SMC2623

difelikefalin solution for injection (Kapruvia®)

CSL Vifor

12 January 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC Executive, advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

difelikefalin (Kapruvia®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.

SMC restriction: for use in patients with an inadequate response to best supportive care for reducing itch.

Difelikefalin, compared with placebo, improved itch for a greater proportion of patients with moderate-to-severe itch who were undergoing haemodialysis for end-stage renal disease.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Difelikefalin is a kappa opioid receptor agonist with low central nervous system (CNS) penetration. It is thought that difelikefalin acts on kappa opioid receptors on peripheral sensory neurons and immune cells to produce antipruritic and anti-inflammatory effects. Difelikefalin 0.5 micrograms per kg dry body weight (target post-dialysis weight) is given by intravenous (IV) bolus injection into the venous line of the dialysis circuit at the end of the haemodialysis three times per week. Administration should be restricted to in-centre haemodialysis use only.[1]

1.2. Disease background

Many patients (>60 %) undergoing dialysis have chronic kidney disease-associated pruritus (uraemic pruritus) characterised by a generalised intractable itch and subsequent mechanical skin damage from scratching. They may suffer from poor sleep, chronic fatigue, social isolation and depression, leading to reduced quality of life. Patients can have increased risks of infection and death, including higher rates of cardiovascular and infection-related mortality. The pathogenesis of this condition is multi-factorial and not completely understood. It has been suggested that it may include an imbalance in the activity of mu opioid receptors (which are pruritus-inducing) and kappa opioid receptors (which are antipruritic).[2]

1.3. Company proposed position

The company has requested that SMC consider difelikefalin when positioned for use in patients with an inadequate response to best supportive care for reducing itch.

1.4. Treatment pathway and relevant comparators

Currently, no other medicine is licensed in the UK specifically for chronic kidney disease-associated pruritus. Treatments, some of which are off-label, comprise antihistamines, corticosteroids, gabapentin and pregabalin. However, chronic kidney disease-associated pruritus remains an issue for some patients and there is an unmet need for more effective therapies.[2]

1.5. Category for decision-making process

Eligibility for a PACE meeting
Difelikefalin meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the similar, placebo-controlled, phase III studies, KALM-1 and KALM-2, detailed in Table 2.1 and from a single-arm phase III safety study, CLIN3105.[2-6]

Table 2.1. Overview of relevant studies.[2, 4]

Criteria	KALM-1	KALM-2
Study design	Double-blind, phase III studies	
Eligible patients	≥18 years (≤85 years in KALM-2); on haemodialysis three times a week for ≥3 months for end-stage renal disease; moderate-to-severe itch (WI-NRS score ≥5)	

Treatments	Difelikefalin 0.5 micrograms/kg of prescription dry body weight or placebo by IV bolus into venous port of the dialysis circuit three times per week for 12 weeks followed by open-label difelikefalin for up to 52 weeks.	
Randomisation	Patients assigned equally to difelikefalin or placebo. Randomisation stratified by: (a) anti-itch medications during the run-in week; (b) history of fall or fracture related to fall; (c) confusional state or mental status change or altered mental status or disorientation; and (d) gait disturbance or movement disorder.	
Primary outcome	Proportion of patients with ≥3 point improvement in WI-NRS at W12.	
Secondary outcomes	Secondary endpoints in hierarchy: (a) change in 5-D Itch Scale at W12; (b) change in Skindex-10 Scale at W12; (c) ≥4-point improv. in WI-NRS at W12.	Secondary endpoints in hierarchy: (a) ≥4-point improv. in WI-NRS at W12 (b) ≥3-point improv. in WI-NRS at W8 (c) ≥3-point improv. in WI-NRS at W4 (d) ≥4-point improv. in WI-NRS at W8 (e) ≥4-point improv. in WI-NRS at W4 (f) change in Skindex-10 Scale at W12 (g) change in 5-D Itch Scale at W12
Statistical analysis	If primary outcome significant, secondary outcomes tested in hierarchy. Primary outcome tested in all randomised patient (ITT) with imputation for missing data.	

Abbreviations: improv. =improvement; W4, W8 and W12 = week 4, week 8 and week 12; ITT = intention-to-treat; IV = intravenous; WI-NRS = Worst Itching Intensity Numerical Rating Scale, which is an 11-point scale (0 to 10) with higher scores indicating greater itch intensity.

In KALM-1 and KALM-2, the primary outcomes and all secondary outcomes in the pre-specified hierarchy significantly improved with difelikefalin, compared with placebo, except for the sixth secondary outcome in KALM-2 (change in Skindex-10 score at week 12). The seventh and final secondary outcome in KALM-2 (change in 5-D Itch Scale at week 12) was not formally tested. Results are detailed in Table 2.2.[2, 3, 7]

Table 2.2: Primary and key secondary outcomes of KALM-1 and KALM-2.[2]

	KALM-1		KALM-2	
	Difelikefalin (n=189)	**Placebo (n=189)**	**Difelikefalin (n=237)**	**Placebo (n=236)**
≥3-point improv. in WI-NRS at W12	51 %	28 %	54 %	42 %
Odd ratio (95% CI), p-value	2.72 (1.72, 4.30) p<0.001		1.61 (1.08, 2.41), p=0.020	
LSM change in 5-D Itch Scale at W12	-5.0	-3.7	-4.9	-3.8
Difference (95% CI), p-value	-1.3 (-2.0, -0.5) p<0.001		-1.1 (-1.7, -0.4)*	
LSM change in Skindex-10 at W12	-17.2	-12.0	-16.6	-14.8
Difference (95% CI), p-value	-5.1 (-8.0, -2.3), p<0.001		-1.8 (-4.3, 0.8) p=0.17	
≥4-point improv. in WI-NRS at W12	39 %	18 %	41 %	28 %
Odd ratio (95% CI), p-value	2.89 (1.75, 4.76)		1.77 (1.14, 2.74), p=0.010	
≥3-point improv. in WI-NRS at W8			49 %	36 %
Odd ratio (95% CI), p-value			1.69 (1.13, 2.53), p=0.010	
≥3-point improv. in WI-NRS at W4			38 %	24 %
Odd ratio (95% CI), p-value			1.99 (1.29, 3.06), p=0.002	
≥4-point improv. in WI-NRS at W8			36 %	24 %
Odd ratio (95% CI), p-value			1.82 (1.16, 2.86), p=0.010	
≥4-point improv. in WI-NRS at W4			26 %	17 %
Odd ratio (95% CI), p-value			1.76 (1.04, 2.98), p=0.036	

* not formally tested as placed after a non-significant result in the hierarchy. Abbreviations: improv.= improvement. CI =confidence interval; LSM = least squares mean; W4, W8 and W12 = week4, week 8 and week 12; WI-NRS = Worst Itching Intensity Numerical Rating Scale, which is an 11-point scale (0 to 10) with higher scores indicating greater itch intensity.

Patients in KALM-1 and KALM-2 who received at least 30 of the 36 planned doses in the double-blind phase were eligible to enter the 52-week open-label phases.[2, 3, 6]

In KALM-1, 313 patients continued into the open-label phase and 60 % (189/313) completed this phase, with reasons for early discontinuation including: other (11 %), adverse events (8.3 %), withdrawal of consent (5.4 %), loss to follow-up (1.6 %) and noncompliance (1.6 %). An additional 12 % of patients could not complete the study due to the sponsor's decision to stop the study early for administrative reasons. Benefits in 5-D Itch score were maintained in patients who remained on treatment during the 52-week open-label phase.[2, 6, 8]

In KALM-2, 399 patients continued into the open-label phase, but only 1.3 % (5/399) completed this phase, with reasons for early discontinuation including: administrative (9.0 %), adverse events (5.3 %), withdrawal of consent (2.8 %), other (2.3 %), lack of efficacy (0.5 %) and loss of eligibility (0.5 %). An additional 78 % of patients could not complete the study due to the sponsor's decision to stop the study early for administrative reasons. Amongst the 52 patients who completed 36 weeks' treatment, benefit in 5-D Itch score was maintained.[2, 6, 9]

2.2. Evidence to support the positioning proposed by the submitting company

The subgroup of patients who met the inclusion criterion for moderate-to-severe itch despite baseline antipruritic medicines may be most representative of patients likely to be treated in practice if difelikefalin is used in patients who have an inadequate response to best supportive care. Subgroup analyses by baseline anti-pruritic medicines are detailed in Table 2.3.

Table 2.3: Subgroup analyses of KALM-1 and KALM-2 by baseline antipruritic medicine use. [6 66]

Antipruritic use at baseline	≥3 point improvement in WI-NRS		≥4 point improvement in WI-NRS	
	Difelikefalin	Placebo	Difelikefalin	Placebo
KALM-1				
Yes (n=72, 78)	52 %	30 %	40 %	21 %
Difference (95% CI)	23 % (7 % to 39 %)		19 % (4 % to 34 %)	
No (n=117, 111)	52 %	32 %	41 %	22 %
Difference (95% CI)	20 % (8 % to 33 %)		19 % (7 % to 30 %)	
KALM-2				
Yes (n=87, 85)	41 %	26 %	42 %	22 %
Difference (95% CI)	15 % (0 to 30 %)		20 % (6 % to 34 %)	
No (n=150, 151)	39 %	32 %	35 %	29 %
Difference (95% CI)	7 % (-4 % to 17 %)		6 % (-5 % to 17 %)	

CI = confidence interval; WI-NRS = Worst Itching Intensity Numerical Rating Scale, which is an 11-point scale (0 to 10) with higher scores indicating greater itch intensity.

2.3. Health-related quality of life outcomes

Health-related quality of life was assessed using the 5-D Itch Scale and Skindex-10 questionnaires. Results, indicating some benefit with difelikefalin, are detailed in Table 2.2.

2.4. Supportive studies

An open-label, phase III safety study (CLIN3105) recruited 222 patients similar to those in the KALM-1 and KALM-2 studies. All patients received the licensed dose of difelikefalin. Improvements from baseline to week 12 on Worst Itching Intensity Numerical Rating Scale (WI-NRS) of ≥3 and ≥4 points were reported by 74 % and 59 % of patients; and on Sleep Quality NRS were noted for 66 %

and 57 % of patients, respectively. There were improvements at week 12 of ≥5 points for 5-D Itch Scale score in 70 % of patients and ≥15 points for Skindex-10 score in 63 % of patients.[5]

3. Summary of Safety Evidence

Difelikefalin is associated with adverse events characteristics of an opioid agonist, including gastrointestinal upset, dizziness, somnolence, mental status changes (including confusion) and paraesthesia.[1, 2, 6]

In pooled data from the 12-week, double-blind phases of KALM-1 and KALM-2, 13 % and 7.3 % of patients discontinued treatment early in the difelikefalin and placebo groups, respectively, with adverse events being the primary reason for early treatment discontinuation, 6.4 % versus 3.8 %. In the respective groups the rates of adverse events were 71 % (302/424) and 65 % (277/424), with these considered treatment-related in 8.0 % and 6.4 %. Non-fatal serious adverse events were reported by 25 % and 23 % of patients, respectively. Common adverse events reported more frequently with difelikefalin than placebo included diarrhoea (9.0 % versus 5.7 %), nausea (6.6 % versus 4.5 %), falls and gait disturbance (7.1 % versus 5.7 %), dizziness (6.8 % versus 3.8 %), headache (4.5 % versus 2.6 %), somnolence (4.2 % versus 2.4 %), mental status change (including confusional state) (3.3 % versus 1.4 %), hyperkalaemia (4.7 % versus 3.5 %), and back pain (2.6 % versus 0.9 %).[2, 6]

In the pooled data from the double-blind phases of KALM-1 and KALM-2, major adverse cardiovascular events (MACE; non-fatal stroke, myocardial infarction, cardiovascular death, heart failure and revascularisation) were reported at a higher rate with difelikefalin than placebo: 3.8 % versus 2.4 % (193.8 versus 128.6 events per 1,000 patient-years), mainly driven by heart failure and myocardial infarction. The European regulatory authority concluded that currently a causal relationship between difelikefalin and cardiac events cannot be conclusively established or excluded and these will be monitored in ongoing pharmacovigilance activities.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In two double-blind phase III studies, difelikefalin compared with placebo increased the proportions of patients at week 12 achieving improvement of itch ≥3 points on WI-NRS by 23 % in KALM-1 and 12 % in KALM-2; and ≥4 points by 21 % and 13 %, respectively. The European regulatory authority considered these modest but clinically relevant benefits.[2]
- Difelikefalin is the first medicine to be specifically licensed in the UK for the treatment of haemodialysis-associated pruritus in patients with chronic kidney disease.

4.2. Key uncertainties

- At week 12, there were more missing WI-NRS scores in the difelikefalin groups compared with placebo: 17 % (32/189) versus 13 % (24/189) in KALM-1; and 19 % (46/237) versus 12 % (29/236) in KALM-2. In the primary analysis, missing WI-NRS data were imputed. In sensitivity analyses where missing data was considered non-response, difelikefalin compared with placebo groups, increased the proportions of patients with improvement ≥3 points on WI-NRS at week 12 by 17 % in KALM-1 and 8 % in KALM-2; and ≥4 points by

15 % and 9 %, respectively.[2, 6] The magnitude of benefit appears smaller than in the primary analyses.

- The subgroups of patients who met the inclusion criterion for moderate-to-severe itch despite baseline anti-pruritic medicines (40 % and 36 % of the population in KALM-1 and KALM-2) may be most representative of patients likely to be treated in practice if difelikefalin is used in patients who have an inadequate response to best supportive care. In these subgroups, difelikefalin compared with placebo increased the proportions of patients with improvement ≥3 points on WI-NRS at week 12 by 23 % in KALM-1 and 15 % in KALM-2; and ≥4 points by 19 % and 20 %, respectively.[6]
- The quality of the available evidence up to 15 months is limited as the 52-week open-label extension phases of KALM-1 and KALM-2 were stopped early by the company (resulting in treatment discontinuation for 12 % and 78 % of patients, respectively). Prior to this 28 % and 20 % of patients in the studies had discontinued study drug treatment for other reasons. Only 60 % and 1.3 % of patients completed the open-label phases of the respective studies. Efficacy was assessed in the open-label extension using the 5-D Itch scale only. Therefore, the number of patients maintaining clinically relevant improvements of ≥3 or ≥4 points on WI-NRS beyond 12 weeks is unknown.[8, 9] This limits the quality of long-term efficacy data.
- Placebo-controlled data are limited to 12 weeks and there is a lack of longer-term efficacy data beyond 15 months. It is not clear if the treatment effect of the opioid agonist, difelikefalin, is maintained at the same level over longer periods.
- There is a lack of long-term safety data beyond 15 months and pharmacovigilance activities are ongoing to monitor longer-term adverse events such as MACE.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that difelikefalin fills an unmet need in this therapeutic area for additional effective therapies. They considered that it is a therapeutic advance due to its novel mechanism of action, efficacy and licence for use specifically in moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis. They noted that it would be used in place of existing therapies such as antihistamines.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Kidney Research UK, which is a registered charity.
- Kidney Research UK has received 4% pharmaceutical company funding in the past two years, including from the submitting company.
- Living with kidney disease makes every day a challenge. Patients report that pruritus is common in people with kidney disease and is under-reported by patients who feel it is not

taken seriously enough by healthcare professionals. It can have a significant impact on the quality of life of kidney patients who already have extremely burdensome haemodialysis treatment, causing sleep disturbance, social isolation, low self-esteem and emotional distress.

- Patients report trying 'everything' to alleviate the symptoms of pruritus. There is significant unmet need for kidney patients with pruritus. This treatment would provide another option where other interventions have failed to manage it.

The patient group reported that people from deprived communities and ethnic minority groups are more likely to require renal replacement therapy and may be more likely to benefit from this treatment.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic text is described in Table 6.1.

Table 6.1 Description of economic analysis

Analysis type	Cost-utility analysis
Time horizon	Lifetime – Maximum 100 years (base case starting age of 58 years)
Population	Adult patients with moderate-to-severe (including very severe) chronic kidney disease-associated pruritus who are on haemodialysis. The starting cohort for the cost-effectiveness analysis has approximately 55% and 35% of patients in a moderate and severe state respectively, with the remainder very severe, as observed in the KALMs data.
Comparators	There are currently no other approved treatments for chronic kidney disease-associated pruritus. The comparator in the model is best supportive care (BSC), which may include off-label anti-itch medicines such as creams and emollients, antihistamines, and gabapentin.
Model description	The analysis is based on a seven-state Markov model. States are the following categories of itch severity based on the 5-D Itch Scale: none (score 5-8), mild (9-11), moderate (12-17), severe (18-21), and very severe (22-25), plus transplant and death. A stopping rule is applied in the analysis whereby patients on difelikefalin who do not achieve a clinically meaningful itch score improvement at 12-weeks discontinue treatment. The submitting company cited a Scottish advisory board endorsing this as suitable since it broadly aligns with the regular patient review conducted by consultant nephrologists. The stopping probabilities are based on proportions observed in the KALM data rather than explicitly modelled criteria.
Clinical data	The main source of clinical data was the pooled KALM-1 and KALM-2 clinical study data. The submitting company undertook an analysis of change in 5-D itch score after multiple imputations for missing data. Each study patient was 'simulated' to have the mean change in score conditional on baseline severity. This change in score was modelled up to weeks 12 and 64 in the BSC and difelikefalin arms respectively. Overall transition probabilities were then calculated based on the simulated scores

	across the studies. These base case transition probabilities were preferred by the submitting company to count based observed transition probabilities.
Extrapolation	Data from the open-label extension to week 64 were used to model on-going transitions for difelikefalin. Data for patients receiving double-blind difelikefalin or placebo were used to estimate these transitions. For usual care the mean change in itch score from baseline is assumed to remain unchanged for BSC arm from week 12 to week 64 (model cycle 4). Alternatives were considered in scenario analyses. Upon reaching the plateau point – at week 64 in the base case - patients in the difelikefalin arm are assumed to remain in their present itch state unless they undergo transplant or die. The usual care arm also retains an element of steady-state, however, in this case a waning effect whereby 10% transition to the next worst state is applied. Patients faced rates of mortality and transplant that differed over the first ten years (and are then assumed constant). Mortality hazards were assumed to depend also on hazard ratios conditional on degree of self-assessed itch in the DOPPS study[10] reported by Sukul et al. (2021), which reported a hazard ratio in very severely bothered patients of 1.24 (95% confidence interval 1.08 – 1.41), compared with patients unaffected by itch.[11]
Quality of life	A separate mapping study was undertaken to provide a basis for generating EQ-5D-3L utilities from Worst Itch Numeric Rating Scale (WI-NRS) scores and 5-D itch scale total scores. The analysis controlled for a number of other covariates and resulted in utilities that decline from 0.617 for minimally impacted to 0.429 for very severely impacted. A utility from the literature for transplant was applied which represented an improvement on all CKD health states; surviving patients in both arms of the model were equally likely to undergo transplant irrespective of their itch state.
Costs and resource use	The model includes medicine costs for BSC, based on data for background chronic kidney disease-associated pruritus treatment collected in the mapping study, and difelikefalin (0.5 micrograms/kg dry body weight). Costing accounted for injection volumes and required number of vials per weight band. Due to recommended single use vials injection volume ranged from 0.40 mL at 40-45kg to 1.30 mL at 125-130kg; one vial is required at or below 95-100kg and 2 vials above this weight. An estimated 2.95 dialysis sessions per week is used in the model. Hospitalisation costs (£2,872 per case) were applied with hospitalisation rate depending upon itch state. Based on the DOPPS study, the submitting company applied hazard ratios for adjusted all-cause hospitalisation compared with patients who reported being not at all bothered by itchy skin.[10] Other costs included nephrologist review and transplant costs.
PAS	Difelikefalin has a list price of £35 per vial. A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price.

6.2. Results

Table 6.1: Base case analysis (with PAS)

Technologies	ICER (£/QALY)
Difelikefalin + BSC vs BSC	17,623

Abbreviations: BSC = Best supportive care; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio

Subgroup analysis was conducted to explore the differences in the target population by use of anti-itch medication at baseline and baseline itch severity.

Table 6.2: Sub-group analyses (with PAS)

Technologies	ICER (£/QALY)
Subgroup analysis A: Only receiving anti-itch medication at baseline	
Difelikefalin + BSC vs BSC	18,079
Subgroup analysis B: Not receiving anti-itch medication at baseline	
Difelikefalin + BSC vs BSC	19,405
Subgroup Analysis C: Severe and Very severe itch at baseline	
Difelikefalin + BSC vs BSC	14,480

Abbreviations: BSC = Best supportive care; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio

6.3. Sensitivity analyses

The company provided sensitivity and scenario analyses exploring areas of uncertainty in the model. A selection of illustrative scenarios are presented in the Table below (with PAS).

Scenario	Description		ICER
Base case deterministic results			**£17,623**
1a.	BSC extrapolation	Mean difference long-term extrapolation for BSC arm.	£22,051
1b		Ratio of means long-term extrapolation for BSC arm	£19,045
2a	Stopping rule applied in Week 8.		£17,503
3a	KALM-1 and KALM-2 separately	KALM-1 trial data only	£19,309
3b		KALM-2 trial data only	£15,220
4a	Efficacy plateau	Efficacy plateau after Year 2	£16,736
5a	Treatment waning	From cycle 5 apply 5% state deterioration per cycle	£19,411
5b		From cycle 5 apply 10% state deterioration per cycle	£21,761
6	Transition matrix estimation using observed method.		£19,255
7	Moderate state utility	Low	£15,811
8		High	£19,902
9	Moderate state mortality HR	Low	£19,058
10		High	£16,630
11	Mortality and hospitalisation HRs	Set all to 1.00	£22,125

6.4. Key strengths

The analysis is based on a clear conceptual model, which is straight forwardly implemented. Assumptions are clearly stated, and a number of limitations are acknowledged.

6.5. Key uncertainties

The analysis is subject to several areas of uncertainty.

- In the submitted base case the 'simulated' transition probabilities are based on a questionable method which applies a universal effect on all patients (conditional on state), and appears to preclude any worsening in terms of itch.
- Despite acknowledged limitations in the modelling of effectiveness, limited analysis was provided to indicate the sensitivity of the model to variation in the effectiveness of treatment in controlling itch, but analyses show the model may be sensitive to relatively small proportionate reductions in the impact on quality of life.
- For both mortality and hospitalisations, the model assigns increasing hazards with greater severity of itch. This is based on observational data showing associations between itch severity and both endpoints, however, despite those analyses having controlled for several potential confounders there is uncertainty as to whether better controlled itch would lead to reductions in the hazards of either mortality or hospitalisation.
- Medium term transition probabilities for difelikefalin are based on analysis of open label extension data for patients who received either difelikefalin or placebo in the double-blind period; the effect of the inclusion of the latter is unclear.
- Patients remaining on difelikefalin after 64 weeks are assumed to maintain their present itch state.
- The model may over-state health benefits to some degree as declining age and sex population health related quality of life is not reflected.

7. Conclusion

After considering all the available evidence, the Committee was able to accept difelikefalin for use in NHSScotland.

8. Guidelines and Protocols

In 2018, the British Association of Dermatologists (BAD) published: British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018.[12]

9. Additional Information

9.1. Product availability date

May 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Difelikefalin	**0.5micrograms/kg intravenously three times per week**	**5,460**

Costs from BNF online on 23 October 2023. Costs based on 70kg body weight and calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated that there would be 368 patients eligible for treatment with difelikefalin in year 1 rising to 591 patients in year 5. This increase is mainly based on the company's assumption that the rate of diagnosis will increase from year 1 to year 5. The estimated uptake rate was 7.0% in year 1 and 55% in year 5. This resulted in 26 patients estimated to receive treatment in year 1 rising to 325 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 15 December 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contr prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive

access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.