favoured difelikefalin and was inadequately justified (para 7.9, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The resubmission used a revised approach to extrapolate treatment effects. Additional benefits between Weeks 12 to 64 for difelikefalin vs BSC were maintained, but the attenuation of placebo effects previously applied to BSC was removed (i.e. no change in pruritus severity after Week 64 for difelikefalin and after Week 12 for BSC). The resubmission claimed the current approach is highly conservative as patients are unlikely to maintain ongoing placebo effects. The resubmission argued the approach was biased against difelikefalin as patients in the BSC arm maintained ongoing benefits with no treatment costs.</p>

Matter of concern (March 2023 meeting)	Addressed in the resubmission
<p>The PBAC considered the assumed cause-effect relationship between high itch scores and death was inappropriate and should be removed from the economic model (para 7.9, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The assumed cause-effect relationship between high itch scores and death (and associated mortality benefit with difelikefalin treatment) was removed.</p>
<p>The PBAC noted the pre-PBAC response presented a revised model base case that attempted to address ESC's concerns regarding attenuating placebo effects in the BSC arm, no costs and disutilities for adverse events and not accounting for patients needing more than 1 vial of difelikefalin per dose. The PBAC considered that the revised model required evaluation, but also retained the same implausibly large utility decrements. The PBAC considered the revised base case ICER/QALY gained of \$█████¹ (including a █████% price reduction) was underestimated and too high given the inherent uncertainty. The PBAC considered a further price reduction would be required for difelikefalin to be considered cost effective (para 7.10, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>In addition to changes described above (utility decrements, extrapolated treatment effects, mortality impacts), the resubmission included costs and utilities for adverse events and accounted for some patients needing 2 vials per dose.</p> <p>The resubmission proposed a reduced AEMP of \$█████. This is a █████% reduction from the March 2023 pre-PBAC response (AEMP \$█████).</p> <p>The resubmission argued the revised base case ICER/QALY gained of \$█████² can be considered good value for money in view of suitably conservative revisions to the economic model that are either more reliable and plausible (e.g. utility values, weight-based dosing, adverse events) or unambiguously biased against difelikefalin (durable placebo response, no mortality impacts).</p>
Utilisation and financial impact of listing	
<p>The PBAC agreed with the DUSC that the estimates in the resubmission were significantly underestimated, with concerns raised regarding key inputs of the budget impact model. The PBAC noted the pre-PBAC response presented revised estimates that addressed some of DUSC's concerns and considered the revised approach may be reasonable, however also noted it had not been independently evaluated. The PBAC advised that a risk sharing arrangement (RSA) would be required to address any residual uncertainty with the potential for use outside the proposed restriction, including in patients with mild pruritus (para 7.11, difelikefalin PSD, March 2023 PBAC meeting).</p>	<p>The resubmission included major structural and methodological changes to the budget impact model, with a simplified prevalence-based approach to uptake, continuation and adherence rates applied to the estimated eligible population in each year. The resubmission also addressed some of DUSC's concerns regarding key inputs of the March 2023 submission's budget impact model.</p> <p>The resubmission argued that many issues with underestimation are addressed by the incorporation of formal criteria (WI-NRS thresholds) in the restriction as well as a proposal for an RSA. The RSA offered by the resubmission was based on predicted financial estimates and a █████% rebate.</p>

Source: Table 2, p19 of the resubmission

Abbreviations: AEMP, ex-manufacturer price; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Dispensed Price for Max. Qty a	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
DIFELIKEFALIN						
Difelikefalin 50 microgram/mL injection, 12 x 1mL vial	<p>Public \$540.00 (published) \$ (effective) \$ (pre-PBAC)</p> <p>Private \$569.97 (published) \$ (effective) \$ (pre-PBAC)</p>	New HSD (Public) New HSD (Private)	1	12	2	Korsuva
Restriction Summary [new 1] / Treatment of Concept: [new 2]						
Category / Program: Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required - Telephone/Online PBS Authorities system						
Administrative Advice: No increase to the maximum number of repeats may be authorised.						
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).						
Administrative Advice: <i>The latest 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) is version [Sponsor to advise]. See the following article for details:</i> <i>[Sponsor to advise]</i>						
Severity: Moderate to severe						
Condition: Pruritus (itching) associated with chronic kidney disease						
Indication: Moderate to severe pruritus (itching) associated with chronic kidney disease						
Treatment Phase: Initial treatment						
Clinical criteria: Patient must have chronic kidney disease						
AND						
Clinical criteria: Patient must be on optimised haemodialysis						
AND						
Clinical criteria: Patient must be on haemodialysis for at least 3 months						
AND						
Clinical criteria: The condition must be confirmed based on both physical examination and patient history (to exclude any factors that may be triggering the pruritus)						
AND						
Clinical criteria Patient must have experienced itch that persists for at least 6 weeks despite best supportive care.						
AND						
Clinical criteria:						

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Patient must have a 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) baseline score of more than 4.
AND
Clinical criteria:
Patient must not receive more than 12 weeks of treatment with this drug under this treatment phase
AND
Treatment criteria:
<i>Must be treated by at least one of (i) a renal physician, (ii) nephrologist, (iii) allergist.</i>
AND
Population criteria:
Patient must be at least 18 years of age
Prescribing Instructions: Prescriber must exclude any other causes of pruritus which include any of the following: (i) drug/dialysis related (e.g., opioid-related pruritus) (ii) drug hypersensitivity or adverse effect; contact dermatitis; allergy (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; liver disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes).
Prescribing Instructions: Best supportive care for patients with chronic kidney disease-associated pruritus is not limited to but includes: (i) optimisation of dialysis, (ii) skin hydration and nutrition (with the use of moisturiser, emollients, barrier creams or oils) (iii) patient education on the importance of avoiding or minimising scratching.
Prescribing instructions: <i>Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.</i>
Prescribing Instructions: <i>At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug, based on the dry body weight of the patient (in kg), adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). Up to a maximum of 2 repeats will be authorised. No more than 4 doses per week will be authorised even if the number of haemodialysis treatments in a week exceeds 4. Requests for increased quantities may be authorised to provide sufficient doses for the initial 12 weeks of therapy based on the weight based dosing table in the approved Product Information.</i>

Name, Restriction, Manner of administration and form	Dispensed Price for Max. Qty a	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
DIFELIKEFALIN						
Difelikefalin 50 microgram/mL injection, 12 x 1mL vial	<p style="text-align: center;">Public</p> <p>\$540.00 (published) \$ (effective) \$ (pre-PBAC)</p> <p style="text-align: center;">Private</p> <p>\$569.97 (published) \$ (effective) \$ (pre-PBAC)</p>	New HSD (Public) New HSD (Private)	1	12	5	Korsuva
Restriction Summary [new 3] / Treatment of Concept: [new 4]						
Category / Program: Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals}						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities system						

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<p>Administrative Advice: No increase to the maximum number of repeats may be authorised.</p>
<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>
<p>Administrative Advice: <i>The latest 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) is version [Sponsor to advise]. See the following article for details:</i></p> <p><i>[Sponsor to advise]</i></p>
<p>Severity: Moderate to severe</p>
<p>Condition: Pruritus (itching) associated with chronic kidney disease</p>
<p>Indication: Moderate to severe pruritus (itching) associated with chronic kidney disease</p>
<p>Treatment Phase: Continuing treatment</p>
<p>Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition</p>
<p>AND</p>
<p>Clinical criteria Patient must have demonstrated / sustained an adequate response to treatment with this drug</p>
<p>AND</p>
<p>Clinical criteria: Patient must have demonstrated / sustained an adequate response to treatment with this drug including at least a 3-point improvement from baseline in 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) score.</p>
<p>AND</p>
<p>Treatment criteria: Must be treated by at least one of (i) a renal physician, (ii) nephrologist, (iii) allergist, (iv) medical practitioner in consultation with one of these specialists.</p>
<p>Prescribing instructions: <i>Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.</i></p>
<p>Prescribing Instructions: <i>At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug, based on the dry body weight of the patient (in kg), adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). Up to a maximum of 5 repeats will be authorised. No more than 4 doses per week will be authorised even if the number of haemodialysis treatments in a week exceeds 4. Requests for increased quantities may be authorised to provide sufficient doses for the 24 weeks (continuing or grandfather) of therapy based on the weight-based dosing table in the approved Product Information.</i></p>
<p>Restriction Summary [new 5] / Treatment of Concept: [new 6]</p>
<p>Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfather treatment</p>
<p>Clinical criteria: Patient must have been receiving non-PBS-subsidised treatment with drug for this condition prior to [PBS listing date]</p>
<p>AND</p>
<p>Clinical criteria:</p>

<p>Patient must have met all other PBS eligibility criteria that a non- 'Grandfather' patient would ordinarily be required to meet, meaning that at the time non-PBS subsidised supply was commenced, the patient:</p> <p>(i) was on optimised haemodialysis, (ii) was on haemodialysis for at least 3 months (iii) had a condition confirmed based on both physical examination and patient history (iv) had experienced itch that persists for at least 6 weeks despite best supportive care. (v) had a 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) of more than 4 at baseline.</p>
AND
Clinical criteria:
<p>Patient must have demonstrated / sustained an adequate response to the most recent non-PBS-subsidised treatment with this drug for this condition, including at least a 3-point improvement from baseline in 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) score.</p>
AND
Treatment criteria:
<p>Must be treated by, or in consultation with, any of the following specialists: renal physician, nephrologist, allergist, or general physician experienced in the management of patients with chronic kidney disease</p> <p>Must be treated by at least one of (i) a renal physician, (ii) nephrologist, (iii) allergist, (iv) medical practitioner in consultation with one of these specialists.</p>
AND
Population criteria:
<p>Patient must be at least 18 years of age</p>
Prescribing instructions:
<p>Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.</p>
Prescribing Instructions:
<p>At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug, based on the dry body weight of the patient (in kg), adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). Up to a maximum of 5 repeats will be authorised. No more than 4 doses per week will be authorised even if the number of haemodialysis treatments in a week exceeds 4. Requests for increased quantities may be authorised to provide sufficient doses for the 24 weeks of therapy based on the weight-based dosing table in the approved Product Information.</p>
Administrative advice:
<p>A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.</p>
Administrative advice:
<p>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</p>

^a DPMQ estimates were incorrectly calculated in in the resubmission using fees and mark-ups associated with a Section 85 listing (1 July 2022 Schedule). During the evaluation and preparation of the PBAC Minutes, DPMQ estimates were calculated for the requested Section 100 – Highly Specialised Drugs Program (Public and Private Hospital) listing using the proposed AEMPs in the resubmission and pre-PBAC response with fees and mark-ups effective 1 July 2023.

- 3.2 The resubmission proposed a special pricing arrangement with an effective AEMP of \$| for 12 vials and a published AEMP of \$540.00 for 12 vials. The effective AEMP was 20% lower than proposed in the March 2023 pre-PBAC response (\$|). The pre-PBAC response offered a |% price reduction resulting in an effective AEMP of \$| for 12 vials (\$| per vial).
- 3.3 The resubmission presented an effective DPMQ of \$| and published DPMQ of \$616.77. These estimates were incorrectly calculated using fees and mark-ups for a General Schedule listing instead of the requested Highly Specialised Drugs (HSD) Public and Private hospital program. The ESC previously noted that Complex Authority

Required (CAR) listings under the HSD Public and Private hospital program would allow difelikefalin to be dispensed by a S90 Community Pharmacy as well as a Public/Private Hospital Pharmacy, which may assist access for patients receiving in-home dialysis (para 3.7, difelikefalin Public Summary document (PSD), March 2023 PBAC meeting).

- 3.4 The resubmission used effective DPMQs of \$█ in the economic model and \$█ in the financial estimates with slight differences due to rounding in the calculations. During the evaluation, DPMQ estimates for the requested Section 100 (HSD) listing were calculated using the proposed effective AEMP of \$█ and 1 July 2023 fees and mark-ups. The economic model and financial estimates were updated using a weighted DPMQ of \$█ assuming most patients would obtain difelikefalin through public hospitals (75% public, 25% private/S90 community pharmacy).
- 3.5 The revised restriction allows for applications for increased quantities associated with weight-based dosing but does not account for increased quantities associated with additional dialysis sessions. This was inconsistent with trial data suggesting approximately 24% of patients required at least 1 additional dose during the 12-week double-blind period. The ESC considered the addition of the following Prescribing Instruction for the initial treatment restriction would be appropriate 'At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug, based on the dry body weight of the patient (in kg), adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). Up to a maximum of 2 repeats will be authorised. No more than 4 doses per week will be authorised even if the number of haemodialysis treatments in a week exceeds 4.' The number of repeats mentioned in the Prescribing Instruction would be modified for the continuing and Grandfathering restriction to allow up to 5 repeats (6 months in total per prescription).
- 3.6 The resubmission reiterated that only the 12-vial pack size will be marketed in Australia. The ESC previously noted the sponsor's intention for dispensed difelikefalin vials to be stored at in-centre facilities and considered the dispensing of a large number of vials at one time and the proposed storage arrangements may lead to quality use of medicines (QUM) issues. The ESC previously considered that such QUM issues were also likely if difelikefalin was used in home-based haemodialysis. The ESC noted smaller pack sizes of 3 vials are approved by the EMA (para 3.5, difelikefalin PSD, March 2023 PBAC meeting).
- 3.7 The requested restriction is narrower than the TGA indication in terms of place in therapy (patients with inadequate response to best supportive care).
- 3.8 Compared to the previous submission, the current restriction allows for at-home dialysis patients to access treatment, is silent on the frequency of haemodialysis and includes formal initial and continuing treatment criteria using the Worst Itching Intensity Numerical Rating Scale (WI-NRS) using trial-based thresholds for disease severity and response. This was consistent with PBAC's previous consideration of difelikefalin (para 7.3, difelikefalin PSD, March 2023 PBAC meeting).

- 3.9 The proposed restriction did not include a lifetime limit for treatment with difelikefalin, which was inconsistent with modelled circumstances of use in the economic evaluation. However, the ESC agreed with the Pre-Sub-Committee-Response that it would be clinically appropriate to allow for episodic treatment with difelikefalin given considerable variability in the clinical presentation of CKD-associated pruritus.
- 3.10 The resubmission claimed that there will still be risk of use outside the restriction given the subjective nature of the WI-NRS instrument. The resubmission acknowledged that usage outside the restriction is inconsistent with the clinical evidence, economic evaluation and financial estimates but proposed that the risk be managed through a Risk Sharing Arrangement based on the financial estimates of the resubmission. The Pre-Sub-Committee Response (PSCR) provided a reference (Vernon 2021) which included a version of the WI-NRS in the supplementary information that can be incorporated in the restriction.¹
- 3.11 There was an additional clinical criterion for adequate response in the continuing treatment restriction which may have been included in error in the resubmission.
- 3.12 The wording for treatment criteria was inconsistent between the proposed restrictions for initial treatment (no wording provided), continuing treatment and grandfathered treatment (different terms used for nominated specialists). The ESC previously noted advice from the Department that general practitioners ‘in consultation with specialists’ cannot initiate treatment but can continue treatment under the S100 Highly Specialised Drugs Program (Attachment 1, difelikefalin ESC advice, March 2023 PBAC meeting). The ESC noted the treatment criteria stated ‘Must be treated by at least one of (i) a renal physician, (ii) nephrologist, (iii) allergist’. The ESC considered the treatment criteria could be simplified to ‘Must be treated by a nephrologist’ as allergists are unlikely to prescribe for these patients and the Committee considered there was no difference between a renal physician and nephrologist.
- 3.13 The resubmission requested grandfathering provisions for patients enrolled in a planned patient access program (up to 50 patients) to transition to PBS-subsidised therapy. The resubmission stated that the program’s inclusion criteria are consistent with eligibility criteria in the proposed restriction. The proposed grandfathering provision also requires that patients demonstrate an adequate response to

¹ Vernon MK, Swett LL, Speck RM, 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. *J Patient Rep Outcomes*. 2021;5(1):134. Published 2021 Dec 24. doi:10.1186/s41687-021-00404-z

difelikefalin treatment, consistent with response criteria for continuing treatment. The grandfather restriction was time-limited to 12 months of treatment.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 CKD is characterised by the gradual loss of kidney function over time which decreases the ability to filter waste products from blood. Earlier stages of this condition are typically asymptomatic, but the condition can progress over time with a variety of symptoms (e.g. tiredness, frequent urination, nausea and vomiting, itchiness, swelling) and complications (e.g. hypertension, heart failure and cardiomyopathy, anaemia, mineral and bone disorders, electrolyte abnormalities). At later stages, when the kidneys can no longer function on their own, people need kidney replacement therapy such as dialysis or kidney transplant to survive.
- 4.2 CKD-associated pruritus, also known previously as uraemic pruritus, is defined as itching directly related to kidney disease without another comorbid condition to explain the itching. It is a common condition in patients with renal failure or end stage renal disease and occurs more frequently in patients undergoing haemodialysis than peritoneal dialysis. The condition is characterised by itch that most commonly affects the back; however, it can also involve the arms, head, and abdomen. More severe conditions can negatively impact sleep, mood, and quality of life; and are associated with additional complications such as infections and worse survival prognosis.
- 4.3 Currently the pathophysiology of CKD-associated pruritus is unknown, with several hypotheses including uraemic toxin build-up, histamine release, immune-mediated response, and opioid receptor dysregulation. The diagnosis of this condition can be challenging due to variability in severity of its clinical presentation during the onset of disease, the time course, the distribution, the exacerbating/relieving factors, and its tendency to occur with co-existing skin manifestations.
- 4.4 Difelikefalin is a highly selective kappa-opioid receptor agonist with low central nervous system penetration. Opioid receptors are known to modulate itch signals and inflammation, with kappa opioid receptor activation reducing itch and producing immunomodulatory effects.
- 4.5 The resubmission positioned difelikefalin as an adjunct to best supportive care in CKD patients on haemodialysis who remain at least moderately bothered by CKD-associated pruritus despite best supportive care for 6 weeks. The ESC previously considered that the management of CKD-associated pruritus in Australian practice is not well-defined (para 5.4, difelikefalin PSD, March 2023 PBAC meeting).
- 4.6 The proposed algorithm indicated that only patients who demonstrate an adequate response to difelikefalin compared to baseline should continue treatment. The optimal duration of treatment with difelikefalin is unclear, particularly in patients with relapsing-remitting pruritus. There are limited long term data for difelikefalin.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated best supportive care as the main comparator. The PBAC previously considered that this was reasonable (para 7.4, difelikefalin PSD, March 2023 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (4), health care professionals (7) and organisations (1) via the Consumer Comments facility on the PBS website. The comments from individuals and health care professionals described the severe impacts of CKD-associated pruritis on quality of life and everyday functioning, including reduced sleep quality, impacts on mental health, decreased compliance with treatment and limited social function. The comments described the current lack of effective treatments options for this very refractory symptom and the potential benefits provided by difelikefalin in terms of elimination of CKD-associated pruritis symptoms or a reduction in their severity.
- 6.3 The PBAC also noted the input from Kidney Health Australia. The input supported that provided by individuals and health care professionals regarding the quality of life impacts of CKD-associated pruritis. The comments stated that there are limited effective therapeutic options available and noted those which may offer some benefit may be challenging to use in patients on dialysis and are associated with many adverse effects. The input also indicated difelikefalin is effective and easy to administer alongside dialysis. Kidney Health Australia also stated that difelikefalin has low central nervous system penetration, so despite being a selective kappa opioid receptor agonist, the potential for dependence and abuse is low.

Clinical trials

- 6.4 The resubmission was based on individual trial results and *post hoc* pooled analyses of data from two head-to-head trials of intravenous difelikefalin versus placebo, conducted in the US (KALM-1) and globally (KALM-2) in patients on haemodialysis with moderate to severe CKD-associated pruritus. The data were previously considered by the PBAC.
- 6.5 The resubmission included supportive outcomes data based on pooled analyses of the KALM-1 and KALM-2 trials (Topf 2022 and 'Difelikefalin 2.7.3 Summary of Clinical

Efficacy' report in Attachment 8 of the resubmission) and supportive safety data based on data from the broader Phase III clinical trial program of difelikefalin for treatment of CKD-associated pruritus in haemodialysis patients (Fishbane 2022). The data were previously considered by the PBAC.

- 6.6 The resubmission included new supportive data based on *post hoc* analyses assessing the correlation between changes in itch severity and sleep quality based on the pivotal trials and a single-arm study of difelikefalin (unpublished, Weiner 2023 draft manuscript provided in the resubmission) and supplementary data based on patient-reported outcomes from 15 patients enrolled in the global difelikefalin managed access program. These data have not previously been considered by the PBAC.
- 6.7 The resubmission excluded Study 3105, a Phase III, single-arm, 12-week study of difelikefalin in patients on haemodialysis with moderate to severe CKD-associated pruritus as it was an uncontrolled study. The primary outcome of the study was to assess the safety profile of difelikefalin, with secondary efficacy outcomes assessed by itch intensity (WI-NRS), itch-related quality of life (5-D Itch, Skindex-10), improvement of sleep (Sleep Quality Numeric Rating Scale) and EQ-5D descriptive data. A summary of EQ-5D data from this study was presented during the evaluation as supportive evidence given quality of life measures from generic instruments were not captured in the key trials. These data have not previously been considered by the PBAC.
- 6.8 There are multiple ongoing Phase II/Phase III trials of an oral formulation of difelikefalin for pruritus associated with advanced non-dialysis dependent CKD (stages 4-5) (NCT05342623, NCT05356403), atopic dermatitis (NCT04018027, NCT05387707), notalgia paresthetica (NCT04706975) and primary biliary cholangitis (NCT03995212). Oral difelikefalin was in early-stage development for these indications and was not considered during the evaluation.
- 6.9 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Randomised Controlled Trials		
KALM-1 (CLIN3102; NCT03422653)	Clinical Study Report (October 2020). A Multicenter, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52 Week Open-Label Extension. Fishbane S et al (2020). A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus.	Internal study report The New England Journal of Medicine 382(3): 222–232
KALM -2 (CLIN3103; NCT03636269)	A Multicenter, Double-Blind, Randomized, PBO Controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52 Week Open-Label Extension.	Internal study report
Uncontrolled studies		
KALM-1 OLE (NCT03422653)	Clinical Study Report for the Open-label Extension Phase (October 2020). A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52 Week Open-label Extension.	Internal study report
KALM-2 OLE (NCT03636269)	Clinical Study Report for the Open-label Extension Phase (November 2020). A Multicenter, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52 Week Open-label Extension	Internal study report
Pooled analyses		
KALM-1 and KALM-2 trials	Topf J et al (2022). Efficacy of Difelikefalin for the Treatment of Moderate to Severe Pruritus in Hemodialysis Patients: Pooled Analysis of KALM-1 and KALM-2 Phase 3 Studies.	Kidney Medicine 4(8):100512
KALM-1, KALM-2 and CLIN2101 trials	Difelikefalin 2.7.3 Summary of Clinical Efficacy, 5 August 2021	Internal analyses report
KALM-1, KALM-2, CLIN3101 and CLIN3105 studies	Fishbane S et al (2022). 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 4(8):100513

Source: Table 14, p67 and Attachment 6 (A to D) of the resubmission

6.10 The key features of the included trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Difelikefalin versus placebo						
KALM-1	378	US, MC, R, DB 12 weeks	Moderate	Patients on haemodialysis with moderate/severe CKD- associated pruritus based on WI-NRS ≥ 4	WI-NRS, Skindex-10 and 5-D Itch scales	No
KALM-2	473	Global, MC, R, DB 12 weeks	Moderate			No
Pooled analysis	851	Based on KALM-1 and KALM-2 whole trial populations				Individual patient data analysis of 5-D Itch scores
Difelikefalin, single-arm studies						
KALM-1 OLE	313	US, MC, OL, cross-over 52 weeks	High	Patients from the KALM trials who received at least 30 of 36 doses of study drug during the double-blind period	Safety, 5-D Itch	No
KALM-2 OLE	399	Global, MC, OL, cross-over 52 weeks	High			No
Pooled analysis	712	Based on patients in the KALM-1 and KALM-2 OLE				Individual patient data analysis of 5-D Itch scores. Based on the subgroup with 5-D Itch score ≥ 12 at baseline and ≥ 5 -point improvement at 12 weeks

Source: Table 15, p72 of the resubmission

Abbreviations: DB, double blind; MC, multi-centre; OL, open label; OLE, open label extension; R, randomised; US, United States; WI-NRS, Worst-Itching Intensity Numerical Rating Scale

- 6.11 The PBAC previously considered the KALM-1 and KALM-2 trials to be at moderate risk of bias due to high and differential missing data (para 7.5, difelikefalin PSD, March 2023 PBAC meeting). The resubmission acknowledged PBAC’s concerns but claimed that the risk of bias was mitigated through sensitivity analyses that produced results consistent with the primary analysis. The resubmission claimed the overall risk of bias should therefore be considered as low to moderate.
- 6.12 The PBAC previously noted the subsequent single-arm open label 52-week extension phases of both trials were ceased early by the sponsor for administrative reasons (para 7.5, difelikefalin PSD, March 2023 PBAC meeting). The decision had a greater impact on the global study, KALM-2, with almost all patients discontinuing early (80% due to the sponsor stopping the study) and results only reported up to Week 36 of the open-label extension. Approximately 40% of patients discontinued early from the open-label extension period of the KALM-1 trial (approximately 20% due to the sponsor stopping the study). It may be difficult to interpret data from later timepoints of the extension studies.
- 6.13 The risk of bias was high for efficacy endpoints based on subjective patient-reported measures (24-hour WI-NRS, Skindex-10 Scale, 5-D Itch Scale and Patient Global Impression of Change) during the open-label extension periods given patients and study personnel were aware of treatments received and measurements were collected at less frequent time points.

Comparative effectiveness

6.14 Table 5 presents key results based on the WI-NRS (range 0-10) in the key trials.

Table 5: Results based on the Worst Itching Intensity Numerical Rating Scale (WI-NRS) in the key trials (ITT)

Analysis	KALM-1		KALM-2		Pooled	
	Difelikefalin N=189	Placebo N=189	Difelikefalin N=237	Placebo N=236	Difelikefalin N=426	Placebo N=427
Proportion of patients with ≥3-point improvement in WI-NRS score from baseline to Week 12 (primary outcome)						
Observed, n/N (%) ^a	82/157 (52.2)	51/165 (30.9)	95/191 (49.7)	77/207 (37.2)	-	-
Missing, n/N (%)	32/189 (16.9)	24/189 (12.7)	46/237 (19.4)	29/236 (12.3)	-	-
LS means estimate, % (95% CI) ^b	51.0 (42.9, 58.9)	27.6 (20.2, 36.6)	54.0 (43.9, 63.9)	42.2 (32.5, 52.5)	51.1 (45.0, 57.2)	35.2 (29.7, 41.1)
Odds ratio (95% CI) ^b	2.72 (1.72, 4.30)		1.61 (1.08, 2.41)		1.93 (1.44, 2.57)	
Proportion of patients with ≥4-point improvement in WI-NRS score from baseline to Week 12 (secondary outcome)						
Observed, n/N (%) ^a	64/157 (40.8)	35/165 (21.2)	72/191 (37.7)	52/207 (25.2)	-	-
Missing, n/N (%)	32/189 (16.9)	24/189 (12.7)	46/237 (19.4)	29/236 (12.3)	-	-
LS means estimate, % (95% CI) ^b	38.9 (29.8, 48.7)	18.0 (12.1, 26.0)	41.2 (33.0, 50.0)	28.4 (21.3, 36.7)	38.7 (32.8, 45.0)	23.4 (18.7, 28.8)
Odds ratio (95% CI) ^b	2.89 (1.75, 4.76)		1.77 (1.14, 2.74)		2.07 (1.51, 2.84)	

Source: Table 25, p106; Table 26, p110 of the resubmission

Abbreviations: CI, confidence interval; LS, least squares

^a Counts and percentages were based on non-missing data

^b Estimated using a logistic regression with terms for treatment group, baseline WI-NRS score, baseline anti-itch medications and presence of specific medical conditions. Region was also included in the model for the KALM-2 analysis while a region/study variable was included in the model for the pooled analysis. Missing values were imputed using multiple imputation under missing at random assumptions

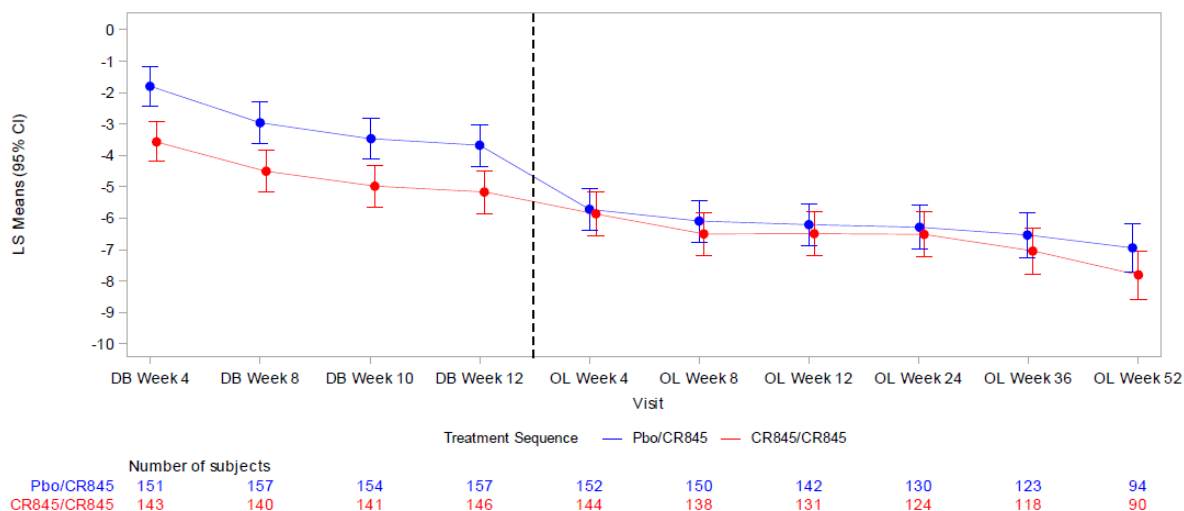
Bold indicates statistically significant results. Pooled analyses were conducted *post hoc* and were unadjusted for multiplicity

- 6.15 A statistically significantly greater proportion of patients treated with difelikefalin achieved a ≥3-point improvement in WI-NRS score at Week 12 from baseline compared to those receiving placebo. Sensitivity analyses using alternative methods of handling missing data including a non-responder analysis produced results that were consistent with the primary analysis.
- 6.16 Results based on the secondary endpoint using a higher 4-point threshold were also statistically significant in favour of difelikefalin. The absolute proportion of patients achieving response in each arm was lower compared to response defined using a 3-point improvement, however, the difference between arms appeared similar.
- 6.17 Response rates in the difelikefalin arms were similar in both trials but varied substantially for the placebo arms (difference exceeding 10%). This difference appears to be the primary driver of a numerically smaller incremental benefit associated with difelikefalin in KALM-2 (12%) compared to KALM-1 (23%).
- 6.18 The resubmission noted the high placebo response rates in both trials but claimed that this was not unexpected given the subjective nature of itch. The resubmission claimed that strong placebo effects have previously been observed in dermatological studies that rely on patient-reported outcomes. The resubmission claimed that specific reasons for the difference in magnitude of placebo response between the trials were unclear but could be due to the larger site number and region-specific variation in the global study. However, additional analyses indicated that similar response rates were

observed across regions and that placebo response rates in US patients were also higher in the global KALM-2 study (37.3%) than in the KALM-1 US study (27.6%).

- 6.19 The key trials also included secondary outcomes based on multi-dimensional itch-related quality of life questionnaires, Skindex-10 (range, 0-60) and 5-D Itch Scales (range, 5-25). The resubmission claimed that a 15-point improvement from baseline total Skindex-10 score and a 5-point improvement from baseline 5-D Itch scores represented clinically meaningful changes. Data to support these claims were not provided in the resubmission.
- 6.20 In KALM-1, treatment with difelikefalin was associated with a statistically significant improvement in the total Skindex-10 score at Week 12 from baseline (-5.1, 95% CI: -8.0, -2.3). In KALM-2, the difelikefalin group showed a numerical improvement in total Skindex-10 score compared to placebo but the result did not achieve statistical significance (-1.8, 95% CI: -4.3, 0.8). Pooled estimates of treatment effect were similar to results from the individual studies.
- 6.21 In KALM-1, difelikefalin treatment was associated with a statistically significant improvement on the 5-D Itch scale at Week 12 from baseline (-1.3, 95% CI: -2.0, -0.5). The result from KALM-2 could not be considered statistically significant based on the hierarchical testing order as the prior secondary endpoint (total Skindex-10 score at Week 12) was not statistically significant.
- 6.22 Results for exploratory outcomes based on the proportion of patients achieving ≥ 15 -point improvement on the Skindex-10 scale and the proportion of patients achieving ≥ 5 -point improvement on the 5-D Itch scale suggested a greater proportion of patients treated with difelikefalin achieved these response thresholds compared to those on placebo. Placebo response rates based on these measures were also high (42-48%), similar to response measures using the WI-NRS scale.
- 6.23 The proportions of patients achieving ≥ 5 -point improvement on the 5-D Itch scale from an analysis of individual patient data in the KALM trials were used to determine response, and consequently treatment continuation rates at 12 weeks for difelikefalin in the economic model (different response rates by pruritus severity of none 92.3%, mild 68.9%, moderate 32.9% and severe 10.7%) and financial estimates (51.3% overall). The 51.3% overall response rate for difelikefalin appeared similar to results from the pooled analyses (52.1%).
- 6.24 The resubmission did not present results from the open-label extension periods of the KALM-1 and KALM-2 trials despite the use of these data in the economic model. Key results from the open-label extension periods were presented during the evaluation, as these are the only long-term data available for difelikefalin.
- 6.25 Figure 1 presents the mean change from baseline in total 5-D itch score in the 12-week double-blind treatment period and 52-week open-label extension of KALM-1.

Figure 1: Mean change from double-blind baseline in total 5-D Itch scale score by visit in KALM-1

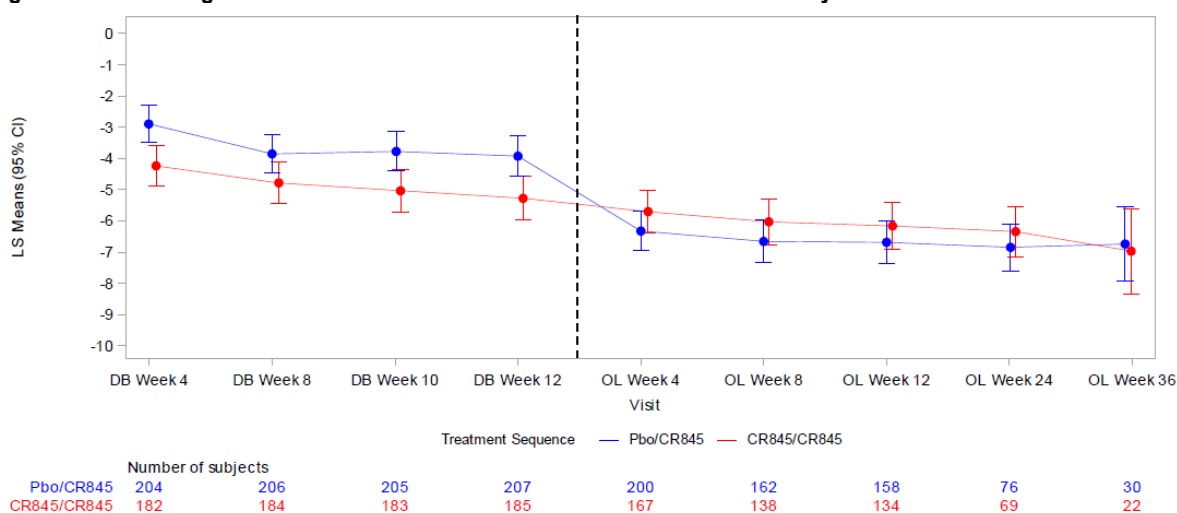


Source: Figure 14, p107 of the 'Difelikefalin 2.7.3 Summary of Clinical Efficacy' report, Attachment 8 of the resubmission
 Abbreviations: CR845, difelikefalin; DB, double-blind; CI, confidence interval; LS, least squares; OL, open-label

6.26 The results suggest that improvements in total 5-D Itch scale scores were maintained over time. Similar improvements were observed in patients randomised to placebo who switched to difelikefalin during the extension period. Observations towards the end of the 52-week study should be interpreted with caution as the sponsor stopped the study early, with approximately 60% of patients completing 52 weeks of treatment.

6.27 Figure 2 presents the mean change from baseline in total 5-D itch score over the 12-week double-blind treatment period and 52-week open-label extension in KALM-2.

Figure 2: Mean change from double-blind baseline in total 5-D Itch scale score by visit in KALM-2



Source: Figure 16, p109 of the 'Difelikefalin 2.7.3 Summary of Clinical Efficacy' report, Attachment 8 of the resubmission
 Abbreviations: CR845, difelikefalin; DB, double-blind; CI, confidence interval; LS, least squares; OL, open-label

6.28 Improvements in 5-D Itch scale score associated with difelikefalin treatment were maintained for both treatment sequence groups through Week 36 of the extension

- period. Data beyond Week 36 was not reported as the sponsor stopped the study early.
- 6.29 No quality of life outcomes based on generic instruments (e.g. EQ-5D, SF-36) were captured in the key trials.
 - 6.30 There were no pre-specified subgroup analyses in the key trials.
 - 6.31 The resubmission presented results from a post hoc subgroup analysis for patients with ≥ 3 -point and ≥ 4 -point improvements in WI-NRS from baseline to Week 12, using pooled data across the KALM-1 and KALM-2 trials. Results were generally consistent with those in the overall population. The results should be interpreted with caution as they were conducted post hoc with no testing for treatment effect interactions.
 - 6.32 No subgroup characteristics or results were presented for patients with 5-D Itch score ≥ 12 at baseline who were responders (defined as ≥ 5 -point improvement at 12 weeks) in the KALM trials, used to inform the extrapolated period of the economic model.
 - 6.33 The following supportive data have not previously been considered by the PBAC.
 - 6.34 The resubmission provided a brief discussion of a correlation study between itch intensity and sleep quality based on *post hoc* analyses of patient reported outcomes from the key trials (KALM-1 and KALM-2) and a Phase III single-arm study of difelikefalin (CLIN3105). The study assessed the relationship between WI-NRS scores, a sleep quality numeric rating scale and 5-D Itch sleep disability question using Spearman correlation coefficients.
 - 6.35 The resubmission claimed the results indicated a moderate to strong correlation between itch reduction and improved sleep quality. The resubmission also claimed that improvements in sleep quality associated with difelikefalin treatment would translate to meaningful improvements in quality of life. These claims were inadequately supported based on data from the post hoc analyses. The study authors stated that the results should be interpreted with caution due to the exploratory nature of the analyses, with additional limitations due to differences in study design and data capture between the KALM trials and CLIN3105 study. The impact of improvements in itch intensity on quality of life remains uncertain given the lack of generic preference-based quality of life data from the placebo-controlled trials. Overall, the results suggest improvements in the proportion of patients reporting no problems in individual domains of the EQ-5D descriptive system and skin irritation measures of the disease-specific EQ-PSO. However, there were relatively small improvements based on the EQ-VAS and no detectable changes based on the EQ-5D QALY weight. These results should be interpreted with caution due to the exploratory nature of the analyses from a single-arm study.
 - 6.36 The resubmission provided a brief description of preliminary data from the sponsor's difelikefalin managed access program in Europe (Kraft 2023, Letter to the Editor). A total of 15 patients on haemodialysis with moderate to severe CKD-associated pruritus (defined as WI-NRS ≥ 4) were treated with difelikefalin from November 2021 to

October 2022. The majority of patients (13 out of 15) achieved a reduction in WI-NRS of at least 3 points. Most patients (12 out of 15) also reported improved quality of life, with 8 patients describing a change from severe impairment (SADS C) to mild impairment (SADS A) of quality of life. Time to response to difelikefalin was between 2 and 8 weeks, with almost half of the patients reporting meaningful improvement 2 weeks after commencing treatment. The study authors noted that the study was uncontrolled therefore placebo effects (which the ESC noted were high in the randomised trials) cannot be ruled out.

- 6.37 The resubmission presented a comparison of selected baseline characteristics between the Australian/New Zealand subgroup (n=31) in the KALM-2 trial with whole trial populations in KALM-1 and KALM-2. The resubmission stated the number of Australian/New Zealand patients in the trial was small, therefore comparisons with whole trial populations should be interpreted with caution. The resubmission claimed that there are no other data available that could be used to characterise Australian haemodialysis patients with CKD-associated pruritus. These data were previously considered by the PBAC.
- 6.38 There were potential differences in terms of demographics and renal disease characteristics (e.g. age, co-morbidities), haemodialysis requirements, the assessment of CKD-associated pruritus and disease severity, and best supportive care treatments. Regional differences in treatment and placebo response rates were also observed in the key trials, with a smaller difelikefalin treatment effect observed in the KALM-2 global trial compared to the US-based KALM-1 trial.
- 6.39 The resubmission argued that results from post hoc subgroup analyses using the pooled KALM-1 and KALM-2 data do not suggest meaningful differences in treatment effect based on any observed differences. The ESC previously considered the post hoc analyses provided were not sufficiently reliable to exclude a different magnitude of benefit in the PBS population compared to the key trials (para 6.58, difelikefalin PSD, March 2023 PBAC meeting).

Comparative harms

- 6.40 Table 6 presents adverse event data from the 12-week double-blind period of the key trials previously considered by the PBAC.

Table 6: Summary of adverse events during the double-blind period of the key trials

	Patients with events, n (%)				Events and incidence rate			
	KALM-1		KALM-2		Pooled			
	DFK N=189	PBO N=188	DFK N=235	PBO N=236	DFK N=424		PBO N=424	
				Events, n	IR/1,000 pt-yrs	Events, n	IR/1,000 pt-yrs	
Any AE	130 (68.8)	117 (62.2)	160 (68.1)	145 (61.4)	302	10,862.9	277	9,597.8
AEs leading to treatment discontinuation	15 (7.9)	9 (4.8)	13 (5.5)	8 (3.4)	29	428.4	29	428.4
AEs leading to study drug interruption	26 (13.8)	17 (9.0)	22 (9.4)	11 (4.7)	NR	NR	NR	NR
Serious AE	49 (25.9)	41 (21.8)	58 (24.7)	51 (21.6)	107	2,040	96	1,860.2
Deaths	2 (1.1)	2 (1.1)	2 (0.9)	2 (0.8)	3 ^a	30.6 ^a	5 ^a	49.5 ^a
Most common adverse events (falls, dizziness, somnolence and mental status changes are reported under adverse events of special interest below)^b								
Diarrhoea	18 (9.5)	7 (3.7)	19 (8.1)	13 (5.5)	38	469.2	24	267.2
Vomiting	10 (5.3)	6 (3.2)	15 (6.4)	14 (5.9)	NR	NR	NR	NR
Nausea	6 (3.2)	9 (4.8)	15 (6.4)	10 (4.2)	28	326.4	19	207.8
Hyperkalaemia	8 (4.2)	5 (2.7)	9 (3.8)	6 (2.5)	20	234.6	15	158.3
Headache	7 (3.7)	4 (2.7)	10 (4.3)	6 (2.5)	19	214.2	11	118.7
Adverse events of special interest								
Falls/gait disturbance	6 (3.1)	7 (3.8)	23 (9.8)	14 (5.9)	28	336.6	23	237.5
Dizziness	13 (6.9)	2 (1.1)	13 (5.5)	12 (5.1)	29	316.2	16	188.0
Somnolence	6 (3.2)	4 (2.1)	11 (4.7)	5 (2.1)	14	142.8	10	98.9
Mental status changes	3 (1.6)	3 (1.6)	3 (1.3)	1 (0.4)	14	142.8	6	59.4
Syncope	1 (0.5)	1 (0.5)	4 (1.7)	3 (1.3)	NR	NR	NR	NR
Tachycardia	2 (1.1)	1 (0.5)	1 (0.4)	6 (2.5)	NR	NR	NR	NR
Palpitations	0	2 (1.1)	3 (1.3)	1 (0.4)	NR	NR	NR	NR
Mood altered	1 (0.5)	0	0	1 (0.4)	NR	NR	NR	NR
Seizure	1 (0.5)	1 (0.5)	NR	NR	NR	NR	NR	NR

Source: Table 33, p130; Table 34, p133; Table 35, p137; Table 41, p152 of the resubmission

Abbreviations: AE, adverse event; DFK, difelikefalin; IR, incidence rate; PBO, placebo; pt-yrs, patient-years; NR, not reported

^a There was a discrepancy in the number of reported in the pooled safety analysis (Fishbane 2022) and in the trial report.

^b Adverse events reported in ≥2% of difelikefalin patients with an incidence ≥1% higher than in placebo patients

Note: IR is calculated as 1,000 times the number of events divided by the total patient-years of exposure

6.41 More patients treated with difelikefalin experienced an adverse event compared to those in the placebo arm. Treatment-emergent adverse events occurring more frequently with difelikefalin compared to placebo were diarrhoea, vomiting, nausea, fall, dizziness, somnolence, hyperkalaemia and mental status change. More patients in the difelikefalin arm experienced adverse events leading to treatment discontinuation and treatment interruption compared to placebo, with dizziness being the most common reason for discontinuation of difelikefalin.

6.42 The frequency of serious adverse events was higher in patients treated with difelikefalin compared to placebo. The most common serious adverse event reported in both trials was infections and infestations, with similar frequencies of occurrence between arms in KALM-1 (difelikefalin 8%, placebo 8%) but with different frequencies in KALM-2 (difelikefalin 9%, placebo 6%). There were also higher incidences of cardiac (difelikefalin 5%, placebo 2%) and respiratory disorders (difelikefalin 4%, placebo 2%) in the difelikefalin arms across the key trials.

- 6.43 During the double-blind treatment period across the key trials, 4 deaths occurred in the difelikefalin arms (2 due to sepsis, 1 due to anaemia/cardiorespiratory failure and 1 due to cardiac arrest) and 4 deaths occurred in the placebo arms (2 due to sepsis, 1 due to dyspnoea/hypotension and 1 due to cardiac arrest). One death of unknown cause occurred in the placebo arm during the discontinuation period of the KALM-1 trial. None of the deaths were deemed related to the study drug.
- 6.44 The frequency of adverse events was similar regardless of treatment sequence during the open-label extension studies. More patients switching from placebo to difelikefalin discontinued treatment due to adverse events. The adverse event profile of difelikefalin during the extension period was similar to the double-blind period.
- 6.45 The resubmission presented data from the first Periodic Benefit-Risk Evaluation Report (PBRER) for the period 23 February 2022 to 22 August 2022, which became available after the lodgement of the March 2023 submission. This was not previously considered by the PBAC.
- 6.46 The PBRER found no important identified risks. Important potential risks were cardiac failure and arrhythmias including atrial fibrillation in haemodialysis patients with a medical history of atrial fibrillation. Missing information included use in pregnant and lactating women, patients with impaired blood brain barrier and patients with severe hepatic impairment. No new safety signals were identified during the reporting interval.
- 6.47 The resubmission also addressed emerging safety signal issues raised during the evaluation of the March 2023 submission. Emerging safety signals, arising from case reports of serious events, were considered by the Advisory Committee on Medicines (ACM) during the TGA approval process related to Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), cardiovascular disorders, hallucinations and failure to thrive. The resubmission stated that these issues were addressed in the finalised product information for difelikefalin. The PBAC previously noted that full TGA registration was approved without any boxed warnings (para 7.7, difelikefalin PSD, March 2023 PBAC meeting).
- 6.48 The resubmission claimed that the extended safety data showed that difelikefalin was well-tolerated with an acceptable safety profile for the target PBS population. There remains limited long-term safety data for difelikefalin, with up to 64 weeks of data from the key trials and post-marketing exposure of approximately 91.08 patient years as of August 2022. The characteristics of Australian patients are uncertain, but they are likely to be older with a potentially greater number of co-morbidities than patients in the trials.

Benefits/harms

- 6.49 On the basis of direct evidence presented in the resubmission (KALM trials pooled cohort), for every 100 patients treated with difelikefalin in comparison with placebo over 12 weeks there would be:

- Approximately 16 more patients achieving an improvement in itch intensity, based on ≥ 3 -point improvement in WI-NRS score from baseline.
- Approximately 14 more events of diarrhoea, 9 more events of nausea, 13 more events of dizziness, 5 more events of falls/gait disturbance, 8 more events of headache, 4 more events of somnolence, 8 more events of mental status change and 5 more events of hyperkalaemia.
- Approximately 3 more patients with serious cardiac disorders and approximately 2 more patients with serious respiratory disorders.

Clinical claim

- 6.50 The resubmission described difelikefalin as superior in terms of efficacy and inferior in terms of safety compared to best supportive care. These claims were unchanged from the previous submission and were primarily based on the same evidence previously considered by the PBAC. In March 2023, the PBAC considered that the claim of superior efficacy and inferior safety was reasonable (para 6.60 and 6.61, difelikefalin PSD, March 2023 PBAC meeting). The ESC noted the key clinical evidence supporting the clinical claim was unchanged and reaffirmed its previously expressed view that the clinical claims appeared reasonable based on the available data (paragraph 6.56, difelikefalin PSD, March 2023 PBAC meeting), whilst noting that the treatment benefit was modest.
- 6.51 The PBAC noted the clinical claims and key clinical evidence supporting them were unchanged from the March 2023 submission and reaffirmed its view that the claims of superior comparative effectiveness and inferior comparative safety compared to best supportive care were reasonable.

Economic analysis

- 6.52 The resubmission presented an economic evaluation of difelikefalin versus best supportive care in patients on haemodialysis with moderate to severe CKD-associated pruritus. The modelled population and treatment effects were based on data from the KALM-1 and KALM-2 double-blind trials and open-label extension studies as well as other modelled variables. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

Table 7: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-utility analysis
Treatments	Difelikefalin versus best supportive care
Outcomes	Quality-adjusted life years (QALYs)
Time horizon	5 years in the model base case versus 12 weeks comparative trial data and up to an additional 52 weeks in the extension studies
Health states	5 health states: none (5-D Itch score 5-8), mild (5-D Itch score 9-11), moderate (5-D Itch score 12-17), severe (5-D Itch score 18-25) and dead
Cycle length	4 weeks
Transition probabilities and extrapolation	<p>Treatment-specific transition probabilities were derived from patient-level data from the KALM trials, informing patient movements between health states defined using total 5-D Itch scores. Data were available for up to 64 weeks for difelikefalin and 12 weeks for placebo. No health state transitions were allowed after Week 64 for difelikefalin treated patients and after Week 12 for patients on best supportive care (including patients who switched after stopping difelikefalin). No waning in treatment effects was assumed for either arm.</p> <p>Per cycle treatment discontinuations were estimated using trial data. Discontinuations due to inadequate response were estimated using an individual patient analysis of patients not achieving ≥ 5-point improvement in 5-D Itch score from baseline at 12 weeks. Patients who discontinued difelikefalin treatment assumed the same transition probabilities as those who were on best supportive care.</p> <p>Background mortality was estimated using death rates for dialysis patients in the ANZDATA 44th Annual Report 2021. The same death rate was applied across all health states.</p> <p>The rate of adverse events was based on the incidence of respiratory and cardiac failure in the KALM trials.</p> <p>99% of incremental QALYs and 93% of incremental costs occur in the extrapolated period after 12 weeks.</p>
Health related quality of life	Health state utilities based on pruritus severity (none 0.6328, mild 0.5800, moderate 0.5203 and severe 0.4420) were derived from 5-D Itch scores in the KALM trials, mapped to EQ-5D-3L estimates using a mapping function developed by the University of Sheffield. The mapping function (mixture model adjusting for age, sex, having diabetes and years on dialysis) was based on an unpublished primary utility study conducted in a sample of UK patients on dialysis from 2020-2021. A utility decrement of 0.054 was used for adverse events based on a 30-90-day post-hospitalisation disutility used in a published cost-effectiveness analysis of sacubitril/valsartan for heart failure (McMurray 2018).
Costs	Drug acquisition costs were estimated using the proposed effective DPMQ for difelikefalin, and no costs were assumed for best supportive care. Health state costs were based on hospitalisation rates estimated from an observational study of haemodialysis patients (Sukul 2020) and costs based on the NHCCDC public sector cost weights for AR-DRG v10.0, Round 23 (2018-2019). Adverse event costs were based on an Australian epidemiological and health resource utilisation study of heart failure (Chan 2016).
Software package	Excel

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; NHCCDC, National Hospital Cost Data Collection

6.53 All patients start in the moderate and severe health states (baseline). All patients are at risk of death in each cycle. Patients on difelikefalin treatment can also discontinue treatment in each cycle and assume the same transition probabilities as patients on best supportive care, with no further treatment costs. A once-off discontinuation rate is also applied at Week 12 of the model to difelikefalin treated patients who did not achieve adequate response.

- 6.54 In the first 12 weeks for patients on best supportive care and over the first 64 weeks for difelikefalin treated patients, surviving patients can either remain in the same health state as the prior cycle, move to an improved health state or move to a worse health state. No health state transitions are allowed after this period (i.e. patients can only remain in the same health state as the prior cycle).
- 6.55 The modelled circumstances of use of difelikefalin were based on a single episode of care. The resubmission assumed persistent responders received ongoing treatment and patients who discontinued treatment (due to inadequate response or other reasons) could not re-initiate treatment. This was inconsistent with the proposed restriction that allows for re-initiation of treatment with difelikefalin. The ESC considered it would be clinically appropriate to allow for episodic treatment rather than a single episode of care. The ESC advised a reduction in the time horizon may be a reasonable approach to account for the disconnect between the treatment assumptions in the economic model and likely use in clinical practice.
- 6.56 The PBAC previously considered the structure of the economic model was overall likely to be reasonable, however agreed with the ESC that key inputs were optimistic and favoured difelikefalin. The PBAC noted that acceptance of the economic evaluation as reliable for decision-making was contingent on acceptance of the utility decrements applied in the model (para 7.8, difelikefalin PSD, March 2023 PBAC meeting). The PBAC considered that a resubmission for difelikefalin should present a revised economic evaluation which addresses multiple concerns including modelled pruritus-related utility decrements, extrapolated treatment benefits, modelled mortality benefit, lack of adverse events and difelikefalin drug costs (para 7.12, difelikefalin PSD, March 2023 PBAC meeting).
- 6.57 Compared to the March 2023 submission, the key changes to the model were:
- Revised transition probabilities for the extrapolated period. No change in pruritus severity was assumed after Week 12 for patients on best supportive care and after Week 64 for difelikefalin treated patients.
 - Removal of the mortality hazard ratio previously applied to the severe pruritus health state, effectively removing mortality benefits associated with difelikefalin treatment.
 - Revised health state utilities. The resulting utility decrements for pruritus severity were lower (mild 0.0528, moderate 0.1125, severe 0.1908) compared to the March 2023 base case (mild 0.0676, moderate 0.1544, severe 0.2606).
 - Revised drug costs of difelikefalin by increasing the average number of vials per dose from 1.00 to 1.06 and using a new proposed effective AEMP of \$| for 12 vials, a 20% reduction from the proposed effective AEMP of \$| in the previous submission pre-PBAC response.

- Inclusion of costs and disutilities due to adverse events associated with difelikefalin based on the incidence of cardiac and respiratory failure in the key trials.

6.58 Drug costs in the resubmission’s base case were incorrectly calculated using fees and mark-ups for a Section 85 (General Schedule) listing rather than the requested Section 100 HSD listing. There was also an error with the implementation of adverse event disutilities in the resubmission. These errors were corrected during the evaluation in a revised base case.

6.59 Key drivers of the economic model are summarised in Table 8.

Table 8: Key drivers of the model

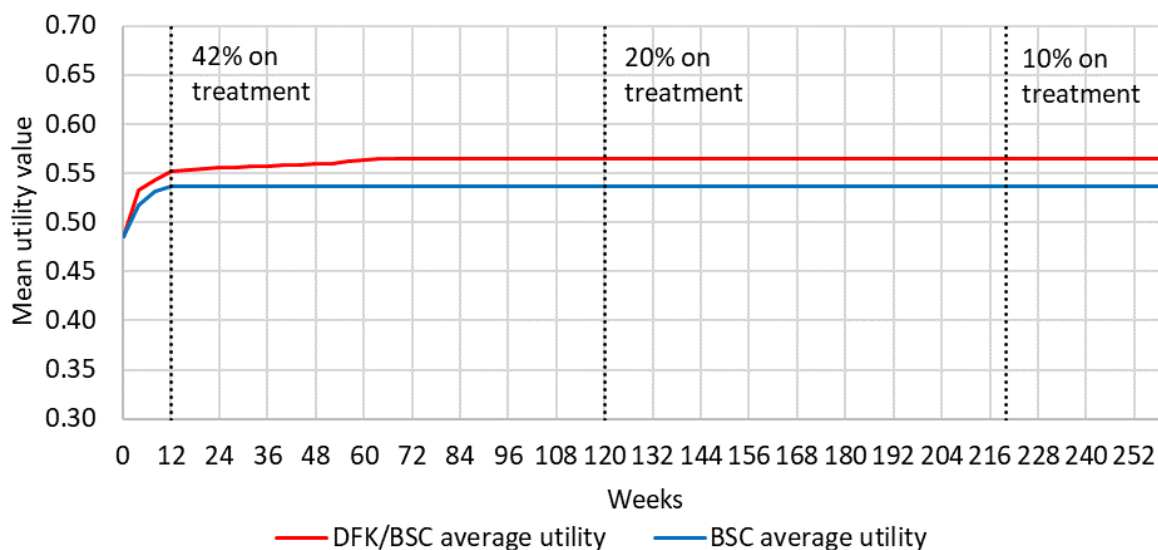
Description	Method/Value	Impact
Extrapolation of treatment benefit	<p>The base case assumes no waning of treatment effects for difelikefalin or best supportive care, resulting in no transitions between health states after 12 weeks for patients on best supportive care and after 64 weeks for difelikefalin treated patients.</p> <p>The removal of unequal placebo response adjustments reduces the modelled incremental benefit associated with difelikefalin treatment compared to the previous model. However, the approach remained in favour of difelikefalin as modelled benefits based on data from the extension studies (Week 12 to 64) were retained. The PSCR argued that the extrapolation of treatment benefits was based on data from the extension studies and therefore the approach should not be considered in favour of difelikefalin. The ESC reiterated its previous advice that the observed data from later timepoints of the extension studies may not be robust as the studies were stopped prematurely, with the KALM-2 extension study only reporting results up to Week 48 from baseline (para 6.79, difelikefalin PSD, March 2023 PBAC meeting). Additionally, the ESC noted that patients who switched to best supportive care after discontinuing difelikefalin maintained all benefits with no ongoing treatment costs. This resulted in improvements in the ICER per QALY gained with increasing treatment discontinuation rates in the model</p>	High, favours difelikefalin

Description	Method/Value	Impact
<p>Utility decrements associated with pruritus severity</p>	<p>The PBAC previously noted concerns with the reliability of the approach for mapping the 5-D Itch scores to utility values and considered the resulting utility decrements applied for pruritus (mild 0.0676, moderate 0.1544 and severe 0.2606) to be implausibly large (para 7.8, difelikefalin PSD, March 2023 PBAC meeting).</p> <p>The resubmission used an updated set of utilities based on a mapping function developed by the University of Sheffield, used to derive EQ-5D-3L utility values from trial-based 5-D Itch data. The remapped utilities were dependent on the same primary data source that informed the previous submission. There were multiple concerns with the robustness of the primary utility study that informed the mapped utilities due to limitations with the cross-sectional study design that does not allow for the identification of cause-effect relationships. There were also anomalous responses to the 5-D Itch questionnaire and variability in the scatterplot of observed EQ-5D-3L estimates against 5-D Itch scores.</p> <p>Utility estimates in the current resubmission were remapped using an adjusted limited dependent variable model, originally developed using data from a trial of patients with rheumatoid arthritis and has not been validated in other disease areas. The mapping model used in the resubmission includes covariates for 5-D Itch score, age, gender, diabetes status and time on dialysis. Adjustments based on the selected covariates may be contributing to lower pruritus-related utility decrements than in the previous submission that was unadjusted for potential confounders. However, there was limited documentation regarding the choice of these covariates, which may not capture the full symptom burden experienced by the sample population (e.g. fatigue, CKD-related complications).</p> <p>The resubmission claimed that the remapped baseline utility (no pruritus) is lower than previous estimates and is more consistent with published estimates for CKD patients on haemodialysis. Mild and moderate pruritus are also associated with slightly lower utility values than the previous submission, while the utility value for severe pruritus was effectively unchanged. The resulting utility decrements (mild 0.0528, moderate 0.1125 and severe 0.1908) were approximately 20-27% lower compared to the previous submission. The resubmission and PSCR argued that these values have greater plausibility than estimates previously considered by the PBAC. The ESC considered the validity of the revised utility decrements remains uncertain.</p>	<p>High, favours difelikefalin</p>

Source: constructed during the evaluation

6.60 Figure 3 below was constructed during the evaluation based on the mean utility value of surviving patients in the model, to illustrate the conversion of 5-D Itch scores to quality of life benefits over the model duration.

Figure 3: Average utility value in patients who are alive in the model



Source: constructed during the evaluation using the 'A10 – A DFK_Section3model_July2023' Excel workbook of the resubmission
 Abbreviations: BSC, best supportive care; DFK, difelikefalin

- 6.61 The utility trace shows improvements in both arms over the first 12 weeks in the model, with continued improvements up to 64 weeks in the difelikefalin arm. There were no changes in quality of life after 12 weeks in the best supportive care arm and after 64 weeks in the difelikefalin arm.
- 6.62 Assumptions of maintenance of treatment effects in both arms during the extrapolated period were in favour of difelikefalin as all benefits attained while on treatment were maintained indefinitely upon treatment discontinuation (i.e. ongoing benefit with no treatment costs). The approach resulted in a fixed, ongoing utility benefit of approximately 0.03 during the extrapolated period despite the decreasing proportion of patients remaining on treatment over time. The PSCR claimed the assumption of maintenance of treatment effects in both arms during the extrapolated period (regardless of treatment status) was a conservative approach that was consistent with the ESC's request for removal of placebo response adjustments. The ESC previously considered that placebo effect adjustments were inappropriately applied to patients on best supportive care only, with no matching adjustments to difelikefalin treated patients, and therefore should be removed (para 7.9, difelikefalin PSD, March 2023 PBAC meeting). However, the ESC did not consider that treatment benefit should be maintained indefinitely regardless of treatment status. The pre-PBAC Response argued that an assumption in which the placebo effect observed over 12 weeks is considered durable for 5 years could not reasonably be considered to favour difelikefalin.
- 6.63 The previous submission modelled elevated mortality as a function of severe pruritus, which resulted in mortality benefits associated with difelikefalin treatment. The ESC noted this was appropriately removed in the resubmission.

- 6.64 The resubmission applied independent estimates for treatment discontinuations due to inadequate response, non-specific treatment discontinuations and background mortality. These estimates were unchanged from the previous submission. The approach may overestimate overall treatment discontinuations as the non-specific treatment discontinuation rate was unadjusted for treatment response and deaths.
- 6.65 The resubmission appropriately accounted for increased vial use (1.06 vials per dose) due to weight-based dosing. However, the resubmission retained an assumed dosing frequency of 3 times per week, which does not account for additional doses in any given week. This was inconsistent with drug exposure data in the trial reports suggesting approximately 24.9% of patients in KALM-1 and 22.6% of patients in KALM-2 received at least 1 additional dose during the 12-week study period.
- 6.66 The resubmission included costs and utilities associated with the increased risk of cardiac and respiratory failure events observed in the key trials to address PBAC's March 2023 concerns regarding the lack of adverse events in the model.
- 6.67 The source of estimated costs was inadequately justified, based on an epidemiological study of heart failure (Chan 2016) with costs calculated using a 'top-down' approach. The calculated cost per heart failure patient per year (\$6,758) was uncertain as it was dependent on incident and prevalent cases of heart failure that could not be accurately quantified, according to the study authors, given the paucity of local data. It may be more appropriate to estimate costs of hospitalisation using data from the National Hospital Cost Data Collection (NHCDC). No justification was provided for the assumption that these costs would be applicable to patients with respiratory failure. Additionally, the resubmission inappropriately applied a 4-week adjusted cost (\$518) to patients experiencing an event each cycle rather than the cumulative number of patients with an event over time. The ESC agreed with the evaluation that this approach effectively underestimates the cost of adverse events in the model. The ESC considered it was more appropriate to use hospitalisation costs based on the NHCDC, as it better reflected the Australian context. The pre-PBAC Response acknowledged the costing of adverse events inadvertently adjusted both the probability and the cost back to a cost per cycle. However, the Response argued that the actual cost itself of \$6,758 per annum for heart failure applied in the model is representative of all heart failure (not just hospitalised cases) and is reasonable for this purpose.
- 6.68 The PBAC previously noted concerns with the reliability of the approach for mapping the 5-D Itch scores to utility values and considered the resulting utility decrements applied for pruritus (mild 0.0676, moderate 0.1544 and severe 0.2606) to be implausibly large (para 7.8, difelikefalin PSD, March 2023 PBAC meeting). The resubmission used an updated set of utilities based on a mapping function developed by the University of Sheffield, used to derive EQ-5D-3L utility values from trial-based 5-D Itch data (see Table 8). The resubmission claimed that the remapped baseline utility (no pruritus) is lower than previous estimates and is more consistent with published estimates for CKD patients on haemodialysis. Mild and moderate pruritus are also associated with slightly lower utility values than the previous submission,

while the utility value for severe pruritus was effectively unchanged. The resulting utility decrements (mild 0.0528, moderate 0.1125 and severe 0.1908) were approximately 20-27% lower compared to the previous submission. The resubmission argued that these values have greater plausibility than estimates previously considered by the PBAC. The validity of the revised utility decrements remains uncertain. The PSCR argued that while the remapped utilities are dependent on the same primary data source that informed the previous submission, they are better matched to the health state definitions in the model and therefore have greater plausibility and reliability. The ESC considered the validity of the revised estimates remains uncertain given multiple concerns with the robustness of the primary utility study and validity of the mapping function used to transform 5-D itch scores to EQ-5D-3L utility values. The ESC noted the Thokala 2023 study (identified in the updated literature review undertaken for the resubmission) used the same primary dataset but instead mapped data from the 'itch intensity' domain rather than 5D itch scores, which resulted in smaller utility decrements than the re-submission (mild 0.0378, moderate 0.1025 and severe 0.1875). The pre-PBAC Response argued the utility values used in the re-submission are supported by evidence from 377 CKD patients living with CKD-associated pruritis. The Response accepted the values may be uncertain, however argued they can be considered reliable evidence and are not biased towards either difelikefalin or placebo. The Response further noted the consumer comments highlighted the quality of life impacts of severe itch in the CKD population.

- 6.69 There was limited documentation regarding the derivation of adverse event disutilities used in the model. The ESC noted that no rationale was provided for the selected 30-90 day post-hospitalisation disutility (-0.054), given the selected source (McMurray 2018) also reported a 0-30 day post-hospitalisation disutility (-0.105). No justification was provided for the assumption that quality of life impacts associated with heart failure hospitalisations would be applicable to hospitalisations due to respiratory failure. The ESC agreed with the evaluation that there were added concerns with the transformation of the 30-90 day post-hospitalisation utility to a 4 week utility decrement applied directly to health state utilities, which further underestimated the QALY loss. There was also an error in the attribution of the adjusted health state utility values that were applied to all patients in the difelikefalin arm regardless of treatment status. This was corrected in the revised base case during the evaluation by applying the utility decrement to on-treatment patients only.
- 6.70 The resubmission presented a stepped economic evaluation from the March 2023 base case to the resubmission's base case, to assess the impact of changes included in the current resubmission's model. Corrections to the drug cost and adverse event disutilities in the revised base case are shown as additional steps to the stepped evaluation of the resubmission (see Table 9 below).

Table 9: Results of the stepped economic evaluation from the March 2023 submission to November 2023 submission

Step and component	Difelikefalin	BSC	Increment
March 2023 submission base case			
Costs (\$)		\$6,870	
QALYs	2.0411	1.8871	0.1540
Incremental cost/QALY gained			
Increased number of vials of difelikefalin (from 1.00 to 1.06) to account for patients needing more than 1 vial/dose			
Costs (\$)		\$6,870	
QALYs	2.0411	1.8871	0.1540
Incremental cost/QALY gained			
Included costs (\$3.71 per 4-week cycle) and utility decrements (-0.00039 per 4-week cycle) for adverse events associated with difelikefalin treatment based on increased rates of cardiorespiratory failure in the key trials			
Costs (\$)		\$6,870	
QALYs	2.0397	1.8871	0.1526
Incremental cost/QALY gained			
Removed mortality benefit associated with difelikefalin treatment (mortality HR for severe pruritus health state changed from 1.24 to 1.00)			
Costs (\$)		\$6,946	
QALYs	2.0471	1.9034	0.1437
Incremental cost/QALY gained			
Revised utilities for pruritus severity health states. Utility decrements for pruritus severity decreased by approximately 20-27% from the March 2023 base case (mild -0.0676, moderate -0.1544, severe -0.2606) to the current resubmission's base case (mild -0.0528, moderate -0.1125, severe -0.1908)			
Costs (\$)		\$6,946	
QALYs	1.9267	1.8227	0.1039
Incremental cost/QALY gained			
Revised transition probabilities for the extrapolated period. No health state transitions were allowed (except for background mortality) after Week 12 for BSC and after Week 64 for difelikefalin treated patients.			
Costs (\$)		\$6,789	
QALYs	2.0294	1.9381	0.0913
Incremental cost/QALY gained			
Decreased effective AEMP per 12 vials of difelikefalin from \$ [redacted] to \$ [redacted] (35% reduction) yielding dispensed drug costs of \$352.83 per 4-week cycle (from \$512.16 in March 2023)			
Costs (\$)		\$6,789	
QALYs	2.0294	1.9381	0.0913
Incremental cost/QALY gained			
Corrected weighted average DPMQ of \$311.03 using the proposed effective AEMP and Section 100 HSD fees and mark-ups, with 75% public hospital and 25% private hospital/community pharmacy weighting			
Costs (\$)		\$6,789	
QALYs	2.0294	1.9381	0.0913
Incremental cost/QALY gained			
Corrected application of adverse event disutilities to difelikefalin treated patients only			
Costs (\$)		\$6,789	
QALYs	2.0304	1.9381	0.0922
Incremental cost/QALY gained			

Source: constructed during the evaluation using the 'A10 – A DFK_Section3model_July2023' Excel workbook and Table 85, p216 of the November 2023 resubmission

Abbreviations: BSC, best supportive care; QALY, quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

- 6.71 Compared with the March 2023 base case, changes to the proposed AEMP for difelikefalin, changes to utility decrements associated with pruritus severity and revised transition probabilities for the extrapolated period had the largest impacts on the current resubmission's model.
- 6.72 Treatment with difelikefalin was associated with an incremental cost per QALY gained of \$45,000 to < \$55,000 compared to best supportive care for the treatment of patients with moderate to severe CKD-associated pruritus. This was similar to the incremental cost per QALY gained of \$45,000 to < \$55,000 in the March 2023 submission.
- 6.73 The economic model included multiple changes that partially addressed PBAC's concerns including the removal of mortality benefits, inclusion of adverse events and reduction in difelikefalin drug costs. However, the evaluation considered the revised extrapolation of treatment effects and assumed benefits after treatment discontinuation were optimistic and in favour of difelikefalin. The revised pruritus-related utility decrements were lower than estimated previously but remained relatively large and uncertain.
- 6.74 The results of key univariate sensitivity analyses are summarised in Table 10.

Table 10: Sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	Change to ICER, %
Revised base case		0.0922	3	-
Resubmission's base case (difelikefalin DPMQ \$352.42; adverse event disutility applied to all patients in difelikefalin arm regardless of treatment status)		0.0913	5	+ ■
Discount rate (base case 5%)				
0%		0.1040	3	- ■
3.5%		0.0956	3	- ■
Time horizon (base case 5 years)				
64 weeks		0.0026	7	+ ■
2 years		0.0396	8	+ ■
10 years		0.1439	9	- ■
Treatment discontinuations (base case 4.6% per 4-week cycle in the first 12 weeks then 2.0% per 4-week cycle ongoing; once-off stopping rule discontinuation, approximately 48.7% at 12 weeks)				
No discontinuations in the extrapolated period after 64 weeks		0.0921	5	+ ■
Week 12+ discontinuation rates increased by 50%		0.0894	9	- ■
Week 12+ discontinuation rates decreased by 50%		0.0949	5	+ ■
No non-specific treatment discontinuations		0.1093	5	+ ■
No stopping rule discontinuations ^a		0.1355	5	+ ■
Trial-based transition probabilities (base case applied up to 64 weeks for difelikefalin treated patients and up to 12 weeks for patients on BSC)				
Removed additional improvement for difelikefalin treated patients between 12 to 64 weeks, with no change in pruritus severity for all patients after 12 weeks		0.0550	3	+ ■
Extrapolated transition probabilities (base case no change in pruritus severity after 64 weeks for difelikefalin treated patients and after 12 weeks for patients on BSC)				
Waning of placebo response for BSC only based on an annual probability of moving to a worse pruritus health state (10% per year after Week 12)		0.1020	9	- ■
Waning of placebo response based on a greater annual probability of moving to a worse pruritus health state while on BSC (10% per year after Week 12) compared to difelikefalin treatment (5% per year after Week 64)		0.0990	9	- ■
Fixed transition probabilities over the whole model duration based on change from baseline to 12 weeks from the trial ('Week 0-12' dataset applied every cycle)		0.0213	11	+ ■
Convergence in average pruritus severity between arms over time. Modelled based on the assumption that patients who discontinue difelikefalin treatment after 12 weeks would assume the same pruritus severity distribution as those in the best supportive care arm		0.0567	3	+ ■
No additional improvement for difelikefalin treated patients after 12 weeks and convergence in average pruritus severity between arms over times (assumptions described above)		0.0330	10	+ ■
Health state utilities (base case baseline utility 0.6328 with utility decrements for mild 0.0528, moderate 0.1125 and severe 0.1908)				
Lower limit of 95% CI for base case estimates (baseline utility 0.5846 with utility decrements for mild 0.0444, moderate 0.1038 and severe 0.2159)		0.0986	9	- ■

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	Change to ICER, %
Upper limit of 95% CI for base case estimates (baseline utility 0.6810 with utility decrements for mild 0.0612, moderate 0.1213 and severe 0.1656)	■	0.0859	■ ³	+ ■
March 2023 submission (baseline utility 0.7024 with utility decrements for mild 0.0676, moderate 0.1544 and severe 0.2606)	■	0.1267	■ ⁴	- ■
Thokala 2023 (baseline utility 0.6168 with utility decrements for mild 0.0378, moderate 0.1025 and severe 0.1875)	■	0.0893	■ ³	+ ■
SHAREHD trial (baseline utility 0.744 with utility decrements for mild 0.018, moderate 0.155 and severe 0.149)	■	0.0938	■ ³	- ■
Decrease utility decrements by 25%	■	0.0691	■ ⁵	+ ■
Decrease utility decrements by 50%	■	0.0459	■ ⁶	+ ■
Adverse event costs (base case 4-week cost of \$518.49 per event based on Chan 2016)				
No adverse event costs	■	0.0922	■ ³	- ■
1 year cost of \$6,758.94 per event based on Chan 2016	■	0.0922	■ ³	+ ■
\$14,907 heart failure hospitalisation costs (AR-DRG F62A) applied to the modelled rate of adverse events per cycle	■	0.0922	■ ⁵	+ ■
\$13,312 for pulmonary oedema and respiratory failure hospitalisation costs (AR-DRG E64A) applied to the modelled rate of adverse events per cycle	■	0.0922	■ ⁵	+ ■

Source: Table 89, p219 and the 'A10 – A DFK_Section3model_July2023' Excel workbook

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups

^a There was an error in the economic model for this sensitivity analysis, as transition probabilities for difelikefalin treated patients were based on the subgroup of responders only. This was corrected during the evaluation, with transition probabilities based on all patients when the stopping rule was removed.

Italicised estimates were calculated during the evaluation

The redacted values correspond to the following ranges:

³ \$45,000 to < \$55,000

⁴ \$25,000 to < \$35,000

⁵ \$55,000 to < \$75,000

⁶ \$95,000 to < \$115,000

⁷ \$255,000 to < \$355,000

⁸ \$75,000 to < \$95,000

⁹ \$35,000 to < \$45,000

¹⁰ \$135,000 to < \$155,000

¹¹ \$155,000 to < \$255,000

6.75 The ESC noted the model was most sensitive to the extrapolation of treatment effects beyond 12 weeks, utility decrements associated with pruritus, treatment discontinuations and adverse event costs.

6.76 The resubmission acknowledged the extrapolation of treatment effects was key to the analysis, particularly for best supportive care due to a lack of data beyond 12 weeks. The resubmission claimed the base case assumption of no loss of placebo response (i.e. no change in pruritus severity) was highly conservative and biased against difelikefalin, as sensitivity analyses including waning of treatment effects resulted in lower ICER per QALY gained estimates compared to the base case. The ESC considered the resubmission's approach was in favour of difelikefalin as it resulted in greater relative treatment benefits than observed in the double-blind trials with no convergence in average pruritus severity between treatment arms regardless of treatment status. The pre-PBAC Response contended the lack of convergence in itch

severity over time in the base case model is a direct consequence of the assumption that placebo responses do not attenuate. The Response argued that, based on the parameters of the ESC advice, convergence will only occur if the model assumes patients treated with difelikefalin are more likely to lose response than untreated patients are to lose a placebo response.

- 6.77 The resubmission acknowledged that changes to treatment discontinuation rates produced unexpected results as the ICER per QALY gained improved with increasing discontinuation rates. This was due to the assumption of no change in pruritus severity in all patients on best supportive care after 12 weeks. The ESC noted the assumption also applied to those who switched to best supportive care after discontinuing difelikefalin treatment, which favoured difelikefalin as treatment benefits were maintained without ongoing treatment costs.
- 6.78 The model was sensitive to alternative adverse event costs based on implementation of a full year of costs per event. The model was also sensitive to higher costs per event based on the Cost Weights for Australian Refined Diagnosis Related Group (AR-DRG) version 11, 2020-2021 (public sector) for heart failure (\$14,907, F62A major complexity) and pulmonary oedema and respiratory failure (\$13,312, E64A major complexity).
- 6.79 Overall, the ESC considered the economic model remained highly uncertain and continued to favour difelikefalin. The ESC advised this was primarily due to optimistic extrapolation of treatment effects and benefits that may not be clinically plausible (see paragraphs 6.62 and 6.76), underestimation of adverse event costs (see paragraph 6.67) and inclusion of revised pruritus-related utility decrements that remained relatively large and uncertain (see paragraph 6.68). In addition, the ESC noted the economic model assumed patients will only have access to difelikefalin once per lifetime and considered a reduction in the time horizon may be appropriate to account for the likelihood of episodic treatment in clinical practice. The pre-PBAC Response noted ESC advice that the model structure was likely to be generally reliable for decision making and offered a 1% price reduction (see paragraph 3.2) to mitigate any remaining uncertainties regarding the economic model. The Response stated this price reduction decreased the resubmission ICER per QALY gained from \$45,000 to < \$55,000 to \$35,000 to < \$45,000 .

Drug cost/patient

Table 12: Drug cost per patient for difelikefalin

	KALM trials (12 weeks)	Economic model	Financial estimates
Dose regimen	Weight-based dose (0.5 µg/kg), 3-4 times per week	1.06 vials (50 µg) 3 times per week	1.06 vials (50 µg) 3 times per week
Adherence	KALM-1: 94.3% KALM-2: 95.4%	94.45% ^a	94.45% ^a
Mean time on treatment	-	1.16 years over 5-year time horizon ^b	Not calculable
Cost of scripts	-	\$	\$ ^c
Drug cost per patient	-	\$ for one course (1.16 years) of treatment ^d	\$ in each year ^e

Source: constructed during the evaluation

^a Calculated as (94.3% + 95.4%)/2

^b Based on mean years in on-treatment health states

^c During the evaluation, the effective DPMQs for public hospitals (\$|) and private hospitals/community pharmacy (\$|) were calculated using the proposed AEMP of \$| for 12 vials and 1 July 2023 fees and mark-ups associated with the requested Section 100 (HSD) CAR listing. A weighted DPMQ of \$| was estimated assuming most patients would obtain difelikefalin through public hospitals (75% public, 25% private/community pharmacy)

^d The estimated drug cost per patient per year was \$| based on an estimated effective DPMQ \$| per vial x 1.06 vials/dose x 3 doses per week, adjusted for 94.45% adherence and 52.17 weeks in a year. This was multiplied by mean time on treatment of 1.16 years.

^e Based on fixed proportions of persistent responders (42.3%), non-persistent responders (8.9%), persistent non-responders (42.2%) and non-persistent non-responders (6.4%) and assumed treatment durations for each category in the financial estimates.

6.80 The estimated drug cost per patient in Table 12 for the financial estimates represents the cost within an individual year whereas the cost for the economic model represents the total cost for one course of treatment. The pre-PBAC response offered a |% price reduction resulting in an effective AEMP of \$| for 12 vials.

Estimated PBS usage & financial implications

6.81 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS/RPBS listing of difelikefalin.

6.82 Key inputs for the financial estimates are summarised in Table 13.

Table 13: Key inputs for financial estimates

Parameter	Values and source	Comment
Prevalence of haemodialysis	13,700 in Year 1 increasing to 17,141 in Year 6. Prevalence of in-centre and at-home haemodialysis patients in the ANZDATA 45th Annual Report (2017-2021), extrapolated over the first 6 years of listing (2024-2029) using an annual growth rate of 4.58%.	The DUSC previously considered the source to be reasonable. The resubmission estimates appropriately include patients on at-home haemodialysis. The extrapolated estimates were appropriately calculated using a growth rate rather than the fixed increment applied in the previous submission.

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Parameter	Values and source	Comment
Proportion of patients with moderate to severe pruritus	43%: based on a sample of 700 Australian and New Zealand haemodialysis patients in the Dialysis Outcomes and Practice Patterns Study, with self-reported moderate-severe pruritus (Sukul 2020, DOPPS data 2009-2015).	<p>The DUSC previously considered the source to be reasonable, but noted the lack of an itch rating scale in the restriction may lead to usage in patients with less severe disease. The DUSC considered this parameter may effectively be underestimated in practice.</p> <p>The resubmission stated that this parameter was not updated to reflect the resubmission PBS restriction (inclusion of a WI-NRS score to determine disease severity) and the resulting financial estimates would inform a risk sharing arrangement.</p>
Rate of CKD-aP diagnosis	83% in Year 1 increasing to 93% in Year 6. Based on a survey of 8,621 patients enrolled at the start of DOPPS phase 5 (2012–2015), 17% of patients nearly always or always bothered by itchy skin had not reported their condition to any healthcare provider (Rayner 2017, DOPPS data 2012-2015). An assumed 2% yearly increment was applied to the diagnosis rate due to increased awareness of treatment availability.	<p>The DUSC previously considered the diagnosis rate in the previous submission was underestimated (83%, fixed over 6 years) given the availability of difelikefalin in the PBS may increase the rate of patients reporting itchy skin. A 2% yearly increment in diagnosis rates was assumed in the resubmission. The ESC noted the DUSC advice provided on this issue was not specific to a simple prevalence-based approach. The pre-PBAC response acknowledged the ESC advice and amended the rate of CKD-aP diagnosis (see paragraph 6.86).</p>
Uptake of difelikefalin	Assumed uptake of difelikefalin of 70% in Year 1, increasing by 4% each year, to 90% in Year 6.	<p>The DUSC previously considered the uptake rates to be reasonable. This parameter was unchanged from the previous submission. The ESC noted the DUSC advice provided on this issue was not specific to a simple prevalence-based approach. The pre-PBAC response acknowledged the ESC advice and reduced the uptake rate (see paragraph 6.85).</p>
Proportion of patients with response	51.3%: based on patients achieving ≥ 5 -point improvement in 5-D Itch score at 12 weeks from baseline in the KALM trials, applied in the economic analysis of the resubmission.	<p>The DUSC previously considered this was underestimated due to a lack of a formal response criterion in the restriction.</p> <p>The resubmission stated that this was not updated to reflect the resubmission PBS restriction (response based on ≥ 3-point improvement in WI-NRS score) and the resulting financial estimates would inform a risk sharing arrangement. It was uncertain whether response based on 5-D Itch would be applicable to response based on the WI-NRS scale. However, the use of trial-based WI-NRS data would have minimal impact on the financial estimates given numerically similar response rates (51.1%).</p>

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Parameter	Values and source	Comment
Treatment persistence in responders	82.6%. Based on treatment discontinuations observed in the KALM OLE studies (23.2% excluding the sponsor stopping the study early). An adjusted discontinuation rate of 17.4% was used assuming perfect persistence during the initial 12 weeks of therapy (calculated as 0.75 x 23.2%).	No justification was provided for the assumption of perfect persistence during the first 12 weeks of treatment, which was inconsistent with trial-based data that informed discontinuations in non-responders (13.3%, see below). Treatment persistence is likely overestimated.
Treatment persistence in non-responders	86.7%. Based on treatment discontinuations observed in the KALM double-blind trials (13.3%).	This appeared reasonable.
Treatment duration in persistent and non-persistent responders	Assumed as 1 year in persistent responders and 32 weeks in non-persistent responders. Non-persistent responders were assumed to have perfect persistence in the first 12 weeks and then discontinued mid-way through the remaining continuation phase of 40 weeks (calculated as 12 weeks + 20 weeks).	No justification was provided for the assumed 1-year treatment duration, with no ability to continue treatment in subsequent years. The evaluation considered the average treatment duration for responders is likely underestimated. The PSCR argued the prevalence-based approach means that the financial estimates do not assume a treatment duration cap of 1 year as patients continuing treatment beyond one year are reflected and counted in the analysis as the subsequent year's prevalent pool of patients on treatment.
Treatment duration in persistent and non-persistent non-responders	12 weeks in persistent non-responders and 6 weeks in non-persistent non-responders. Non-persistent non-responders were assumed to stop treatment mid-way through the induction period (i.e. at 6 weeks).	The simplified approach used to estimate the average treatment duration for non-persistent patients (linear trend) may be reasonable given the relatively short induction period with likely minimal impact on financial estimates.
Treatment adherence	94.45% based on the KALM trials	Trial-based adherence may not be applicable to clinical practice.
Scripts per year	Based on 1.06 vials per dose (derived from trial-based weight data) administered 3 times a week, estimated durations of therapy (see above) and 94.45% adherence. <u>Initial scripts</u> 3.0 per persistent and non-persistent responder, 3.0 per persistent non-responder and 1.5 per non-persistent non-responder. <u>Continuing scripts</u> 10.1 per persistent responder, 5.0 per non-persistent responder and none for non-responders. These estimates were corrected during the evaluation as the resubmission's estimates were calculated based on 1 vial per dose rather than 1.06 vials per dose.	The DUSC previously considered the script parameters (assuming 1 vial per dose) were underestimated as some patients (those whose weight exceeds 104 kg) may require 2 vials per dose. The resubmission appropriately accounted for increased vial use due to weight-based dosing. However, the resubmission did not account for additional doses (exceeding 3 times per week) which was inconsistent with trial data suggesting approximately 23-25% of patients in the key trials received ≥1 additional dose over the 12-week double-blind period.

Source: Sections 4.1-4.2, pp223-233 of the resubmission

Abbreviations: OLE, open-label extension; WI-NRS, Worst Itching Intensity Numerical Rating Scale

6.83 The evaluation noted the observed differences between submissions (see Table 14) were primarily due to structural changes with the use of a simple, prevalence-based approach that did not include additional mortality or prior treatment exposure adjustments that were applied in the previous submission. The removal of additional

mortality adjustments was consistent with recommendations from the DUSC. The ESC acknowledged that the resubmission had adopted the simple prevalence approach advised by DUSC in March 2023. However, the ESC considered the resubmission had not adjusted key input assumptions to account for the change to a simple prevalence-based approach.

- 6.84 The ESC considered the uptake rate was a key input assumption that required adjustment with the adoption of a simple prevalence approach. The ESC acknowledged the PSCR argument that the resubmission used the same uptake rates as per the March 2023 submission and noted that these had previously been considered reasonable by DUSC when applied to an eligible population that was adjusted for prior treatment exposure and mortality. However, the ESC considered the application of this approach in the current resubmission resulted in treated patient estimates that were implausibly large as it was based on relatively high uptake rates applied to the unadjusted eligible population estimates. The ESC considered that, given the proportion of patients with a response was assumed to be 51.3%, the assumption that the proportion of the eligible population treated with difelikefalin would continue to increase from 70% in Year 1 to 90% in Year 6 was not appropriate. The pre-PBAC Response acknowledged the advice of the ESC and provided revised financial estimates that amended the uptake rate to 30% in Year 1, 45% in Year 2 and, increasing by 10% per year up to a total of 75% in Year 6.
- 6.85 The ESC acknowledged that the increasing rate of CKD-associated pruritus used in the resubmission was consistent with the March 2023 DUSC advice. However, like the uptake rate, the ESC considered this assumption should be amended to account for the simple prevalence approach used in the resubmission. The ESC considered that the application of a constant rate of diagnosis across time (83%) would likely be more appropriate in this context. The pre-PBAC Response provided revised financials that included a constant rate of diagnosis across time (83%) as per ESC advice.
- 6.86 All treated patients in each year were assumed to receive initial treatment for up to 12 weeks. The evaluation considered there were also additional concerns regarding the inconsistent application of discontinuation rates between responders (perfect persistence in the first 12 weeks of treatment) and non-responders (13.3% discontinuation rate in the first 12 weeks of treatment) (see Table 13 above). The ESC considered the proportion of patients experiencing a response was not adequately incorporated in the simple prevalence approach presented in the submission. As such, the ESC considered the estimated script numbers were also implausibly large. The pre-PBAC Response argued the model applied discontinuations appropriately and that these have been additionally accounted for in the reduced uptake rates of the revised financial estimates provided.
- 6.87 The estimated use and financial impact of difelikefalin to the PBS/RPBS over the first 6 years of listing is summarised in Table 14. The financial estimates were corrected during the evaluation using a revised effective DPMQ of \$| instead of \$| in the resubmission. There was also an error in the continuing script estimates of the

resubmission that were based on 1 vial per dose of difelikefalin instead of 1.06 vials per dose. This was also corrected during the evaluation. The revised financial estimates provided in the pre-PBAC Response are included in the below table. The pre-PBAC Response estimates did not correct for the error in the continuing script estimates identified during the evaluation and applied a DPMQ of \$| which is incorrect. The error in the continuing scrips has been addressed and a DPMQ of \$| (75% public and 25% private hospital weighting) has been applied in the corrected pre-PBAC Response revised estimates presented in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated eligible population						
Eligible patients	1	2	2	2	2	2
Estimated eligible population – pre-PBAC response						
Eligible patients	1	2	2	2	2	2
Estimated extent of use						
Number of patients treated	1	1	1	1	2	2
Estimated extent of use – pre-PBAC response						
Number of patients treated	1	1	1	1	1	1
March 2023 submission treated patients (initiating and continuing from previous years)	1	1	1	1	1	1
Number of scripts dispensed						
Total scripts dispensed ^a	4	4	5	5	6	6
- Initial	2	3	3	3	3	3
- Continuing ^a	3	3	4	4	4	4
Number of scripts dispensed – pre-PBAC response						
Total scripts dispensed	3	3	4	4	5	5
- Initial	1	2	2	3	3	3
- Continuing ^b	2	3	3	3	4	4
March 2023 submission total scripts	4	4	3	3	3	3
Estimated financial implications of difelikefalin						
Cost to PBS/RPBS less co-payments ^{a, c}	7	7	7	8	8	8
Estimated financial implications of difelikefalin – pre-PBAC response						
Cost to PBS/RPBS less co-payments ^{b, d}	7	7	7	7	7	7
March 2023 submission						
Net cost to PBS/RPBS	7	7	7	7	7	7

Source: Section 4.2-4.4, pp227-235, the 'A12 – DFK_Section4model_July2023' Excel workbook of the resubmission, Table 1 of the pre-PBAC response and the ATTACHMENT 3 – A12 – DFK Revised section 4 model from the pre-PBAC Response.

^a Calculated during the evaluation using corrected continuing script estimates based on 1.06 vials per dose

^b Calculated during the preparation of the PBAC minutes using corrected continuing script estimates based on 1.06 vials per dose

^c Calculated during the evaluation using a revised effective DPMQ for difelikefalin

^d Calculated during the preparation of the PBAC minutes using a revised effective DPMQ for difelikefalin.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ 20,000 to < 30,000

⁵ 30,000 to < 40,000

⁶ 40,000 to < 50,000

⁷ \$0 to < \$10 million

⁸ \$10 million to < \$20 million

6.88 The estimated net cost to the PBS/RPBS for difelikefalin in the resubmission was \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, a total of \$60 million to < \$70 million over 6 years (\$70 million to < \$80 million in the resubmission's base case prior to the corrections made during the evaluation and \$60 million to < \$70 million in the March 2023 submission). There were substantial differences between the current resubmission and previous submission in terms of the size of the eligible population, treated patients and script estimates. This led to

contrasting trends over time with the initial submission estimating greater utilisation at the start that decreased over time while the current resubmission estimated continuous growth in utilisation over time. The corrected pre-PBAC Response revised estimates resulted in an estimated net cost to the PBS/RPBS for difelikefalin of \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, with a total net cost of \$30 million to < \$40 million over 6 years.

- 6.89 The resubmission provided an analysis for the requested grandfathering provision in the budget impact model. The resubmission estimated 0.35% of the prevalent haemodialysis population would meet the proposed restriction. The grandfathered patients were not added separately but assumed to be included in the prevalence estimates of the budget impact analysis.

Quality Use of Medicines

- 6.90 Quality use of medicines was not addressed in the resubmission. The DUSC previously considered the following issues (difelikefalin DUSC advice, March 2023 PBAC meeting):
- Falls risk may be greater for at-home patients who have less supervision and for this group of patients who may have an increased cumulative risk of falls given concomitant medicines and comorbidities.
 - Access for Indigenous patients in remote areas was not addressed.
 - At-home dialysis patients would have to be highly trained.
 - The presence of an itch may be a sign that the dialysis is not optimised.

Financial Management – Risk Sharing Arrangements

- 6.91 The resubmission proposed a Risk Sharing Arrangement based on PBS/RPBS expenditure estimated in the budget impact analysis. The resubmission proposed a 1% rebate for expenditure exceeding the predicted estimates, based on a multivariate sensitivity analysis of the economic model that was intended to estimate the cost-effectiveness of difelikefalin for the treatment of mild pruritus. The analysis was not informative as there were no changes to the baseline distribution of pruritus severity or transition probabilities, which were based on patients with moderate to severe pruritus only. The ESC considered a 1% rebate would be more appropriate given the lack of data for the use of difelikefalin in patients with mild pruritus. The pre-PBAC Response accepted the ESC view and stated a 1% rebate would be acceptable for a Risk Sharing Arrangement.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (Telephone/Online) listing of difelikefalin for the treatment of moderate to severe pruritus associated with chronic

kidney disease (CKD) in patients who are undergoing haemodialysis, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program). The PBAC was satisfied that difelikefalin provides, for some patients, a significant improvement in efficacy over best supportive care for the management of moderate to severe pruritus in the requested population. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of difelikefalin would be acceptable at the price proposed in the pre-PBAC response.

- 7.2 The PBAC noted the consumer comments discussed the severe impact of the condition on quality of life and the current lack of effective treatment options. The PBAC noted that health care professionals described the effectiveness of difelikefalin in reducing CKD-associated pruritis symptoms observed in patients accessing it through special access programs. The Committee noted the consumer comments for the resubmission concurred with those for the March 2023 submission, with the severe impact of the condition being a consistent theme. The PBAC reaffirmed its March 2023 advice that there was a clinical need for effective treatments options for moderate to severe pruritus (para 7.2, difelikefalin PSD, March 2023 PBAC meeting). The Committee accepted the proposed clinical place of difelikefalin, for patients with moderate to severe symptoms, was reasonable and consistent with the available clinical evidence.
- 7.3 The PBAC noted that, consistent with its March 2023 advice, the requested restriction included the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) scale and allowed use in patients receiving dialysis in the home. The PBAC noted a Complex Authority Required (CAR) listing would allow difelikefalin to be dispensed by a S90 Community Pharmacy as well as a Public/Private Hospital Pharmacy and advised that this was appropriate. The PBAC agreed with the ESC regarding the addition of a Prescribing Instruction that allows for flexibility on the quantity of vials required for individual patients (see paragraph 3.5). The PBAC also considered prescribing of initial treatment should be limited to nephrologists only and considered the proposed term 'renal physician' would be adequately captured under the term 'nephrologist' in the restriction. However, continuing treatment can be prescribed by a nephrologist or by a medical practitioner in consultation with a nephrologist. The PBAC considered the inclusion of a grandfather restriction was appropriate.
- 7.4 The PBAC reaffirmed its previously expressed view that the proposed comparator of best supportive care was reasonable (see paragraph 5.1).
- 7.5 The PBAC noted the key clinical evidence in the resubmission was unchanged, with the comparative effectiveness claim based on the results of the KALM-1 and KALM-2 studies. The PBAC recalled that, for the pooled population, a statistically significantly greater proportion of patients treated with difelikefalin achieved a ≥ 3 -point improvement in WI-NRS score at Week 12 from baseline compared to those receiving best supportive care (OR 1.93, 95% CI 1.44, 2.57). The PBAC reaffirmed its March 2023 advice that the claim of superior comparative effectiveness compared to best supportive care was likely to be reasonable (see paragraph 6.50).

- 7.6 The PBAC noted no new safety data were available and that the trial evidence indicated difelikefalin was associated with increased occurrence of gastrointestinal adverse events, falls/gait disturbances, dizziness, and somnolence. Overall, the Committee reaffirmed its previous view that the claim of inferior comparative safety to best supportive care was reasonable (see paragraph 6.50).
- 7.7 The PBAC recalled that in March 2023 it had considered the structure of the economic model as overall likely to be reasonable, however key inputs were optimistic and favoured difelikefalin (see paragraph 6.56). The PBAC noted the resubmission made multiple changes to the model in an attempt to address the concerns raised in March 2023 (see paragraph 6.57). The PBAC acknowledged the ESC advice that while some changes to the economic model in the resubmission were appropriate, other components of the model likely favoured difelikefalin (see paragraph 6.79). The PBAC noted the pre-PBAC Response subsequently offered a 10% price reduction (see paragraph 3.2) to mitigate any remaining uncertainties regarding the economic model. The PBAC noted the pre-PBAC Response price reduction decreased the resubmission ICER per QALY gained from \$45,000 to < \$55,000 to \$35,000 to < \$45,000. The PBAC accepted the economic model was structurally reliable for decision-making and advised that, with the pre-PBAC Response price offer, the listing was acceptably cost effective in this population with a clinical need for effective treatment options.
- 7.8 The PBAC noted the concerns raised by the ESC that the size of the eligible population, subsequent treated patient and script estimates were highly uncertain and substantially overestimated due to the lack of adjustments to key input assumptions to account for the change to a simple prevalence based approach in the resubmission (see paragraphs 6.83 to 6.85). The PBAC acknowledged the pre-PBAC Response responded to the concerns raised by providing revised financial estimates with lower uptake rates (see paragraph 6.84) and removal of the diagnosis rate modifier as had been requested by ESC (see paragraph 6.85). The PBAC also accepted the pre-PBAC response argument that discontinuations have been applied appropriately and are accounted for in the revised estimates (see paragraph 6.86). The PBAC noted that grandfathered patients are accounted for in the prevalence estimates of the budget impact analysis. The PBAC noted that, including the pre-PBAC response price reduction and once corrected for an error in the continuing script estimates, the revised estimates reduced the total number of scripts from 40,000 to < 50,000 to 30,000 to < 40,000 in year 6 and the net predicted cost to the PBS/RPBS over 6 years from \$60 million to < \$70 million to \$30 million to < \$40 million. The PBAC considered it was reasonable to accept the revised financial estimates presented in the pre-PBAC response (see Table 14) as an appropriate basis for a risk sharing arrangement.
- 7.9 The PBAC reiterated its March 2023 advice that a Risk Sharing Arrangement would be required to address any residual uncertainty with the potential for use outside the proposed restriction, including in patients with mild pruritis (see Table 2). The PBAC noted the 10% rebate for expenditure exceeding the predicted estimates offered in the

pre-PBAC response and considered it appropriate.

- 7.10 The PBAC advised that difelikefalin should not be treated as interchangeable with any other drugs.
- 7.11 The PBAC advised that difelikefalin is not suitable for prescribing by nurse practitioners, given its advice the listing should be restricted to specialist medical practitioners only.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for difelikefalin:
- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over best supportive care, as while clinically relevant the treatment benefit is likely to be modest;
 - The treatment is expected to address a high and urgent unmet clinical need because there are limited current treatment options and none with high-quality evidence supporting their use;
 - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
DIFELIKEFALIN					
Difelikefalin 50 microgram/mL injection, 12 x 1mL vial	New HSD (Public) New HSD (Private)	1	12	2	Korsuva
Restriction Summary [new 1] / Treatment of Concept: [new 2]					
	Category / Program: Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals}				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities system				

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	<p>Administrative Advice: No increase to the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>
	<p>Administrative Advice: See the following article for details on the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS):</p> <p>Vernon MK, Swett LL, Speck RM, 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. <i>J Patient Rep Outcomes</i>. 2021;5(1):134. Published 2021 Dec 24. doi:10.1186/s41687-021-00404-z</p> <p>The WI-NRS scale is available as downloadable document in the supplementary information section at: www.ncbi.nlm.nih.gov/pmc/articles/PMC8709801/</p>
	<p>Indication: Moderate to severe pruritus (itching) associated with chronic kidney disease</p>
	<p>Treatment Phase: Initial treatment</p>
	<p>Clinical criteria:</p>
	<p>Patient must be on optimised haemodialysis</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must be on haemodialysis for at least 3 months</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The condition must be confirmed based on both physical examination and patient history to exclude any factors that may be triggering the pruritus</p>
	<p>AND</p>
	<p>Clinical criteria</p>
	<p>Patient must have experienced itch that persists for at least 6 weeks despite best supportive care.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have a 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) baseline score of more than 4.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must not receive more than 12 weeks of treatment with this drug under this treatment phase</p>
	<p>AND</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a nephrologist.</p>
	<p>AND</p>
	<p>Population criteria:</p>
	<p>Patient must be at least 18 years of age</p>
	<p>Prescribing Instructions: Prescriber must exclude any other causes of pruritus which include any of the following: (i) drug/dialysis related (e.g., opioid-related pruritus) (ii) drug hypersensitivity or adverse effect; contact dermatitis; allergy (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; liver disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes).</p>
	<p>Prescribing Instructions: Best supportive care for patients with chronic kidney disease-associated pruritus is not limited to but includes:</p>

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	(i) optimisation of dialysis, (ii) skin hydration and nutrition (with the use of moisturiser, emollients, barrier creams or oils) (iii) patient education on the importance of avoiding or minimising scratching.
	Prescribing instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug, based on the dry body weight of the patient (in kg), adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). Up to a maximum of 2 repeats will be authorised. No more than 4 doses per week will be authorised even if the number of haemodialysis treatments in a week exceeds 4.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
DIFELIKEFALIN					
Difelikefalin 50 microgram/mL injection, 12 x 1mL vial	New HSD (Public) New HSD (Private)	1	12	5	Korsuva
Restriction Summary [new 3] / Treatment of Concept: [new 4]					
	Category / Program: Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities system				
	Administrative Advice: No increase to the maximum number of repeats may be authorised.				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).				
	Administrative Advice: See the following article for details on the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS): Vernon MK, Swett LL, Speck RM, 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. J Patient Rep Outcomes. 2021;5(1):134. Published 2021 Dec 24. doi:10.1186/s41687-021-00404-z The WI-NRS scale is available as downloadable document in the supplementary information section at: www.ncbi.nlm.nih.gov/pmc/articles/PMC8709801/				
	Indication: Moderate to severe pruritus (itching) associated with chronic kidney disease				
	Treatment Phase: Continuing treatment				
	Clinical criteria:				
	Patient must have previously received PBS-subsidised treatment with this drug for this condition				
	AND				
	Clinical criteria:				
	Patient must have demonstrated an adequate response to treatment with this drug including at least a 3-point improvement from baseline in 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) score.				
	AND				

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	Treatment criteria:
	Must be treated by at least one of the following prescriber types: (i) a nephrologist, (ii) a medical practitioner in consultation with a nephrologist.
	Prescribing instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug, based on the dry body weight of the patient (in kg), adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). Up to a maximum of 5 repeats will be authorised. No more than 4 doses per week will be authorised even if the number of haemodialysis treatments in a week exceeds 4.
Restriction Summary [new 5] / Treatment of Concept: [new 6]	
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfather treatment
	Clinical criteria:
	Patient must have been receiving non-PBS-subsidised treatment with drug for this condition prior to [PBS listing date]
	AND
	Clinical criteria:
	Patient must have met all other PBS eligibility criteria that a non- 'Grandfather' patient would ordinarily be required to meet, meaning that at the time non-PBS subsidised supply was commenced, the patient: (i) was on optimised haemodialysis; (ii) was on haemodialysis for at least 3 months; (iii) had a condition confirmed based on both physical examination and patient history to exclude any factors that may be triggering the pruritus; (iv) had experienced itch that persists for at least 6 weeks despite best supportive care; (v) had a 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) of more than 4 at baseline.
	AND
	Clinical criteria:
	Patient must have demonstrated an adequate response to the most recent non-PBS-subsidised treatment with this drug for this condition, including at least a 3-point improvement from baseline in 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) score.
	AND
	Treatment criteria:
	Must be treated by a nephrologist.
	AND
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug, based on the dry body weight of the patient (in kg), adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). Up to a maximum of 5 repeats will be authorised. No more than 4 doses per week will be authorised even if the number of haemodialysis treatments in a week exceeds 4.
	Administrative advice:

	A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.
	Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

Document incorporated by reference	Listed drug	Description of document	Document access
24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS)	Difelikefalin	WI-NRS measures itching intensity over 24 hours. instrument is provided as "Supplementary Materials" for which there is a weblink.	Key publication: Vernon MK, Swett LL, Speck RM, 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. J Patient Rep Outcomes. 2021;5(1):134. Published 2021 Dec 24. doi:10.1186/s41687-021-00404-z PDF link: www.ncbi.nlm.nih.gov/pmc/articles/PMC8709801/pdf/41687_2021_Article_404.pdf Journal link: https://jpro.springeropen.com/articles/10.1186/s41687-021-00404-z

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.