5.09 DIFELIKEFALIN, Solution for I.V. injection 50 mcg in 1 mL vial, Korsuva®, Vifor Pharma Pty Limited.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drug Program), Authority Required (telephone/online) listing for the treatment of moderate to severe pruritus associated with chronic kidney disease 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 submission

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, p28 of the submission

2 Background

Registration status

2.1 TGA status at time of PBAC consideration: Difelikefalin was TGA registered on 10 November 2022. The finalised Product Information was provided alongside the Pre-Sub-Committee Response (PSCR).

2.2 The TGA indication for difelikefalin is for the treatment of moderate to severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.

2.3 In August 2022, the Advisory Committee for Medicines (ACM) considered that difelikefalin has an overall positive benefit-risk profile for the proposed indication but proposed multiple amendments to the Product Information. The suggested amendments included that the administration of difelikefalin be 'under the guidance of health care professionals' rather than 'doctor or nurse must administer'. The ACM considered that many patients are well-trained to self-administer drugs and dialysis and therefore requiring administration by health professionals may disadvantage patients living in remote areas who have home haemodialysis with frequent healthcare professional visits. The ESC noted the finalised Product Information states administration should be 'under the guidance of health care professionals'.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. Essential elements for grandfathered treatment were added during the evaluation, assumed to be the same as initial treatment (when they initiated non-PBS treatment) and for continuing treatment.

Name, Restriction, Manner of administration and form	Dispensed Price for Max. Qty	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer
DIFELIKEFALIN						
Difelikefalin 50 mcg/mL solution for injection, 1mL vial (as acetate)	$616.77 (published) $[redacted] (effective)	New HSD (Public) New HSD (Private)	1	12	2	Korsuva Vifor Pharma (trading as CSL Vifor)

Restriction Summary [new 1] / Treatment of Concept: [new 2]		
Concept ID		**Category / Program:** Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals}
		Prescriber type: ☒Medical Practitioners
		Restriction Level / Method: ☒Authority Required – Telephone/Electronic/~~Emergency~~
		Administrative Advice: *No increase to the maximum number of repeats may be authorised.*
		Prescribing instructions: *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.*
		~~**Administrative advice:**~~ ~~Other causes of pruritus include drug/dialysis related (e.g., opioid-related pruritus; drug hypersensitivity or adverse effect; contact dermatitis; allergy) or differential diagnoses (e.g., xerosis; infestations; iron deficiency; liver disease; polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes).~~ ~~Best supportive care for patients with chronic kidney disease-associated pruritus is not limited to but includes: optimisation of dialysis, skin hydration (with the use of moisturiser, emollients, barrier creams or oils) and nutrition; and patient education on the importance of avoiding or minimising scratching.~~
		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).*
		Severity: Moderate to severe
		Condition: *Pruritus (itching) associated with chronic kidney disease* ~~Chronic kidney disease-associated pruritus~~
		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 ~~**in-centre**~~ haemodialysis, ~~stable for at least 3 months~~
	AND
	Clinical criteria:
	Patient must be ~~***stable***~~ *on haemodialysis at least 3 times per week 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:
	Patient must not receive more than 12 weeks of treatment with this drug under this ~~restriction~~ *treatment phase*
	AND
	Treatment criteria:
	~~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~~ *Must be treated by at least one of (i) a renal physician, (ii) nephrologist, (iii) allergist.*
	AND
	Population criteria:
	Patient must be *at least* 18 years *of age* ~~or older.~~
	~~**Administrative advice:**~~ ~~If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.~~
	~~**Administrative advice:**~~ ***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) ~~or~~ (iii) differential diagnoses (e.g., xerosis; infestations; iron deficiency; liver disease; - polycythaemia vera/leukemia/lymphoma; hypothyroidism; uncontrolled diabetes).
	~~**Administrative advice:**~~ ***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) ~~and nutrition~~; ~~and~~ (iii) patient education on the importance of avoiding or minimising scratching.

Name, Restriction, Manner of administration and form	**Dispensed Price for Max. Qty**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Proprietary Name and Manufacturer**
DIFELIKEFALIN						
Difelikefalin 50 mcg/mL solution for injection, 1mL vial (as acetate)	$616.77 (published) $[redacted] (effective)	New HSD (Public) New HSD (Private)	1	12	**5**	Korsuva Vifor Pharma (trading as CSL Vifor)

Restriction Summary [new 3] / Treatment of Concept: [new 4]		
		Administrative Advice: *No increase to the maximum number of repeats may be authorised.*
		Prescribing instructions: *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.*
		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).*
		Treatment Phase: Continuing treatment
		Clinical criteria:
		Patient must have previously received PBS-subsidised ~~initial~~ treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must have demonstrated /~~or~~ sustained an adequate response to ~~the most recent PBS-subsidised~~ treatment with this drug ~~for this condition~~
		AND
		Treatment criteria:
		~~Must be treated by a renal physician, nephrologist, allergist or general physician experienced in the management of patients with chronic kidney disease~~ *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.*
		Administrative advice: ~~A patient who fails to respond to treatment with non-PBS-subsidised treatment with this medication for chronic kidney disease associated pruritus will not be eligible to receive PBS-subsidised treatment with this medication for this condition.~~
		~~**Administrative advice:**~~ ~~At the time of the authority application, medical practitioners should request the appropriate quantity and number of repeats to provide for a continuing course of this medicine consisting of the recommended number of doses for the dry body weight of the patient (refer to the TGA-approved Product Information), sufficient for up to 24 weeks of therapy.~~
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 ~~previously~~ *been* receiv*ing* non-PBS-subsidised treatment with drug for this condition prior to [PBS listing date]
		AND
		Clinical criteria:
		~~Patient must be receiving non-PBS treatment with this drug for this condition at the time of application~~
		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* ~~***in-centre***~~ *haemodialysis,* *(ii) was* ~~***stable***~~ *on haemodialysis at least 3 times per week 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.
	AND
	Clinical criteria:
	Patient must have demonstrated /~~or~~ sustained an adequate response to the most recent non-subsidised treatment with this drug for this condition
	AND
	Treatment criteria:
	~~Must be treated by, or in consultation with, a renal physician, nephrologist, allergist or general physician experienced in the management of patients with chronic kidney disease~~ *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*
	~~**Administrative advice:**~~ ~~A patient who fails to respond to treatment with non-PBS-subsidised treatment with this medication for chronic kidney disease associated pruritus will not be eligible to receive PBS-subsidised treatment with this medication for this condition~~.
	~~**Administrative advice:**~~ ~~At the time of the authority application, medical practitioners should request the appropriate quantity and number of repeats to provide for a continuing course of this medicine consisting of the recommended number of doses for the dry body weight of the patient (refer to the TGA-approved Product Information), sufficient for up to 24 weeks of therapy.~~
	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 subsequent continuing treatment criteria.
	Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

3.2 The sponsor proposed a special pricing arrangement for both initial and continuing scripts, with a DPMQ effective price of $[redacted] for 12 vials of difelikefalin and a published price of $616.77. The proposed effective and published prices appear to include fees and mark-ups associated with private hospital and community scripts only. For public hospitals, prices would be based on an effective AEMP of $[redacted] for 12 vials and a published AEMP of $540. The drug cost of difelikefalin in the economic model and financial estimates was based on the proposed prices including fees and mark-ups. The pre-PBAC response offered a [redacted]% price reduction (AEMP $[redacted] per vial ($[redacted] per 12 vials) reduced to $[redacted] AEMP per vial ($[redacted] per 12 vials).

3.3 Notes regarding requests for greater quantities based on the dry body weight of patients (>104 kg requires more than 1 vial per dose) were included in the continuing and grandfathering restrictions but not in the initial restriction. The ESC considered increased quantities would be required for patients who required 4 administrations a week and/or weigh >104 kg and was concerned there was a potential for wastage in these patients which has not been considered elsewhere in the submission (including the economic model and financial estimates).

3.4 None of the proposed restrictions appear to allow for requests for more vials or repeats, which may be required for patients requiring additional, potentially unplanned administrations. This was inconsistent with the administration of

difelikefalin in the trials and the Product Information that recommends up to 4 doses per week in patients who require additional haemodialysis treatment.

3.5 The submission stated that only the 12-vial pack size will be marketed in Australia. Any applications for more vials would require breaking an additional pack, which may result in potential wastage and/or additional costs to the pharmacy. The ESC 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 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.

3.6 The requested restriction is narrower than the proposed TGA indication in terms of treatment setting (in-centre haemodialysis) and place in therapy (patients with inadequate response to best supportive care).

3.7 No justification was provided in the submission for limiting treatment eligibility to patients on in-centre haemodialysis. The ACM was of the view that this may disadvantage some patients, particularly those who live in remote settings. Uneven access to treatment may also cause a shift for some patients from home haemodialysis to in-centre haemodialysis. The PSCR noted the sponsor was open to amending the restriction to permit difelikefalin administration in the home haemodialysis setting, consistent with the views of the ACM. The ESC agreed this change was appropriate and would minimise potential inequities in access. The ESC 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. The ESC considered such an approach may assist access by home haemodialysis patients.

3.8 The terms 'optimised' and 'stable' haemodialysis were not defined in the restriction. The submission did not specify the frequency of haemodialysis, based on advice from the sponsor's advisory board, that clinical trials for incremental dialysis were making progress and less frequent haemodialysis (twice weekly) may become standard in the future. This was inconsistent with the trials that required patients to be on haemodialysis 3 times a week for at least 3 months prior. The administration of difelikefalin is dependent on the frequency of haemodialysis and was given at the end of each haemodialysis session (maximum of 4 doses per week) in the trials. The ESC noted the PSCR requested removal of the word 'stable' from the restriction, as the word has no clear definition and the term 'optimised haemodialysis' would generally be understood by prescribers.

3.9 The submission claimed that the assessment of CKD-associated pruritus is challenging in practice, proposing instead that treatment eligibility be determined using the judgement of the treating physician based on physical examination of the patient and clinical history taking. Therefore, no specific diagnosis criteria or use of instruments to

determine pruritus severity were specified in the restriction. The evaluation considered this may be reasonable as there is currently no formal guidance on the assessment and diagnosis of CKD-associated pruritus. The ESC considered suspicion of CKD-associated pruritis is likely to be high given it is a common condition in dialysis patients. The ESC considered the inability to reliably classify the severity of itch in practice suggests difelikefalin may be used in patients with milder disease, despite a lack of evidence in this population. The ESC considered the use of the Worst-Itching Intensity Numerical Rating Scale (WI-NRS) in practice, and hence in the restriction, was feasible to define the moderate-severe pruritis. The pre-PBAC response acknowledged the use of the WI-NRS instrument was feasible, however questioned the value it would add to the restriction as it is a simple numeric rating scale based on a subjective assessment of symptoms.

3.10 The initial restriction requires patients to have persistent itch for at least 6 weeks despite best supportive care. The submission claimed the 6-week duration was based on a general definition of chronic pruritus. The restriction appears targeted at a subset of patients with chronic, persistent CKD-associated pruritus, which may be appropriate based on the key trials of difelikefalin. The ESC noted the 6-week threshold aligns with accepted definitions for chronic itch, however, appears relatively short compared to the duration of pruritus experienced by most patients in the KALM trials (mean 3.3 years, median 2.5 years), and considered the impact on the benefit/risk profile in the PBS population was unclear.

3.11 The submission proposed initial script coverage of 12 weeks as this is consistent with the double-blind treatment period of the key trials. The intent is that patients who demonstrate adequate response to treatment would be eligible for continuing treatment. The purpose of having separate initial and continuing restrictions was unclear given the absence of objective response criteria. However, the ESC agreed with the evaluation that the use of a continuation rule was consistent with assumptions in the economic model and financial estimates of the submission, but considered the expected discontinuation in practice was likely overestimated. The pre-PBAC response argued that given no medication is without risk of adverse side effects and patients on haemodialysis undergo regular medication review, it would be unlikely that a treating nephrologist would allow a patient to continue with a treatment (such as difelikefalin) where the patient was not tolerating the medicine well or not receiving a positive benefit.

3.12 The submission acknowledged the simplified restriction may lead to use outside the restrictions (i.e. patients with mild pruritus and continuing treatment in patients without adequate response), but proposed that the risk be managed through a risk sharing arrangement (RSA) and cap based on the financial estimates of the submission. Details of the RSA were not provided, with the sponsor indicating that they are willing to work with the Department of Health to agree on an appropriate rebate over agreed levels of expenditure. The PSCR argued the expectation was that use in patients with mild pruritis would be low as patients with mild symptoms would

not seek treatment with difelikefalin and prescribers would be educated on the appropriate use of the drug. Furthermore, the PSCR also emphasised a RSA had been proposed based on the estimates of how difelikefalin was intended to be used. The ESC considered use in patients with milder disease was highly likely given it is easy to administer alongside haemodialysis and the lack of objective criteria for assessing itch severity in the proposed restriction. The pre-PBAC response argued the use of difelikefalin in patients with milder symptoms was highly unlikely to be widespread and stated clinicians will adopt a best supportive care approach for the management of their patients, with topical treatments and anti-itch medications likely to be used first.

3.13 The submission included a broad definition of best supportive care in the notes of the initial restriction. It may also be appropriate to include treatment of biochemical abnormalities (e.g. calcium, phosphate, parathyroid, vitamin D) that are common in patients with CKD. It was unclear whether the definition should include the use of off-label treatments (e.g. gabapentinoids, antihistamines, antidepressants) given the risk-benefit profile of these treatments for CKD-associated pruritus remains uncertain.

3.14 The submission requested a grandfather restriction for patients who have received difelikefalin as part of a patient access program. The submission anticipated that up to 50 patients will be enrolled. Eligible patients are those receiving optimised, in-centre haemodialysis three times a week. In addition, moderate to severe disease would be determined using the WI-NRS and Self-Assessment of Disease Severity (SADS) tools. The proposed restriction also requires that patients demonstrate adequate response to difelikefalin treatment (no proposed instrument). The enrolment criteria appeared narrower than the proposed restriction in terms of haemodialysis frequency and use of instruments to determine disease severity.

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

4 Population and disease

4.1 Chronic kidney disease (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 a 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.

4.3 Currently the pathophysiology of CKD-associated pruritus is unknown, with several emerging hypotheses including uraemic toxin build-up, histamine release, immune-mediated response, and opioid receptor dysregulation. The diagnosis of this condition is 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 submission 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 optimal duration of best supportive care measures is likely to vary substantially given the broad range interventions that can be initiated, with timing of assessments dependent on both patient- and clinician-related factors.

4.6 The optimal duration of treatment with difelikefalin is unclear, particularly in patients with relapsing-remitting pruritus. There are limited long-term data for difelikefalin.

4.7 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).

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

5 Comparator

5.1 The submission nominated best supportive care as the main comparator. The ESC considered this was reasonable.

5.2 The submission claimed that difelikefalin would be used in addition to best supportive and not as alternative treatment. This was reasonable given the proposed place in therapy and restriction positions difelikefalin for the treatment of patients with persistent pruritus despite best supportive care.

5.3 The submission claimed that there are currently no treatments that are approved specifically for the treatment of CKD-associated pruritus. The submission listed a range of interventions that are part of best supportive care including the optimisation of dialysis and skin hydration (with the use of topical emollients, moisturisers, barrier creams) as well as off-label use of systemic treatments such as antihistamines,

gabapentinoids, antidepressants or UVB therapy. The listed treatments were largely based on literature reviews and expert opinion due to a lack of formal guidelines and high-quality evidence for both pharmacological and non-pharmacological interventions. There was consensus amongst the published reviews, however, that patients on haemodialysis with persistent pruritus should consider kidney transplantation as symptoms would generally resolve following transplantation.

5.4 The submission claimed that the off-label use of systemic treatments was consistent with the pivotal trials of difelikefalin as these therapies were permitted as concomitant treatment. The submission acknowledged, however, that the use of best supportive care measures in the Australian setting is unclear. The submission claimed the relative effectiveness of the identified interventions is uncertain given the weak body of evidence and the cost-effectiveness of these treatments for CKD-associated pruritus has not previously been considered by the PBAC. Overall, the ESC agreed with the evaluation that the management of CKD-associated pruritus in practice is not well-defined.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician highlighted the impact of pruritus in patients with CKD undergoing dialysis, the lack of treatment options with good quality evidence and the need for effective treatment options. The clinician also discussed the proposed PBS restriction and stated that the measurement of itch severity was subjective, although simple tools like rating scales were used in the difelikefalin clinical trials. The clinician further stated that use with patients in mild disease was unlikely to occur regularly in practice and that clinicians would be unlikely to continue patients on treatment if it was not helpful for them.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from health care professionals described the high prevalence of pruritus symptoms in the CKD population undergoing dialysis and the impact on patients quality of life, especially for those with intractable itch. The comments also noted the lack of effective treatments for patients with moderate to severe symptoms and the problems with tolerability and side-effects with existing treatments for some patients.

6.3 The PBAC noted the advice received from Kidney Health Australia, the Australian and New Zealand Society of Nephrology (ANZSN) and the Renal Society of Australia discussing the impact of pruritus on the quality of life of patients with CKD, issues with current treatment options and the apparent benefits of difelikefalin based on the KALM trials. The advice also noted the limitations of the IV route of administration

difelikefalin which effectively restricts use to patients receiving haemodialysis. The PBAC noted the input from Kidney Health Australia discussed pruritus symptoms in the CKD population as being a particularly distressing symptom associated with advanced kidney disease and highlighted the effectiveness and tolerability of difelikefalin. The Committee also noted the input from the ANZSN which outlined the impacts of pruritus in patients with CKD, including disturbed sleep, lethargy, fatigue, depression and poor life participation. The input from ANZSN also discussed the adverse events associated with off-label use of the gabapentinoid family of drugs, which can cause sedation, confusion and dizziness. The PBAC also noted the input from the Renal Society of Australia, which discussed the wide range of treatments which were often used in CKD-associated pruritus including moisturisers, antihistamines, gabapentinoids, phosphate binders, phototherapy, corticosteroids and other treatments and highlighted the mostly unproven and often ineffective nature of current treatment options.

Clinical trials

6.4 The submission 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.

6.5 The submission also included supportive data based on pooled analyses using data from the KALM-1 and KALM-2 trials and open-label extensions (Topf 2022) and pooled analyses of safety data from the broader Phase III clinical trial program of difelikefalin for treatment of CKD-associated pruritus in haemodialysis patients (Fishbane 2022).

6.6 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

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 12, p70; Attachments 4 and 5 of the submission

6.7 The key features of the included trials are summarised in Table 3.

Table 3: 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	Low	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	Low			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
KAML-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 with response defined as ≥5-point improvement at 12 weeks

Source: Table 13, p273 of the submission
Abbreviations: DB, double blind; MC, multi-centre; OL, open label; R, randomised; US, United States; WI-NRS, Worst-Itching Intensity Numeric Rating Scale

6.8 The submission acknowledged that the efficacy endpoints in the key trials were based on subjective patient-reported measures (24-hour WI-NRS, Skindex-10 Scale, 5-D Itch Scale and Patient Global Impression of Change), which can be prone to bias. The submission claimed the use of double-blinding and collection of measurements at multiple time points may help mitigate the risk of bias. The risk of bias was high for efficacy endpoints 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.

6.9 There was differential discontinuation between treatment arms during the 12-week double-blind treatment period, with more patients discontinuing in the difelikefalin arm compared to placebo in both KALM-1 (difelikefalin 14%, placebo 10%) and KALM-2 (difelikefalin 12%, placebo 6%) trials. The difference was primarily due to adverse events. Clinical data were not collected following treatment discontinuation, which may have an impact on any differences observed between treatment arms after discontinuations. Multiple imputation methods were used to handle the missing data, with sensitivity analyses using different assumptions and imputation algorithms.

6.10 The open-label extension periods in both trials were stopped early due to sponsor decision, with the trial reports stating that it was due to administrative reasons and not safety or lack of efficacy concerns. The decision had a greater impact on the global

study, KALM-2, with almost all patients discontinuing early (80% due to 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.

6.11 The primary outcome in the key trials was the proportion of patients achieving a ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind treatment period. The submission acknowledged that the assessment of pruritus severity is highly subjective but argued that the 3-point threshold used to define treatment response in the trials would represent a minimal clinically important difference (MCID).

6.12 The submission claimed the nominated MCID was supported by an anchor- and distribution-based analysis of data from a Phase II trial of difelikefalin versus placebo in haemodialysis patients with moderate to severe CKD-associated pruritus (CLIN2101) (Vernon 2021a, published in a research letter). The results of the analysis were not presented or discussed in the submission.

6.13 The submission also acknowledged, however, that the FDA prefers a higher threshold of ≥4-point change in WI-NRS to define treatment response. Outcomes based on a ≥4-point change were assessed as secondary endpoints in the trials.

6.14 Other key secondary endpoints in the trials included measures of itch-related quality of life using 2 multi-dimensional questionnaires (5-D Itch Scale and Skindex-10 Scale). The submission claimed that the Phase II trial dataset (CLIN2101) showed 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 submission. The Patient Global Impression of Change (PGIC) scale was assessed an exploratory outcome.

6.15 No health-related quality of life outcomes using generic instruments (e.g. EQ-5D or SF 36) were captured in the key trials.

Comparative effectiveness

6.16 Table 4 presents key results based on the WI-NRS (range, 0-10) in the pivotal trials of difelikefalin.

Table 4: 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 23, p107; Table 24, p111 of the submission; Table 12, p61; Table 13, p64 of the 'CLMD DFK – Summary of Clinical Efficacy' report of the submission

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

6.17 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. More patients in the difelikefalin arm had missing data compared to the placebo arm. This is likely due to more patients discontinuing difelikefalin (primarily due to adverse events) compared to placebo. Sensitivity analyses using alternative methods of handling missing data including a non-responder analysis produced results that were consistent with the primary analysis.

6.18 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.

6.19 Estimated response rates in the difelikefalin arms were similar in both trials but varied substantially for the placebo arms (difference exceeding 10%). The placebo response rate in KALM-2 was higher than in KALM-1 and appears to be the primary driver of a numerically lower difference in treatment response associated with difelikefalin (KALM-1, approximately 23%; KALM-2, approximately 12%).

6.20 The submission noted the high placebo response rates in both trials but claimed that this was not unexpected given the subjective nature of itch. The submission claimed that strong placebo effects have previously been observed in dermatological studies that rely on patient-reported outcomes. The submission 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%).

6.21 Results for key secondary outcomes based on the multi-dimensional itch-related quality of life questionnaires, Skindex-10 (range, 0-60) and 5-D Itch Scales (range, 5-25) are presented in Table 5.

Table 5: Results based on the Skindex-10 and 5-D Itch scales 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
Change from baseline to Week 12 in total Skindex-10 score (secondary outcome)						
LS mean change (95% CI) [a]	-17.2 (-19.6, -14.7)	-12.0 (-14.5, -9.6)	-16.6 (-19.3, -14.0)	-14.8 (-17.4, -12.2)	-16.1 (-17.7, -14.5)	-12.8 (-14.5, -11.2)
Difference (95% CI) [a]	**-5.1 (-8.0, -2.3)**		-1.8 (-4.3, 0.8)		-3.3 (-5.2, -1.4)	
Change from baseline to Week 12 in total 5-D Itch score (secondary outcome)						
LS mean change (95% CI) [a]	-5.0 (-5.7, -4.4)	-3.7 (-4.4, -3.1)	-4.9 (-5.6, -4.2)	-3.8 (-4.5, -3.1)	-4.8 (-5.3, -4.4)	-3.7 (-4.1, -3.3)
Difference (95% CI) [a]	**-1.3 (-2.0, -0.5)**		-1.1 (-1.7, -0.4) [b]		-1.1 (-1.6, -0.6)	

Source: Table 26, p118; Table 28, p123 of the submission

Abbreviations: CI, confidence interval; LS, least squares

[a] Estimated using an analysis of covariance, ANCOVA, with fixed effects for treatment, baseline score, use of anti-itch medication at baseline and the 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 the missing at random assumption.

[b] Could not be considered statistically significant based on the hierarchical testing order (prior secondary endpoint not statistically significant)

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

6.22 In KALM-1, treatment with difelikefalin was associated with a statistically significant improvement in the total Skindex-10 score at Week 12 from baseline. 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. Pooled estimates of treatment effect were similar to results from the individual studies.

6.23 Difelikefalin treatment was associated with an improvement on the 5-D Itch scale at Week 12 from baseline. The result from KALM-1 was statistically significant. 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.

6.24 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.

6.25 The proportion of patients achieving ≥5-point improvement on the 5-D Itch scale from pooled individual patient data analyses of the KALM trials were used to determine

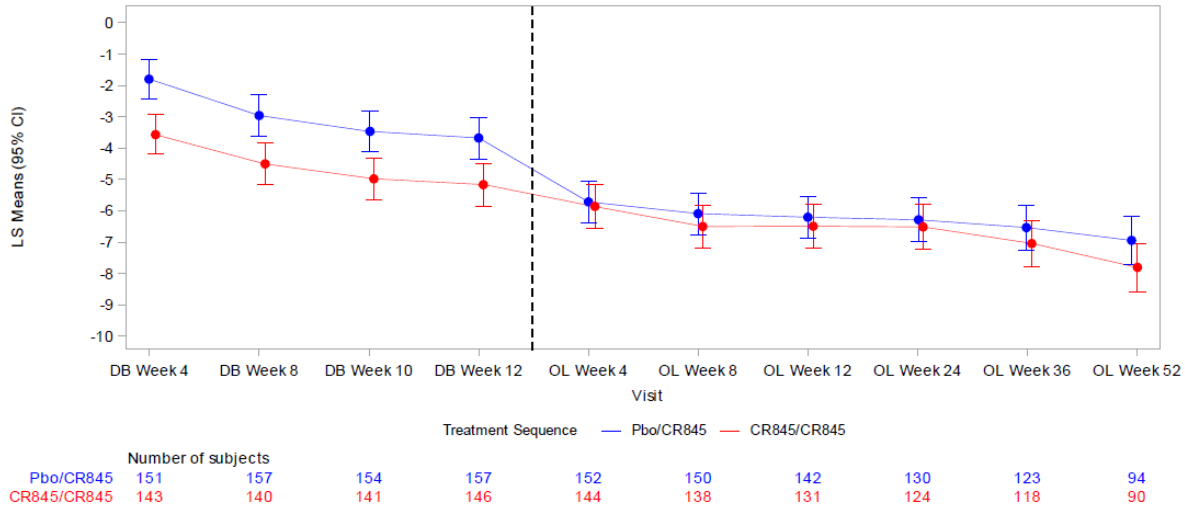
response and consequently, treatment continuation rates for difelikefalin in the economic model (different response rates by pruritus severity of none 92.3%, mild 68.9%, moderate 32.9% and severe 10.7%) and financial estimates (51.3% overall). These estimates could not be validated during the evaluation due to poor documentation in the submission, with response rates of 52.1% for difelikefalin and 42.3% for placebo based on aggregate data from the trials. The ESC considered the clinical relevance of the nominated threshold for improvement was uncertain.

6.26 Results based on the Patient Global Impression of Change (PGIC) exploratory outcome suggested that a greater proportion of patients in the difelikefalin arm compared to placebo were responders at Week 12, defined as those with a global impression of 'very much improved' or 'much improved'. The difference in response rates was greater in KALM-1 (approximately 24%) compared to KALM-2 (approximately 10%).

6.27 The submission did not present results from the open-label extension periods of the KALM-1 and KALM-2 trials. Patients who received at least 30 doses of study drug (difelikefalin or placebo) during the double-blind treatment period could enter the extension period and receive treatment with difelikefalin for up to 52 weeks. The submission considered these data as supportive evidence, with transition matrices for the economic model based on a pooled analysis of individual patient data. Key results from the open-label extension periods were presented during the evaluation, as these are the only long-term data available for difelikefalin.

6.28 Figure 1 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-1.

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



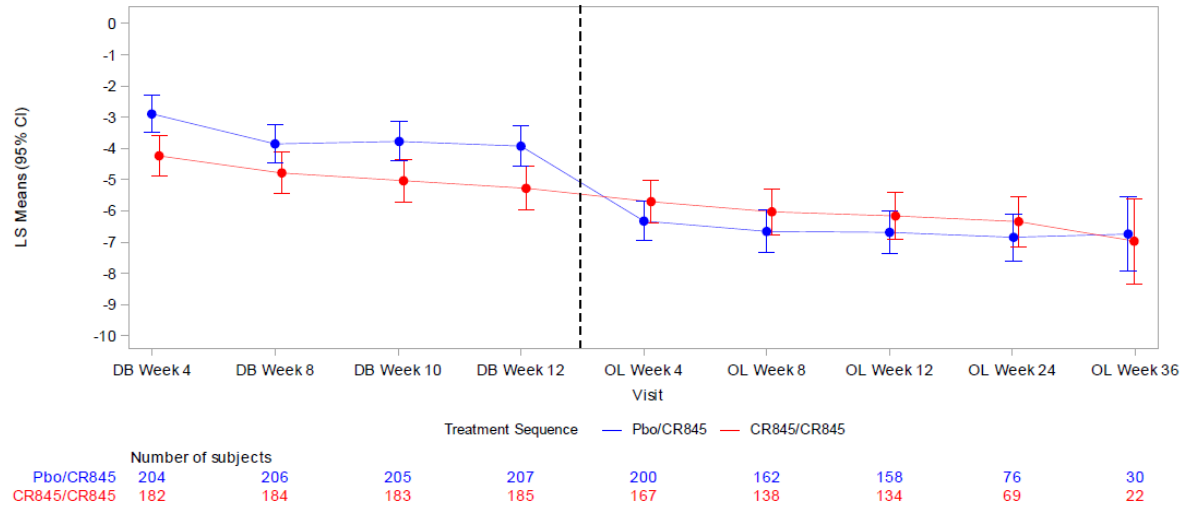
Source: Figure 14, p107 of the 'CLMD DFK – Summary of Clinical Efficacy' report of the submission
Abbreviations: CR845, difelikefalin; DB, double-blind; CI, confidence interval; LS, least squares; OL, open-label

6.29 The results suggest that improvements in total 5-D Itch scale scores associated with difelikefalin treatment during the double-blind treatment period 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.

6.30 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 'CLMD DFK – Summary of Clinical Efficacy' report of the submission
Abbreviations: CR845, difelikefalin; DB, double-blind; CI, confidence interval; LS, least squares; OL, open-label

6.31 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.

6.32 There were no pre-specified subgroup analyses in the key trials.

6.33 The submission 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. Improvements in itch intensity did not appear to favour difelikefalin in patients who reported their race as 'Other', however, the size of this subgroup was relatively small compared to the other categories.

6.34 Summaries of descriptive subgroup analyses by randomisation stratification factors were identified in the KALM-1 and KALM-2 trial reports during the evaluation. The treatment difference in patients without anti-itch medications at baseline appeared numerically smaller than those with prior use of anti-itch medications. Response rates across the regions were varied, with numerically smaller differences observed in patients from Western Europe/European origin and the US compared to patients from Eastern Europe and Asia.

6.35 Additional post hoc subgroup analyses by baseline WI-NRS pruritus severity were requested from the sponsor by the TGA evaluator. Results based on WI-NRS categories of moderate (≥4 to <7), severe (≥7 to <9) and very severe (≥9) pruritus appeared consistent with the primary analysis in regard to the proportion of patients with either a ≥3-point or ≥4-point improvement at Week 12 from baseline. Results based on mean change in WI-NRS from baseline to Week 12 according to baseline pruritus severity suggested numerically greater response and placebo effect in those with more severe baseline pruritus.

6.36 Overall, results from available subgroup analyses should be interpreted with caution as the analyses were conducted post hoc and were largely descriptive. There was no testing for treatment effect interactions.

6.37 No subgroup characteristics or results were presented for the subgroup of 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.

6.38 The submission 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 submission 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 submission claimed that there are no other data available that could be used to characterise Australian haemodialysis patients with CKD-associated pruritus. The evaluation considered it may be informative to use published data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) to at least characterise the Australian population on haemodialysis given CKD-associated pruritus in these patients is relatively common, with 43% of patients estimated to have at least moderate pruritus in the financial estimates of the submission.

6.39 There are potential differences between the trial populations and the Australian population 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.

6.40 The PSCR acknowledged the potential for differences between the trial populations and the proposed PBS population, however it also noted the post hoc subgroup analyses using the pooled KALM-1 and KALM-2 data do not suggest meaningful differences in treatment effect based on age, gender, best supportive care, anti-itch medication use or the presence of medical conditions. On that basis, the PSCR argued any differences in demographic or disease characteristics between the trials and Australian populations were unlikely to manifest into a meaningful impact on

treatment effect. The ESC considered the post hoc subgroup analyses provided in the submission and re-presented in the PSCR were not sufficiently reliable to exclude a different magnitude of benefit in the PBS population compared to the key trials. The pre-PBAC response reiterated the arguments in the PSCR.

Comparative harms

6.41 Patients in KALM-1 were evaluated for potential signs and symptoms of opioid withdrawal during the 2-week double-blind discontinuation period of KALM-1, during which no study drug was administered. Outcomes were measured using the Short Opioid Withdrawal Scale (ShOWS), a self-administered scale for grading opioid withdrawal symptoms over a 24-hour period and the investigator-assessed Objective Opiate Withdrawal Scale (OOWS). The results suggest no differences between arms on either scale following discontinuation of the study drug.

6.42 Table 6 presents a summary of adverse events reported during the 12-week double-blind period of the key trials.

Table 6: Summary of adverse events reported during the double-blind treatment 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 32, p134; Table 33, p138 of the submission; Table 2 of the Fishbane 2022 publication of safety and tolerability of difelikefalin
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 deaths occurring in each arm reported in the pooled safety analysis (Fishbane 2022) and in the trial report. The reason for this discrepancy was unknown.
[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

6.43 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.

6.44 The PSCR reiterated the subgroup analyses from the KALM trials did not suggest meaningful differences in treatment effect based on age or medical conditions. The PSCR noted a subgroup analysis using the primary safety pool data on the incidence of 1 or more treatment-emergent adverse events (TEAEs) by age showed the relative risk for difelikefalin compared to placebo subjects were similar and close to 1 regardless of age grouping. However, the PSCR acknowledged that older difelikefalin

subjects experienced more TEAEs of somnolence compared to younger subjects (7.0% for ≥65 years and 2.8% for <65 years). The ESC was concerned the higher rates of falls in the clinical trials were of particular concern for the PBS population, which was likely to be older than the clinical trial populations. The ESC considered the higher rates of somnolence observed further exacerbated this risk. Overall, the ESC considered the costs and impact of adverse events had not been adequately accounted for throughout the submission, especially in the economic model and financial estimates.

6.45 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.

6.46 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.

6.47 The frequency of adverse events was similar between treatment arms during the open-label extension studies in both trials regardless of treatment sequence. More patients switching from placebo to difelikefalin discontinued treatment due to adverse events.

6.48 The most common treatment-emergent adverse events occurring in ≥10% of all patients in the KALM-1 open-label extension were diarrhoea (16%), fall (15%), nausea (15%), hypotension (14%), hyperkalaemia (12%), vomiting (12%), dyspnoea (11%) and pneumonia (11%). The most common serious adverse events (occurring in at least 10 patients) were pneumonia (7%), fluid overload (5%), hyperkalaemia (4%), cardiorespiratory failure (4%), and metabolic encephalopathy, sepsis and dyspnoea (3%). Twenty-two deaths were reported during the open-label extension, none of which were deemed related to difelikefalin.

6.49 In the KALM-2 open-label extension, the most common treatment-emergent adverse events occurring in ≥5% of all patients were fall (8%), pneumonia (7%), diarrhoea (6%) and hypotension (6%). The most common serious adverse events (occurring in at least 10 patients) were pneumonia (6%), sepsis (4%) and chest pain (3%). Ten deaths were reported during the open-label extension, none of which were deemed related to difelikefalin.

6.50 The submission provided data on potential safety concerns beyond those identified in the clinical trials from the EU Risk Management Plan (March 2022), the Australian-Specific Annex to the EU Risk Management Plan (June 2022) and an integrated safety

summary that includes safety data from the broader difelikefalin clinical trials program (December 2020).

6.51 The Australian and EU Risk Management Plans included cardiac failure and arrythmias including atrial fibrillation in haemodialysis patients with a medical history of atrial fibrillation as an important potential risk. Missing information included use in patients with severe hepatic impairment, in pregnant and lactating women and in patients with impaired blood brain barrier.

6.52 The submission claimed that difelikefalin has only recently been approved for marketing in any jurisdiction, therefore no post-marketing safety data were available at the time. Difelikefalin was approved by the FDA in August 2021 and by the EMA in April 2022. The Product Information approved by the EMA stated that marketing authorisation was conditional upon submission of the first Periodic Safety Update Report (PSUR) for difelikefalin within 6 months following authorisation.

6.53 During the evaluation, a request was made for any updated safety data including any available post-marketing safety reports. No PSUR was provided, however, the sponsor provided a summary of serious unexpected adverse drug reactions (13 July 2022 cut-off date) considered by the ACM in October 2022. The summary included four cases of drug reactions that were not yet reported to the TGA at the time of ACM's consideration of difelikefalin in September 2022. Two were considered to be serious unexpected adverse drug reactions potentially related to difelikefalin: DRESS (managed access program); and hallucination and failure to thrive (spontaneous report). The two other cases (COVID-19 and cardiac disorder) were considered unlikely to be related to difelikefalin. The PSCR and ESC noted an updated Periodic Benefit Risk Evaluation Report (PBRER) was available which did not show additional safety signals. Additionally, the PSCR noted full TGA registration has been approved without any boxed warnings.

6.54 The submission claimed that the extended safety data showed that difelikefalin was well-tolerated with an acceptable safety profile for the target PBS population. There are limited long-term safety data based on trials only (up to 64 weeks), with no published post-marketing safety data and emerging serious safety signals. The characteristics of the Australian PBS population is uncertain but likely to be older with a potentially greater number of co-morbidities than in the trials. The safety and tolerability of difelikefalin in the PBS population is uncertain.

Benefits/harms

6.55 On the basis of direct evidence presented in the submission (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 (see Table 4).

- 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 (see Table 6).
- Approximately 3 more patients with serious cardiac disorders and approximately 2 more patients with serious respiratory disorders (see paragraph 6.45).

Clinical claim

6.56 The submission described difelikefalin as superior in terms of efficacy and inferior in terms of safety compared to best supportive care. The ESC agreed with the evaluation that this claim appeared reasonable based on the data from the key trials.

6.57 There were limited clinical data on difelikefalin use beyond 64 weeks in the key trials. No post-market safety reports were available at the time of evaluation, with emerging safety signals such as DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), cardiovascular disorders and hallucinations from recent case reports of serious events. However, the ESC noted the PBRER provided with the PSCR did not show any additional safety signals (see paragraph 6.53) and TGA approval had been granted without any boxed warnings.

6.58 It was unclear whether the magnitude of benefit observed in the key trials is applicable to the PBS population. There are 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. The ESC considered the post hoc subgroup analyses provided were not sufficiently reliable to exclude a different magnitude of benefit in the PBS population compared to the key trials.

6.59 The risk-benefit profile of difelikefalin in the Australian PBS population is uncertain as the eligible population is likely to be older, with one or more medical conditions that may increase the risk of adverse events associated with difelikefalin including somnolence, falls/gait disturbances and cardiovascular disorders. There are also evidence gaps for subgroups that may access treatment through the simplified restriction:

- There are no efficacy or safety data for difelikefalin in patients with mild pruritus or those with acute or relapsing-remitting pruritus. The PSCR argued that as standard care is likely to be used first for all patients, the risk of use in mild pruritus was low. However, the ESC considered the use in people with milder disease was likely given the ease of administration with haemodialysis and lack of alternative highly effective treatments.
- The risk-benefit profile of continuing treatment in patients without adequate response is unknown. No subgroup characteristics or results were presented for

the subgroup of patients who were responders (defined as ≥5-point improvement on the 5-D Itch scale at 12 weeks) in the KALM trials, used to inform the extrapolated period of the economic model and financial estimates. The PSCR argued the intent of the restriction was that patients who do not response would not continue treatment, as they would be receiving no benefit but at risk of adverse events.

6.60 The PBAC considered, based on the available data, that the claim of superior comparative effectiveness was likely to be reasonable.

6.61 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.62 The economic evaluation was based on 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 pooled 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: Key components of the economic evaluation

Component	Description
Treatments	Difelikefalin versus best supportive care
Outcomes	Life years and 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	Three sets of transition probabilities were estimated for Weeks 0-12, 12-64 and 64+ of the model for difelikefalin-treated patients and best supportive care separately, based on the double-blind period of the KALM trials, open-label extension periods and assumptions. In the extrapolated period (Week 12+) transition probabilities for best supportive care were assumed based on data from difelikefalin-treated patients in the extension studies with adjustments for placebo effects (i.e. patients can no longer improve). Transition probabilities for difelikefalin treated patients in the extrapolated period were derived from unadjusted data from the extension studies. 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. Background mortality was estimated using death rates for dialysis patients in the ANZDATA 44th Annual Report 2021. Estimates in the severe pruritus health state were adjusted for increased mortality based on data from the Sukul 2020 observational study. 99.9% of incremental QALYs and 80.1% of incremental costs occur in the extrapolated period (after 12 weeks).
Health related quality of life	Based on an unpublished primary utility study in the UK general population undergoing haemodialysis. A linear curve was fitted to mean EQ-5D-3L estimates plotted against total 5-D Itch scores. The midpoints of lower and upper thresholds of each 5-D Itch score health state were used to represent the utility value for each health state (none 0.7024, mild 0.6348, moderate 0.5480 and severe 0.4418).
Costs	Drug acquisition costs were estimated using the proposed 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 NHCDC public sector cost weights for AR-DRG v10.0, Round 23 (2018-2019).
Software package	Excel

Source: Table 42, p160 of the submission
Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; NHCDC, National Hospital Cost Data Collection

6.63 The submission used a Markov cohort model structure, with health states defined using 5-D Itch scores of 5-8, 9-11, 12-17 and 18-25 as proxies for different levels of pruritus severity. The submission claimed the 5-D Itch scale was used in preference to WI-NRS given the longer recall period of the 5-D Itch scale (2 weeks) relative to the WI-NRS (daily) and was therefore more suitable to the structure of the economic model and 4-week cycle length. The submission claimed the multi-dimensional design of the 5-D Itch scale would also correlate with quality of life.

6.64 The use of total 5-D Itch score to define the health states was inadequately justified as the clinical relevance of changes in 5-D Itch scores is uncertain. There were

additional concerns with scores derived from the 5-D Itch scale, due to the 'response' domain of the questionnaire. Patients with no prior itch in the past month who responded 'unchanged' could end up with higher scores than those with some level of prior itch but indicated that their condition had improved. This appeared counterintuitive as higher scores on the scale would be interpreted as having worse pruritus severity.

6.65 The reliability of cost-effectiveness estimates based on the model structure was uncertain as modelled benefits were dependent on the assumption that changes in 5-D itch scores (mapped to levels of pruritus severity) would translate to meaningful differences in costs and quality of life.

6.66 The PSCR stated that any economic model of difelikefalin in this setting would require translation of the trial outcomes to utility values and QALYs. The PSCR argued that the health states were defined by 5-D itch scores as this was the only outcome in the trials from which utility values could be reliably derived. The PSCR noted the 5-D itch score captures the impact of the itch on daily living and quality of life whereas other scales such as WI-NRS only capture the severity of the itch itself. The PSCR also stated the economic model was structured around health states defined by 5-D itch scores, with upper and lower values for each health state informed by Lai 2017, and noted the health state thresholds employed correlated with the numerical rating scale categories of no, mild, moderate, severe and very severe pruritus. The PSCR argued the mapping study used to translate 5-D itch scores to EQ-5D values showed a clear correlation and therefore the model structure based on this scale was reasonable and reflected the most reliable evidence available. The ESC considered that whilst the approach may reflect the best available evidence, the reliability of the mapping approach used was unknown.

6.67 Health states defined using 5-D Itch scores of 5-8, 9-11, 12-17 and 18-25 in the submission were referred to as none, mild, moderate and severe in the commentary.

6.68 All patients start in the moderate and severe health states (baseline). All patients can die 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.

6.69 In the first 12 weeks, all 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. After the first 12 weeks, patients on best supportive care (including those who discontinued from difelikefalin treatment) could only remain in the same health state as the prior cycle or move to a worse health state. Throughout the model duration, patients on difelikefalin treatment could remain in the same health state as the prior cycle, or move to an improved or worse health state.

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

Table 8: Key drivers of the model

Description	Method/Value	Impact
Extrapolation beyond 12 weeks	Methods used to extrapolate transition probabilities for difelikefalin treated patients resulted in continuing improvements in treatment benefit up to 64 weeks in the model, which are then maintained over the model duration. This approach may not be appropriate due to concerns with the robustness of data from the extension studies that were stopped prematurely, and unknown applicability of the responder subgroup to patients continuing treatment in practice. Extrapolated transition probabilities for best supportive care were adjusted for placebo effects, assuming patients could no longer improve. No matching adjustments were applied to transition probabilities for difelikefalin-treated patients. This approach was in favour of difelikefalin. Patients discontinuing from difelikefalin treatment assumed the same transition probabilities as best supportive care. This resulted in patients largely retaining treatment benefit over time without ongoing treatment costs. The impact of assumptions applied in the extrapolated period were further explored in a validation exercise conducted during the evaluation period (see Figure 3 below).	High, favours difelikefalin
Utility decrements associated with pruritus severity	The model included relatively large utility decrements (mild -0.0676, moderate -0.1544 and severe -0.2606) for changes in pruritus and no disutility for adverse events. There were multiple concerns with the robustness and applicability of results from the unpublished primary utility study used to inform the utility values for each health state of the model. The submission assumed a cause-effect relationship between itch scores and quality of life. The lack of disutilities for adverse events was inappropriate given the claim of inferior safety versus best supportive care. Difelikefalin is associated with a higher frequency of central nervous system (e.g. dizziness, somnolence) and gastrointestinal events (e.g. nausea, vomiting, diarrhoea) as well as serious adverse events such as cardiovascular disorders which are likely to have an impact on quality of life.	High, favours difelikefalin

Source: constructed during the evaluation

6.71 The PSCR noted the primary data used for the mapping of 5-D itch scale results to EQ-5D values was conducted in a population meeting the defined criteria of age (over 18 years) and haemodialysis (receiving for at least 3-months). Further, the PSCR clarified the utility values do not necessarily reflect a relationship between itch severity and quality of life; rather, they reflect a relationship between the 5-D itch scale and quality of life. The PSCR reiterated there are 5 dimensions to the 5-D itch scale, of which severity is only one, alongside location of itch and impact on daily activities, which will also clearly be related to quality of life.

6.72 The PSCR acknowledged the magnitude of the utility gains may be considered relatively large, however argued this was subject to opinion and noted there was precedent for comparable changes in utility for conditions such as severe chronic plaque psoriasis, where the post-market review of the use of biologics had applied a utility gain of 0.3 for treatment responders (0.89 versus 0.59; 9.01 Biologics for the treatment of chronic plaque psoriasis: Cost-effectiveness review Public Summary Document (PSD), July 2020 PBAC Meeting).

6.73 The ESC remained uncertain about the reliability of the mapping study to derive the utility decrements for pruritus severity states, however acknowledged precedents for

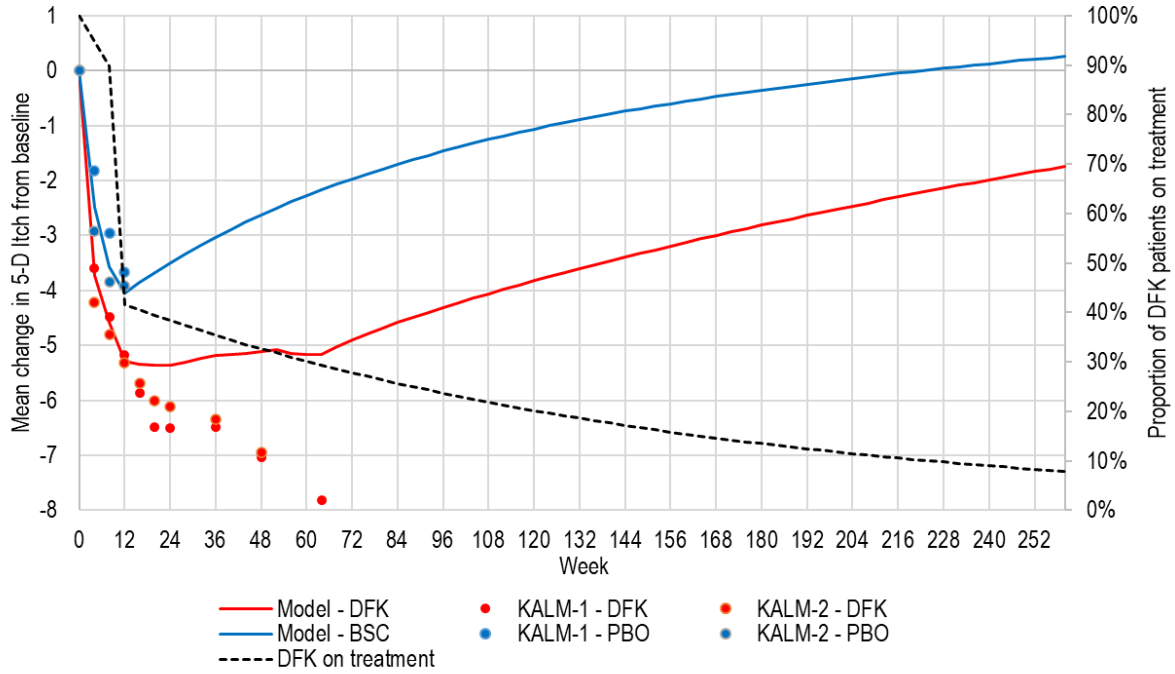
similar gains in utility for responders had been considered in both the cost-effectiveness review of biologics for severe chronic plaque psoriasis and in the March 2020 consideration of dupilumab for severe atopic dermatitis (Table 13, dupilumab PSD, March 2020 PBAC Meeting). The ESC noted concerns that the utility gain of 0.3 for treatment responders in the review of biologics for the treatment of chronic plaque psoriasis was a possible overestimate and was used primarily for consistency in the review (paragraph 7.7, deucravacitinib PSD, November 2022 PBAC Meeting; paragraph 4.10, 9.01 Biologics for the treatment of chronic plaque psoriasis: Cost-effectiveness review PSD, July 2020 PBAC Meeting). The ESC advised that accepting the model structure as potentially reliable for decision-making (albeit with changes to key inputs) was contingent upon accepting at least the plausibility of the utility decrements applied in the model, as there did not appear to be an alternative basis upon which to derive utilities for CKD-associated pruritus in patients receiving haemodialysis. The pre-PBAC response acknowledged the precedents of similar utility gains in other skin conditions and argued that end-stage kidney disease represents a small, well defined, high clinical need population relative to other more common skin conditions, such as atopic dermatitis and psoriasis, and therefore it would be expected the quality of evidence may not be as robust in the proposed difelikefalin population. The pre-PBAC response argued that because the values are of a similar order of magnitude to other skin conditions – despite the weaknesses in the underlying methods – suggests the utility values are appropriate for decision making.

6.74 The submission presented a comparison of trial outcomes and modelled outputs for up to 64 weeks, based on mean change in total 5-D Itch score from baseline during the double-blind and open-label extension periods of the trials. Model values were estimated based on mid-points scores for each health state as an approximation for the validation exercise. The 12-week difelikefalin stopping rule was also switched off in the submission for this exercise, to enable a comparison with data from the extension studies.

6.75 There was an error in the economic model, as transition probabilities for the difelikefalin arm (and linked transitions for best supportive care) were based on the subgroup of responders only despite switching off the stopping rule. This was corrected during the evaluation. Modelled outputs from both treatment arms appeared similar to trial outcomes up to 64 weeks.

6.76 A separate validation exercise was conducted during the evaluation using a similar approach to the submission based on estimated mean change in 5-D Itch scores, with the stopping rule included as per the base case (see Figure 3 below).

Figure 3: Trial outcomes compared to the economic model with stopping rule (base case)



Source: constructed during the evaluation based on difelikefalin economic model of the submission
Abbreviations: DFK, difelikefalin; PBO, placebo; SOC, best supportive care

6.77 Modelled outputs showed improvements in 5-D Itch scores in both treatment arms during the first 12 weeks of the model, with greater improvements associated with difelikefalin treatment. This appeared consistent with trial outcomes during the double-blind period.

6.78 From Weeks 12 to 64, trial data were only available for difelikefalin treated patients. Modelled outputs for the difelikefalin arm did not appear to match data from the extension studies, however, this was due to approximately half of difelikefalin-treated patients discontinuing treatment due to inadequate response. Patients who discontinue treatment are attributed the same transition probabilities as patients on best supportive care and can only maintain their prior pruritus severity level or become worse over time. The graph shows that the subgroup of patients continuing difelikefalin treatment continue to improve up to week 64, with greater improvements than observed in the extension studies maintained over the modelled duration.

6.79 The PSCR argued the model was based on evidence demonstrating patients treated with difelikefalin maintain an effect for up to 64 weeks (open-label extension data for difelikefalin-treated patients achieving the defined response at week 12). The ESC considered 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.

6.80 There is an inflection point for patients in the best supportive care arm at Week 12, as transition probabilities were adjusted for attenuation in placebo effects over time. This results in a gradual loss of improvements gained in the initial 12-week period. Towards the end of the model, patients on best supportive care develop worse pruritus severity than at baseline due to an accumulation of patients in the most severe pruritus health state.

6.81 Overall, the graph shows an increase in treatment benefit associated with patients in the difelikefalin arm between Weeks 12 and 64 of the model. The difference was driven by the assumption of attenuating placebo effects for patients on best supportive care with no matching adjustments to difelikefalin treated patients who also continued to improve up to Week 64. The PSCR argued that a deterioration of the placebo effect was a reasonable assumption to apply to the best supportive care arm. This was on the basis that longer-term placebo effects appear to require some form of conditioning that may in the clinical trial setting (where patients received IV placebo) that would not occur in practice. The ESC considered such adjustments to the best supportive care arm of the model were not well justified and in favour of difelikefalin in the model as placebo effects would apply equally to both arms in the trial. The ESC considered the assumption of attenuating placebo effects for patients on best supportive care should be removed from the model.

6.82 Treatment benefits associated with difelikefalin appear to be maintained over time. This result did not appear clinically plausible given the majority of patients are no longer on treatment from Week 12, with few patients (<10%) on treatment at the end of the model. Modelled benefits in the extrapolated period appear to be driven by treatment benefit due to initial exposure to difelikefalin treatment, which is then largely retained when discontinuing to best supportive care only. This assumption is in favour of difelikefalin as patients maintain ongoing benefit without corresponding treatment costs. The PSCR argued that the overall modelled incremental benefits were aligned with the trial data, with greater gains in difelikefalin treatment responders over time based on an enriched population (due to stopping rule). The PSCR argued that the extrapolation of a 1.24-point improvement in 5-D Itch score at week 12 to a 2-point improvement at 5 years on the basis of the stopping rule and declining placebo response does not seem implausible (see Figure 3). The ESC considered that larger gains in total incremental benefit over time may not be plausible given the majority of difelikefalin patients were no longer on treatment towards the end of the model.

6.83 The model included mortality benefits associated with difelikefalin treatment, based on the application of a higher mortality rate in the severe pruritus health state and a reduction in time spent with severe pruritus. The approach assumes a cause-effect relationship between high itch scores and death, which was inappropriate given limitations with the observational study design of the Sukul 2020 study. Assumed mortality benefits were not supported by clinical evidence and may not be clinically plausible given difelikefalin is not a chronic kidney disease-modifying treatment.

6.84 The derivation of health state costs in the submission was inadequately justified, with the submission acknowledging uncertainty in the cause-effect relationship between itch score and hospitalisation rates based on the Sukul 2020 study.

6.85 The submission claimed that the incidence of adverse events was similar between treatment arms of the key trials, therefore adverse event costs were unlikely to have a significant impact on the economic analysis. The lack of adverse event costs was inappropriate given the clinical claim of inferior safety versus best supportive care, with a higher incidence of serious adverse events including cardiorespiratory disorders in the difelikefalin arm of the key trials. The ESC agreed with the evaluation and considered any revised economic model should include costs and disutilities associated with adverse events.

6.86 The stepped analysis presented in the submission included results from trial-based analyses using 12-week results from the key trials. Three sets of results were presented for the individual trials and pooled analysis, based on the incremental cost per responder defined as: ≥3-point improvement in WI-NRS, ≥5-point improvement in 5-D Itch and total 5-D Itch <12. These outcomes were not outputs from the economic model but appear to be calculated using non-missing counts of individual patient data, which differed from matching analyses in the key trials that included adjustments for missing data. Cost-effectiveness results differed, depending on the dataset and response definition applied, due to differences in the magnitude of incremental benefit.

6.87 During the evaluation, an expanded stepped economic evaluation was conducted starting with the pooled cohort individual patient analysis used in the economic model. Responder outcomes were based on additional patients with mild or no disease (5-D Itch score <12, as per health state definitions).

Table 9: Results of the stepped economic evaluation

Step and component	Difelikefalin	BSC	Increment
Step 1: Pooled cohort IPD analysis (transition probabilities based on non-missing data, no treatment discontinuations, no mortality), include drug costs, 12-week time horizon*			
Costs	$[redacted]	$0	$[redacted]
Patients with mild or no disease (5-D Itch score <12)	0.5080	0.4007	0.1073
Incremental cost per additional patient with mild or no disease			**$[redacted]** [1]
Step 2: Apply fixed treatment discontinuation rate to difelikefalin arm*			
Costs	$[redacted]	$0	$[redacted]
Patients with mild or no disease (5-D Itch score <12)	0.4991	0.4007	0.0984
Incremental cost per additional patient with mild or no disease			**$[redacted]** [1]
Step 3: Apply background mortality*			
Costs	$[redacted]	$0	$[redacted]
Patients with mild or no disease (5-D Itch score <12)	0.4894	0.3929	0.0965
Incremental cost per additional patient with mild or no disease			**$[redacted]** [2]
Step 4: Adjust baseline disease distribution, assuming all patients have at least moderate disease (i.e. no patients with 5-D Itch score <12 at baseline, transition probabilities unchanged)*			
Costs	$[redacted]	$0	$[redacted]
Patients with mild or no disease (5-D Itch score <12)	0.4795	0.3858	0.0937
Incremental cost per additional patient with mild or no disease			**$[redacted]** [2]
Step 5: Extrapolate to 5 years (modelled transition probabilities for difelikefalin beyond 64 weeks, modelled transition probabilities for BSC beyond 12 weeks)*			
Costs	$[redacted]	$0	$[redacted]
Patients with mild or no disease (5-D Itch score <12)	0.2169	0.0080	0.2088
Incremental cost per additional patient with mild or no disease			**$[redacted]** [3]
Step 6: Add health state costs*			
Costs	$[redacted]	$7,793	$[redacted]
Patients with mild or no disease (5-D Itch score <12)	0.2169	0.0080	0.2088
Incremental cost per additional patient with mild or no disease			**$[redacted]** [3]
Step 7: Add health state utility values*			
Costs	$[redacted]	$7,793	$[redacted]
QALYs	2.4363	2.1275	0.3089
Incremental cost per QALY gained			**$[redacted]** [4]
Step 8: Apply hazard ratio of 1.24 to mortality in the 'severe to very severe' health state*			
Costs	$[redacted]	$7,676	$[redacted]
QALYs	2.4255	2.1011	0.3244
Incremental cost per QALY gained			**$[redacted]** [4]
Step 9: Add stopping rule (only patients with ≥5-point improvement continue difelikefalin after Week 12)*			
Costs	$[redacted]	$7,676	$[redacted]
QALYs	2.2743	2.1011	0.1732
Incremental cost per QALY gained			**$[redacted]** [4]
Step 10: Include 5% discount rate			
Costs	$[redacted]	$6,871	$[redacted]
QALYs	2.0411	1.8871	0.1540
Incremental cost per QALY gained			**$[redacted]** [4]

Source: Table 63, p188 of the submission and the difelikefalin economic model, Attachment 8 of the submission
Abbreviations: IPD, individual patient data; LY, life years; QALY, quality-adjusted life year
*calculated during the evaluation
The redacted values correspond to the following ranges:
[1] *$5,000 to < $15,000*
[2] *$15,000 to < $25,000*
[3] *$55,000 to < $75,000*
[4] *$45,000 to < $55,000*

6.88 Based on the economic model, treatment with difelikefalin was associated with an incremental cost per QALY gained of $45,000 to < $55,000 compared to best supportive care. The extrapolation beyond the 12-week time horizon and utilities had the largest impacts on the stepped economic evaluation.

6.89 The submission acknowledged that the economic model may not be representative of the cost-effectiveness of the PBS population that may include patients with mild pruritus, but also patients who may continue treatment despite inadequate treatment response. The submission claimed that an appropriate risk-sharing arrangement and financial caps could address these uncertainties.

6.90 The results of key sensitivity analyses are summarised in Table 10.

Table 10: Results of sensitivity analyses

Analyses	Incremental cost ($)	Incremental QALY	ICER ($)	Change to ICER, %
Base case	[redacted]	**0.1540**	[redacted][1]	**-**
Discount rate (base case 5%)				
0%	[redacted]	0.1732	[redacted][1]	4%
3.5%	[redacted]	0.1594	[redacted][1]	1%
Time horizon (base case 5 years)				
12 weeks	[redacted]	0.0038	[redacted][2]	716%
1 year	[redacted]	0.0278	[redacted][3]	149%
2 years	[redacted]	0.0678	[redacted][4]	53%
Background mortality (base case 8.2% per year in none to moderate health states, 15.6% per year in severe)				
8.2% per year in all health states (no increased mortality with severe pruritus)	[redacted]	0.1456	[redacted][1]	5%
12.6% per year in none to moderate health states, 10.1% per year in severe*	[redacted]	0.1416	[redacted][1]	1%
12.6% per year in all health states*	[redacted]	0.1302	[redacted][1]	10%
Treatment discontinuations (base case 4.6% per 4-week cycle in the first 12 weeks then 2.0% per 4-week cycle ongoing)				
Week 12+ discontinuation rates increased by 50%	[redacted]	0.1379	[redacted][1]	-5%
Week 12+ discontinuation rates decreased by 50%	[redacted]	0.1752	[redacted][1]	6%
Treatment discontinuations at Week 12 due to inadequate response (base case discontinuations by health state: 7.7% none, 31.1% mild, 67.1% moderate, 89.3% severe)				
All patients continue difelikefalin treatment [a]	[redacted]	0.2645	[redacted][1]	7%
No discontinuations from none or mild health states*	[redacted]	0.1747	[redacted][1]	3%
Extrapolated transition probabilities Weeks 12+ (base case difelikefalin on-treatment using 'Week 12-24-36-52-64' followed by 'All Week 12-64' for weeks 64+; BSC based on 'All Week 12-64 with no improvement' set)				
BSC based on 'Week 0-12' using 2 timepoints only	[redacted]	0.0737	[redacted][5]	110%
BSC based on 'All Week 0-12' using all available data	[redacted]	0.0569	[redacted][3]	173%
Difelikefalin on-treatment and BSC based on 'Week 0-12' using 2 timepoints only*	[redacted]	0.0326	[redacted][6]	322%
Difelikefalin on-treatment and BSC based on 'All Week 0-12' using all available data*	[redacted]	0.0323	[redacted][6]	382%
BSC fixed (no improvements or worsening)	[redacted]	0.1259	[redacted][4]	23%
Health state utilities (base case baseline utility 0.7024 with utility decrements for mild -0.0676, moderate -0.1544 and severe -0.2606)				
Increase utility decrements by 50%	[redacted]	0.2241	[redacted][7]	31%
Decrease utility decrements by 50%	[redacted]	0.0838	[redacted][8]	84%
Mapped utilities using KALM trial data (0.6168 none with utility decrements for mild -0.0378, moderate -0.1025 and severe -0.1875)*	[redacted]	0.1133	[redacted][4]	36%

Source: Table 67, p191 and the difelikefalin economic model of the submission

[a] There was an error in the economic model, as transition probabilities for the difelikefalin arm (and linked transitions for BSC) were based on the subgroup of responders only. This was corrected during the evaluation, with transition probabilities based on the 'ALL' patient set.

*Calculated during the evaluation

The redacted values correspond to the following ranges:

[1] $45,000 to < $55,000

[2] $255,000 to < $355,000

[3] $115,000 to < $135,000

[4] $55,000 to < $75,000

[5] $95,000 to < $115,000

[6] $155,000 to < $255,000

[7] $25,000 to < $35,000

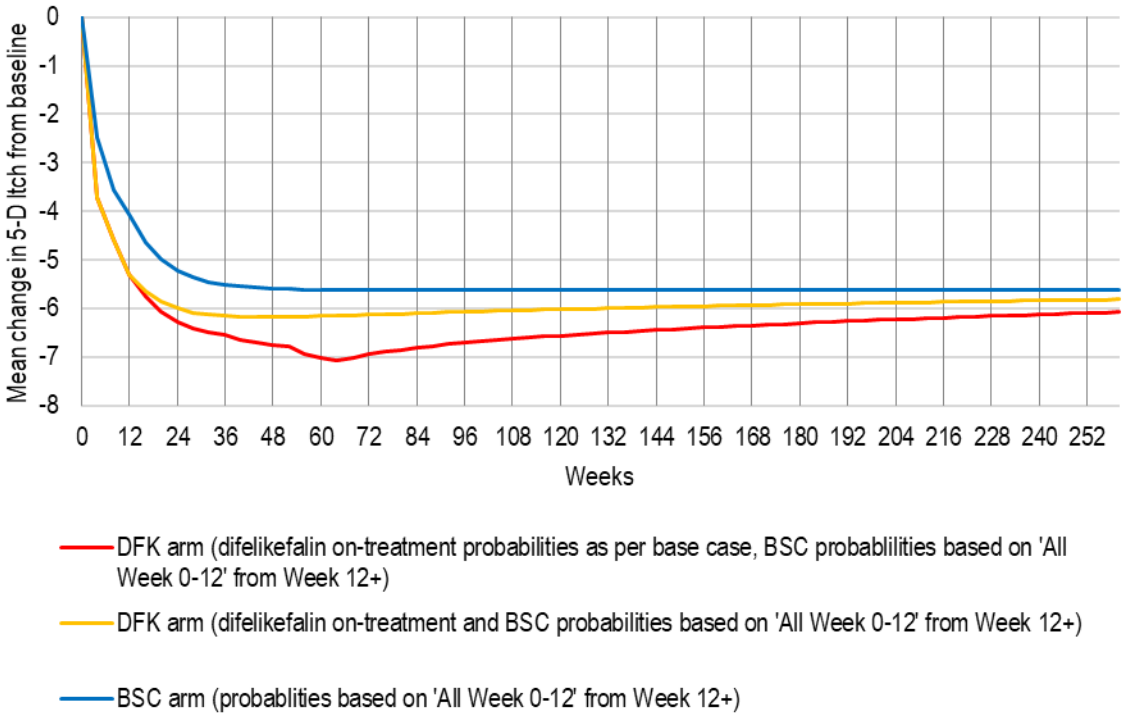
[8] $75,000 to < $95,000

6.91 The model was most sensitive to the extrapolation beyond 12 weeks and health utility decrements associated with increasing pruritus severity.

6.92 The submission tested alternative extrapolation methods for best supportive care after 12 weeks. The submission noted that the results were most sensitive to the use of 'Week 0-12' data (based on two assessment points only). The submission claimed that the cost-effectiveness results are likely to be a substantial overestimate as this approach does not account for placebo effects captured during the trial that should diminish over time. It may be reasonable to consider attenuating placebo effects over time, however, matching adjustments should also be applied to extrapolated transitions for difelikefalin treated patients.

6.93 During the evaluation, additional sensitivity analyses were conducted using alternative transition probabilities based on the use of 'All Week 0-12' data from the individual patient analysis (uses all available timepoints) to inform the extrapolation of difelikefalin and best supportive care arms over time (see Table 10 above). A plot of mean change in 5-D Itch over time is presented in Figure 4.

Figure 4: Modelled outcomes based on sensitivity analysis, with difelikefalin on-treatment and BSC transition probabilities based on 'All Week 0-12' set from Week 12 onwards



Source: constructed during the evaluation using the difelikefalin economic model of the submission
Abbreviations: BSC, best supportive care; DFK, difelikefalin

6.94 The graphs illustrate the impact of removing placebo effect adjustments to the best supportive care arm and removing additional improvements to patients on difelikefalin treatment after 12 weeks. Removal of these assumptions resulted in decreased incremental benefits with convergence between mean change in scores

over time. This may be more reflective of expected outcomes given the majority of patients had discontinued difelikefalin treatment after 12 weeks.

6.95 Modelled mortality benefits were inadequately justified in the submission. However, the impact of mortality was minimal given the time horizon of 5 years.

6.96 The use of alternative treatment discontinuation rates had minimal impact on the cost-effectiveness analysis. However, the use of lower discontinuation rates resulted in unexpectedly higher ICER per QALY estimates. This is likely due to the assumption that patients who discontinue difelikefalin would largely maintain treatment benefit without ongoing treatment costs.

6.97 The exclusion of the stopping rule due to inadequate treatment response had minimal impact on cost-effectiveness results. The incremental cost increased as more patients continued on difelikefalin treatment, however, there were also corresponding gains in incremental benefit compared to best supportive care.

6.98 The ESC considered that, while the derivation of utilities remained a key source of uncertainty, if these were accepted a revised base case model should remove the adjustments for placebo responses from the best supportive care arm. The ESC noted that removing the adjustments for placebo responses (i.e. by basing extrapolated transition probabilities for best supportive care on 'Week 0-12' using 2 timepoints) increased the ICER from $45,000 to < $55,000 per QALY gained to $95,000 to < $115,000 per QALY gained. In addition, the ESC considered that costs and disutilities for adverse events should be included in any revised model (see paragraph 6.85) and patients needing additional vials should be accounted for given weight-based dosing and the potential for additional haemodialysis sessions (see paragraph 6.101).

6.99 The pre-PBAC response acknowledged the revised base case proposed by the ESC but disagreed with removing the adjustments for placebo responses from the best supportive care arm in isolation. While arguing that costs and disutilities for adverse events were not included in the model as they were small in number and low in severity, the pre-PBAC response accepted that these could be included in some manner. In addition, the pre-PBAC response accepted an adjustment for the need for additional vials due to the weight-based dosing regimen of difelikefalin. As such, the pre-PBAC response presented a revised base case which included:

- No health state transitions in either arm of the model after the conclusion of the clinical trial evidence (i.e. a placebo response is kept for the duration of the model, as is a difelikefalin response).
- Adverse event costs and disutilities for cardiorespiratory failure.
- An increased number of vials (1.00 to 1.06) to address the issue of increased quantities for patients requiring more than one vial (due to weight based dosing).

The pre-PBAC response noted the revised base case ICER accounting for these three inputs was $55,000 to < $75,000 per QALY. The pre-PBAC response then offered a [redacted]%

price reduction (see paragraph 3.2) to maintain the original base case ICER of $45,000 to < $55,000 per QALY.

Drug cost

Table 11: Drug cost per patient for difelikefalin

	KALM trials (12 weeks)	Economic model	Financial estimates
Cost of scripts	-	$	$
Dose regimen	Weight-based dose (0.5 µg/kg), 3-4 times per week	1 vial (50 µg) 3 times per week	1 vial (50 µg) 3 times per week
Adherence	KALM-1: 94.3% KALM-2: 95.4%	94.45% [b]	93.5% [c]
Mean time on treatment	-	1.16 years over 5-year time horizon [d]	1.34 years in the first 5 years of treatment [e]

Source: constructed during the evaluation

[a] Based on proposed effective price including fees and mark-ups

[b] Calculated as (94.3% + 95.4%)/2

[c] Weighted average based on reported adherence in each trial. Calculations not provided in the submission.

[d] Based on mean years in on-treatment health states

[e] Based on 500 to < 5,000 patients initiating treatment in Year 1 and receiving 3 scripts; 500 to < 5,000 patients continuing treatment beyond Week 12 and receiving 9.1871 (8.5899 scripts adjusted to remove 93.5% adherence) continuing scripts in Year 1; and 500 to < 5,000 and < 500 patients continuing treatment in Years 2-5, respectively, receiving 11.5473 scripts per year (10.7967 scripts adjusted to remove 93.5% adherence). Dividing the 50,000 to < 60,000 scripts by the number of initiating patients (500 to < 5,000), resulted in 17.52 scripts per initiating patient; which was multiplied by 28 days per script and divided by 365.25 days per year to produce an average of 1.34 years of treatment per initiating patient.

6.100 Drug costs in the economic model and financial estimates were based on effective prices including fees and mark-ups, which do not apply to scripts provided through public hospitals (i.e. based on effective AEMP only).

6.101 The submission did not adequately justify the assumed dose regimen used to estimate the drug cost of difelikefalin in the economic model and financial estimates. The cost is likely underestimated as it does not account for patients needing additional vials given weight-based dosing and potential for additional haemodialysis sessions.

6.102 Estimated adherence rates differed between the economic model and financial estimates due to differences in calculation methods (simple versus weighted average of trial estimates).

6.103 The mean duration of treatment used in the financial estimates was longer than estimated in the economic model. This was due to the assumption of perfect persistence during the first 12 weeks of treatment in the financial estimates while 13.8% of patients discontinued from treatment after 12 weeks in the economic model.

6.104 The pre-PBAC response offered a % price reduction (AEMP $ per vial ($ per 12 vials) reduced to $ AEMP per vial ($ per 12 vials).

Estimated PBS usage & financial implications

6.105 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the listing of difelikefalin.

6.106 Key inputs for the financial estimates are summarised in Table 12.

Table 12: Key inputs for financial estimates

Parameter	Values and source	Comment
Prevalence of in-centre haemodialysis (2024-2029)	The prevalence of in-centre haemodialysis patients was derived from the ANZDATA 45th Annual Report (2017-2021), extrapolated over the first 6 years of listing (2024-2029) using a fixed annual increment of 434 per year.	The use of a fixed increment rather than percentage growth does not account for overall population growth. The calculated increment also incorporated lower estimates reported in 2020 due to COVID-19. DUSC agreed that the source is reasonable. However, since the at-home population was excluded in the submission, the DUSC considered this parameter was underestimated.
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).	The prevalence of moderate-severe pruritus in the eligible population is highly uncertain given the subjective experience of pruritus and absence of validated instruments in clinical practice. The submission proposed that this uncertainty could be addressed using an appropriate risk-sharing arrangement. DUSC considered that the estimated prevalence of moderate-severe pruritus may be reasonable, but noted there is no itch rating scale in the restriction, so there is high potential for less severe disease to be classified as moderate by the prescriber. Thus, the DUSC considered this parameter may effectively be underestimated in the submission.
Rate of CKD-aP diagnosis	83%: 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).	The haemodialysis population surveyed in Rayner (2017) included patients with persistent mild-severe symptoms of pruritus, which may not be applicable to patients with moderate to severe symptoms. In addition, the listing of difelikefalin on the PBS may increase the proportion of eligible patients seeking treatment. DUSC agreed with the evaluation that this parameter was underestimated in the submission.
Uptake of difelikefalin	The submission assumed uptake of difelikefalin of 70% in Year 1, increasing by 4% each year, to 90% in Year 6.	Uptake rates appeared high given potential safety concerns with the use of difelikefalin, particularly in the older Australian population with a potentially greater number of specific conditions that may preclude the use of difelikefalin. DUSC considered the uptake rates to be reasonable.
Death rate per annum	8.3%: based on the reported death rate of 8.3 deaths per 100 patient years for patients on dialysis aged 45-64 (midpoint 54.5 years) in the ANZDATA 44th Annual Report 2021. Assumed to be consistent with the pooled KALM-1 and KALM-2 population median age of 58.7 years. Applied to patients exposed to treatment only.	Background mortality may be underestimated, as Australian patients are likely to be older (mean age of 67 years in the Australian/New Zealand subgroup of the KALM-2 trial). Published literature also indicated potentially increased mortality in patients experiencing severe pruritus, which may be associated with other factors including co-morbidities and other complications related to end stage renal disease (Sukul 2020). DUSC agreed with the evaluation that this parameter may be underestimated.

Parameter	Values and source	Comment
Proportion of patients with response (once-off)	51.3%: based on patients achieving ≥5-point improvement in 5-D Itch score at 12 weeks from baseline in the KALM trials, using an individual patient data analysis performed for the economic analysis of the submission.	The submission acknowledged that response rates in practice are highly uncertain due to the subjective nature of the condition. The submission proposed that this uncertainty could be addressed using an appropriate risk-sharing arrangement. DUSC noted the restriction for the continuing treatment phase states "the patient must have demonstrated or sustained an adequate response", however this is not quantified using an improvement in an itch rating score. DUSC considered that PBS prescribers may more likely deem an adequate response than in the trial where an itch rating score was used. Thus, this parameter was underestimated in the submission.
Treatment discontinuation (reasons other than inadequate response)	No discontinuations assumed for patients during the first 12 weeks of treatment. 23.2% per annum estimated for patients on continuing treatment, based on data from the KALM open-label extension studies (23.2% over 52 weeks). Estimates in the first year were adjusted for perfect persistence during the initial 12 weeks (17.4% over remaining duration).	No justification was provided for the assumption of perfect persistence during the first 12 weeks of treatment. This was inconsistent with trial data and the economic model that estimated 13.8% discontinuations in the first 12 weeks. Treatment discontinuations based on the extension studies were uncertain as the studies were stopped prematurely. The KALM-1 trial had the longest follow-up with 25.2% discontinuations reported over median follow-up duration of 51.6 weeks. DUSC considered this parameter was underestimated in the submission, which would lead to an overestimation of utilisation.
Proportion of patients who are alive and naïve to prior difelikefalin treatment	Year 1: 100%, Year 2: 38%, Year 3: 20%, Year 4: 15%, Year 5: 14%, Year 6: 13%. These proportions were calculated based on the ratio of (patients exposed to treatment in the prior year excluding patients who died)/(total prevalent population diagnosed with moderate/severe pruritus).	Mortality adjustments were applied to account for deaths in the treatment exposed population as deaths are also incorporated in the prevalence estimates used as the basis of the eligible population. The approach however, resulted in anomalous results as sensitivity analyses in the submission using higher death rates resulted in unexpectedly higher budget impact estimates. The submission assumed that any patient with prior exposure to difelikefalin would no longer be eligible for future treatment. This assumption was inappropriate as the PBS restriction allows for patients to recommence treatment.

Parameter	Values and source	Comment
Initial scripts per patient	3. Assuming perfect adherence and persistence.	The assumption of perfect adherence and persistence was inconsistent with trial data and estimates used in the economic model and is likely to overestimate the number of initial scripts. Script estimates were calculated assuming patients only require 1 vial per dose with a fixed dosing frequency of 3 times per week. This assumption was inappropriate as it does not account for patients requiring more than 1 vial per dose (patients whose weight exceeds 104 kg) and additional doses required with extra haemodialysis sessions. DUSC agreed with the evaluation that 100% adherence and persistence in the first 12 weeks would give an overestimate of utilisation. However, DUSC considered the assumption of 1 vial per dose (it could be 2 vials for a patient over 104 kg) and 3 dialysis treatments per week to be underestimates for these parameters which would result in underestimation of utilisation. Combining these factors DUSC considered the initial scripts per patient to be underestimated.
Continuing scripts per patient per year	Initiating year: 8.58; subsequent years: 10.79. Initial year scripts were calculated as 10.06 scripts (52.25 weeks/4 minus 3 initial scripts), adjusted for adherence (93.5%) and assuming patients discontinue mid-way (1-17.4%/2). Subsequent year scripts were calculated assuming 13.06 scripts per year, adjusted for adherence (93.5%) and assuming patients discontinue mid-way through the year (1-23.2%/2).	These estimates were highly uncertain, due to uncertainties with treatment discontinuation rates and assumed dose regimen for difelikefalin (1 vial per dose, 3 times per week; as described in initial scripts per patient above). DUSC considered these parameters were underestimated in the submission.

Source: Table 68, p194 of the submission.
Abbreviations: ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; DOPPS, Dialysis Outcomes and Practice Patterns Study; PBS, Pharmaceutical Benefits Scheme

6.107 No discussion was provided in the submission with regards to grandfathered patients, although the epidemiological approach may capture the financial impact associated with this group of patients.

6.108 The estimated use and financial impact of difelikefalin to the PBS/RPBS over the first 6 years of listing is summarised in Table 13.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients initiating treatment	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Initial year responders	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Subsequent year patients who are alive and are persistent to treatment	-	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Initial scripts	[redacted][3]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
First year continuing scripts	[redacted][4]	[redacted][3]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Subsequent year continuing scripts	[redacted][2]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total scripts	[redacted][5]	[redacted][5]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Estimated financial implications of difelikefalin						
Cost to PBS/RPBS less copayments ($)	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][7]

Source: Section 4.2-4.4, pp198-205 of the submission; difelikefalin utilisation and cost model workbook.xlsx, Attachment 9 of the submission.
The redacted values correspond to the following ranges:
[1] *500 to < 5,000*
[2] *< 500*
[3] *5,000 to < 10,000*
[4] *10,000 to < 20,000*
[5] *20,000 to < 30,000*
[6] *$10 million to < $20 million*
[7] *$0 to < $10 million*

6.109 The estimated net cost to the PBS/RPBS for difelikefalin was $10 million to < $20 million in Year 1, decreasing to $10 million to < $20 million in Year 6, a total of $60 million to < $70 million over the first 6 years of listing.

6.110 The submission did not adequately justify the use of prevalence estimates as the basis of all eligible population estimates. The size of the prevalent pool of patients in the first year may be reasonable, however, eligible population estimates in subsequent years were highly uncertain due to the interaction between prevalence estimates that already capture mortality and additional mortality adjustments that were included to determine the proportion of patients who were alive and treatment naïve. The use of alternative mortality rates resulted in anomalous results, with higher mortality rates yielding a larger financial impact.

6.111 The submission acknowledged that the absence of objective criteria for pruritus severity in the proposed PBS restriction may lead to PBS-subsidised use of difelikefalin in patients with mild pruritus. The submission claimed that this uncertainty can be managed through an appropriate risk-sharing arrangement.

6.112 The submission claimed the treatment continuation rule applied in the budget impact model was consistent with the cost-effectiveness model such that only responders are able to continue to access difelikefalin treatment after 12 weeks. The submission also acknowledged that eligible population estimates were reliant on the assumption that patients will only have access to difelikefalin once per lifetime. The submission claimed that these assumptions were necessary to ensure that PBS/RPBS expenditure aligns with assumptions used to determine the cost-effectiveness of difelikefalin. The

submission acknowledged that this may result in an underestimate of actual expenditure due to the absence of objective treatment response criteria and lifetime limit in the proposed PBS restriction. However, the submission claimed that the estimates could be used to form the basis of financial caps in the risk-sharing arrangement.

6.113 There was substantial patient attrition in the model, dependent on estimated mortality rates, treatment continuation criteria (based on response) and treatment discontinuations (for reasons other than inadequate response). These were applied as mutually exclusive estimates in the model assuming no relationship between treatment discontinuation rates derived from the trial with treatment response or death. This assumption was inadequately justified in the submission.

6.114 The submission did not consider the impact of patients receiving kidney transplants, which was not captured in trial-based discontinuation rates. In 2019, the estimated transplant rate in all adult Australian patients on dialysis was 11.6 per 100 dialysis-years, although the rate of transplant in patients aged 65-74 years was 4.8 per 100 dialysis-years (ANZDATA 43rd Annual Report 2020). Published estimates in 2020 suggest a decline in the rate of transplants; however the report noted that procedures were likely impacted by COVID-19 (ANZDATA 44th Annual Report 2021).

6.115 DUSC considered the estimates presented in the submission to be significantly underestimated. The main issues were:

- Exclusion of at-home dialysis patients from the eligible population.
- Underestimation of the proportion of patients deemed to have moderate to severe pruritus (43%) due to the lack of an objective disease severity test in the restriction.
- Underestimation of rate of CKD-aP diagnosis (83%). DUSC considered that the rate of patients reporting itchy skin may increase as the PBS listing of difelikefalin will increase awareness of the possibility of effective treatment.
- Underestimation of proportion of patients with response at 12 weeks (51.3%) due to lack of objective response test in the restriction.
- Underestimation of scripts per patient.

6.116 The pre-PBAC response noted the advice of the DUSC and presented a revised set of utilisation and financial estimates based on a prevalence-only approach with the changes outlined in Table 14

Table 14 Summary table of changes to the utilisation and financial estimates (Pre-PBAC Response)

Parameter	2024	2029	Notes
ANZDATA (prevalence of HD)	13,700	17,141	Included home dialysis patients, and increased and updated the growth rate as per DUSC advice.
DOPPS (patients bothered by moderate/severe itch)	43%	43%	Not updated so that the financial estimates reflect the PBS restriction in case they are to form the basis of an RSA.
Diagnosis rate of CKD-aP	83%	83%	DUSC stated this was an underestimate, however, if the population grows due to availability for DFK then this is conservative because this 17% of patients are eligible for treatment and are cost effective. Unchanged.
DFK uptake rate	70%	90%	Accepted by DUSC as reasonable.
DFK response rate	51.3%	51.3%	Not updated so that the financial estimates reflect the PBS restriction in case they are to form the basis of an RSA.
Total patients treated	[redacted][1]	[redacted][1]	Product of all the above
Scripts (initial and continuing)	[redacted][2]	[redacted][3]	DUSC noted underestimation of scripts per patient for those greater than 104 kg, requiring 2 vials per dose. This has been updated in the model with Australia's subgroup population in the KALM trials translating to 6% requiring a second dose. Adherence and persistence in the first 12 weeks of treatment was also updated in line with DUSC advice, resulting in 12.21 to 12.42 vials per patient per year (depending on initial or continuing).
Total PBS/RPS expenditure* ($)	[redacted][4]	[redacted][4]	Revised AEMP of $[redacted] per vial

Source: Table 1 pre-PBAC response
*428.26 per script net of copayment
The redacted values correspond to the following ranges:
[1] *500 to < 5,000*
[2] *20,000 to < 30,000*
[3] *30,000 to < 40,000*
[4] *$10 million to < $20 million*

Quality Use of Medicines

6.117 Quality use of medicines was not addressed in the submission. The TGA ACM August 2022 meeting minutes noted that it may be beneficial for the sponsor to provide education regarding the use of difelikefalin in the hospital setting. The ACM advised that the Product Information should clearly state that difelikefalin is to be used only for the approved indication as off-label use may be inappropriate given the complex nature of the drug. It may also be reasonable to emphasise that difelikefalin should not be used in patients on peritoneal dialysis.

Financial Management – Risk Sharing Arrangements

6.118 The sponsor acknowledged that a risk-sharing arrangement would be required in order to ensure that PBS expenditure is limited to a level consistent with the trial data and cost-effectiveness estimates presented in the submission.

6.119 The sponsor acknowledged that the budget impact analysis presented may underestimate script numbers and expenditure. However, the sponsor claimed that these estimates were based on how difelikefalin should be used (i.e. consistent with the evidence) rather than how it may be used in practice with the potential for leakage. The sponsor claimed that these estimates would be an appropriate basis for a risk-sharing arrangement. The submission stated that the sponsor will work with the Department of Health to agree upon an appropriate rebate over agreed levels of expenditure.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of difelikefalin for the treatment of moderate to severe pruritus (itching) associated with chronic kidney disease (CKD) in adult patients who are receiving haemodialysis. The PBAC acknowledged there was a clinical need for effective treatment options as current alternatives were of limited effectiveness and/or prescribed off-label with limited evidence to support their use. The PBAC considered that based on the evidence presented, difelikefalin is likely to be effective for some patients, but noted limited long-term data were available. However, the PBAC considered the incremental cost-effectiveness ratio (ICER) for difelikefalin was high and underestimated with the economic model incorporating optimistic assumptions, and that a price reduction would be required for difelikefalin to be considered cost-effective.

7.2 The PBAC noted the comments from health professionals and organisations which highlighted the impact of moderate to severe pruritus on patients' quality of life, and the generally poor effectiveness and supportive evidence for the range of treatments currently used in practice. The PBAC acknowledged there was a clinical need for effective treatment options for moderate to severe pruritus.

7.3 With respect to the proposed restriction, the PBAC considered the submission's original proposal to limit treatment to patients receiving in-centre haemodialysis inappropriately excluded patients undergoing haemodialysis in the home. The Committee noted use in the at-home haemodialysis setting was supported by the Advisory Committee for Medicines (ACM) and considered it would be important for these patients to also have access to difelikefalin treatment if it was listed on the PBS. The PBAC noted the sponsor had indicated its willingness to amend the restriction to include this population in its PSCR (see paragraph 3.7). In addition, the PBAC noted the proposed restriction did not include formal criteria for assessing pruritus severity at baseline, nor did it define a response to treatment threshold for continuing therapy. The PBAC agreed with the ESC that use of the Worst Itch Numeric Rating Scale (WI-NRS) in the restriction would be feasible with baseline severity and response criteria based upon the thresholds used in the clinical trials (i.e.: severity: a WI-NRS score > 4; response criteria: at least a 3-point improvement in WI-NRS). The Committee noted

the pre-PBAC response argued that the ratings scales used in the clinical trials were subjective; however, considered that given there were limited effective treatment options for pruritus in this population, there was a high risk of leakage to patients with milder disease and therefore criteria for defining baseline pruritus severity and response to treatment were appropriate. The PBAC also 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. Given changing haemodialysis regimens, the PBAC considered the restriction should be silent on the frequency of haemodialysis. The PBAC considered that a grandfathering restriction was appropriate with criteria as suggested by the secretariat.

7.4 The PBAC considered that the nominated comparator of best supportive care was reasonable.

7.5 The PBAC noted the key clinical trials, KALM-1 and KALM-2, were 12 week head-to-head trials of intravenous difelikefalin versus placebo. The PBAC considered the trials to be at moderate risk of bias due to high and differential missing data. The PBAC noted the subsequent single-arm open label 52 week extension phases of both trials were ceased early by the sponsor for administrative reasons (see paragraph 6.10).

7.6 The PBAC considered the results of the randomised phases of KALM-1 and KALM-2 demonstrated that difelikefalin appears to be effective for treating moderate to severe pruritus in the CKD population undergoing dialysis, over 12 weeks of treatment (pooled WI-NRS improvement of ≥3 points, OR 1.93, 95% CI 1.44, 2.57). The PBAC noted the placebo response rate was high in the clinical trials. The Committee also considered that, while there was greater uncertainty with the longer-term effectiveness of difelikefalin due to the single-arm nature of the extension studies and their early termination, that improvements experienced in early treatment may be maintained over time. Overall, the PBAC considered that the claim of superior comparative effectiveness was likely to be reasonable.

7.7 The PBAC noted the trial evidence indicated treatment with difelikefalin was associated with increased occurrence of gastrointestinal adverse events, falls/gait disturbances, dizziness and somnolence. While there are limited clinical data on difelikefalin use beyond 64 weeks in the key trials, a summary of serious unexpected adverse drug reactions was considered by the ACM in their October 2022 meeting (see paragraph 6.53). The PBAC noted that full TGA registration had subsequently been approved without any boxed warnings. Overall, the PBAC considered that the claim of inferior comparative safety was reasonable.

7.8 The PBAC 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 the acceptance of the utility decrements applied in the model. The PBAC noted the concerns regarding the reliability of the approach for mapping the 5D-Itch scores to utility values (see

paragraphs 6.65 and 6.66), and considered the resulting utility decrements applied for pruritis (mild 0.0676, moderate 0.1544 and severe 0.2606) to be implausibly large. The PBAC noted the PSCR and pre-PBAC response argued that there was precedent for comparable changes in utility for conditions such as severe chronic plaque psoriasis and severe atopic dermatitis (see paragraph 6.73). However, the PBAC considered that these examples were not applicable to patients with CKD requiring haemodialysis who would be expected to have lower baseline utility values due to multiple sources of disutility in addition to pruritus (e.g. fatigue, CKD-related comorbidities).

7.9 The PBAC noted the economic model assumed an attenuating placebo effect for patients on best supportive care 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. In addition, the PBAC noted the economic model assumed a cause-effect relationship between high itch scores and death and considered this was inappropriate and should be removed.

7.10 The PBAC noted the pre-PBAC response presented a revised base case model that attempted to address ESC's concerns regarding the adjustments for placebo responses in the best supportive care arm, not including costs and disutilities for adverse events and not accounting for patients needing more than one vial of difelikefalin (see paragraph 6.99). The PBAC considered that the revised model required evaluation however, noted it retained the same utility decrements which as noted in paragraph 7.8 were considered implausibly large. On this basis the PBAC considered the base case ICER presented in the pre-PBAC response of $45,000 to < $55,000 per QALY gained (which included a price reduction of 20%) to be underestimated, and given the inherent uncertainty to be too high. The PBAC considered a further price reduction would be required for difelikefalin to be considered cost effective.

7.11 The PBAC agreed with the DUSC that the estimates presented in the submission were significantly underestimated and with the concerns raised by the Committee in paragraph 6.115. The PBAC noted the pre-PBAC response presented revised estimates that addressed some but not all of the concerns raised by DUSC (see Table 14). The PBAC considered this revised approach may be reasonable, however also noted it had not been independently evaluated. The PBAC considered that a risk sharing arrangement (RSA) would be required to address any residual uncertainty with the potential for use outside of the proposed restriction, including in patients with mild pruritis.

7.12 The PBAC considered a resubmission for difelikefalin should address the following issues:

- Present a revised restriction with initial and continuing criteria identifying moderate to severe pruritus and response scale based on the clinical trials;

- Present a revised economic evaluation which addresses concerns regarding optimistic inputs and additional concerns raised by ESC as outlined in paragraphs 7.8, 7.9 and 7.10;
- Present revised financial estimates updated with any price reduction; and
- Present an RSA to address any residual uncertainty with the potential for use outside of the proposed restriction (e.g. in patients with mild pruritis or continued use in those without an adequate response to treatment).

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.