

## National Institute for Health and Care Excellence

## Single Technology Appraisal (STA)

## Difelikefalin for treating pruritus in people having haemodialysis [ID3890]

## Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Vifor Pharma	Yes, the wording of the remit appropriately captures the objective of appraising difelikefalin.	Thank you for your comment. No change to scope required.
Timing Issues	Vifor Pharma	Given the prevalence of pruritus in haemodialysis patients, its impact on morbidity and mortality and the absence of approved or effective treatments; it is desirable to ensure guidance on the use of difelikefalin can be issued to the NHS as close as possible to the date of its anticipated marketing authorisation.	Thank you for your comment. An appraisal of difelikefalin has been scheduled into NICE's technology appraisal work programme (see <a href="https://www.nice.org.uk/guidance/proposed/gid-ta10793">https://www.nice.org.uk/guidance/proposed/gid-ta10793</a> ). No change to scope required.
	The Renal Association UK	Moderately urgent – uraemic itching interferes with quality of life of dialysis patients	Thank you for your comment. Please see

Section	Consultee/ Commentator	Comments [sic]	Action
			response above. No change to scope required.

**Comment 2: the draft scope**

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Background information	Vifor Pharma	<p>Although often used interchangeably, the term uraemic pruritus is not synonymous with chronic kidney disease associated pruritus (CKD-aP). Historically, uraemic pruritus was associated with markers of inefficient dialysis, including elevated levels of serum phosphorus and calcium and may be responsible for itch in a subset of patients on haemodialysis. Whilst the aetiology and pathophysiology of CKD-aP have yet to be fully elucidated, peripheral neuropathy, immune system dysregulation, and opioid imbalance have been causally linked with the development of CKD-aP.</p> <p>For consistency with the remit of the appraisal and proposed marketing authorisation of difelikefalin we suggest the term 'chronic kidney disease associated pruritus' (CKD-aP), rather than 'uraemic pruritus', be used throughout the document.</p> <p>To align with the subsequent description of difelikefalin in the scope we suggest the background includes reference to opioid imbalance as a causative factor in the development of CKD-aP.</p>	<p>Thank you for your comment. References to uraemic pruritus have been changed to 'pruritus associated with chronic kidney disease' throughout.</p> <p>The background section is intended to provide a brief summary of the condition.</p>
	The Renal Association UK	<p>1. 'The prevalence of moderate to severe pruritus in people having haemodialysis in the UK has been estimated to be 50%.' Please use the current reference on DOPPS study - <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5718267/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5718267/</a></p>	Thank you for your comment.

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		<p>2. 'Data from the most recent UK Renal Registry report suggests that there are approximately 10,000 people having haemodialysis and with moderate to severe pruritus in the UK.' Is it the correct reference? UKRR doesn't collect data on pruritus.</p> <p>3. 'Treatment instead focuses on symptom management and can include topical emollients and antihistamines.' This statement is not entirely correct. There are studies showing benefit of using gabapentin and pregabalin in uraemic itching.</p> <p>4. Gabapentin used as first line agent in many UK dialysis units and also in other countries (references DOPPS study above)</p>	<p>1. The suggested reference has been included in the scope.</p> <p>2. This figure was obtained by applying the 50% estimate of moderate to severe pruritus in people having haemodialysis in the UK to most recent UK data on the number of people currently having haemodialysis in the UK, as cited in the Renal Registry report. The scope has been amended to clarify this.</p> <p>3 &amp; 4. Please see response to the issue of comparators, below.</p>
The technology/ intervention	Vifor Pharma	Reference should be made to activation of kappa opioid receptors on sensory neurons as well as on immune cells, resulting in the combination of anti-pruritic and anti-inflammatory effects of difelikefalin.	Thank you for your comment. This section of the scope is intended to be a very brief overview of the technology. The activation of opioid receptors and its

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			suppression of itch and inflammation is referred to. No change to scope required.
	The Renal Association UK	Yes.	Thank you for your comment. No change to scope required.
Population	Vifor Pharma	The population studied includes patients where other treatment options have failed. All patients with moderate-to-severe CKD-aP benefit in a similar way and no subgroups have been identified where difelikefalin would be more beneficial.	Thank you for your comment. No change to scope required.
	The Renal Association UK	I wonder if Stages 4 and 5 CKD (non-dialysis). and ESKD on peritoneal dialysis be added.	Thank you for your comment. The scope population is aligned with the populations in the key clinical trials, which were defined as people with moderate to severe pruritus. No change to scope required.
Comparators	Vifor Pharma	The NICE accredited British Association of Dermatologists' guidelines recommend ensuring adequate dialysis, normalize calcium-phosphate balance, control PTH to accepted levels, correct any anaemia with erythropoietin and use simple emollients (for xerosis) in patients with uraemic pruritus before using other treatment strategies.	Thank you for your comment. The comparator has been updated to 'Established clinical management without difelikefalin,

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		<p>The guideline notes that no single topical or systemic treatment strategy is effective but advises to consider capsaicin cream, topical calcipotriol or oral gabapentin.</p> <p>In practice capsaicin can cause a transient burning feeling on the skin that is not well tolerated and, although not recommended, antihistamines are widely used.</p> <p>Although a wide range of CKD-aP treatments (topical, systemic and phototherapy) are used in clinical practice, they are used off label and with limited evidence of clinical effectiveness.</p>	including gabapentin and pregabalin’.
	The Renal Association UK	As mentioned above gabapentin, an evidence based treatment, is used as the first line agent many dialysis centres in the UK. As such it should be compared with gabapentin.	Thank you for your comment. The comparator has been updated to ‘Established clinical management without difelikefalin, including gabapentin and pregabalin’.
Outcomes	Vifor Pharma	Yes, the outcome measures included in the scope will capture the most important health related benefits (and harms) of the technology.	Thank you for your comment. No change to scope required.
	The Renal Association UK	Suggest add: <ul style="list-style-type: none"> <li>• Depression</li> <li>• Sleep disturbance</li> </ul>	Thank you for your comment. These outcomes are captured within health-related quality of life. No change to scope required.

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Economic analysis	Vifor Pharma	The economic analysis submitted will be in accordance with the reference case.	Thank you for your comment. No change to scope required.
	The Renal Association UK	It will be important to compare cost effectiveness with that of gabapentin, which used in many UK centres as first line agent.	Thank you for your comment. Please see response to comment in section on relevant comparators, above.
Equality and Diversity	Vifor Pharma	Vifor Pharma are not aware of any issues of inequality or discrimination arising from the proposed scope.	Thank you for your comment. No change to scope required.
Innovation	Vifor Pharma	Difelikefalin is a novel, peripherally restricted, highly selective kappa opioid receptor agonist. If approved, difelikefalin will be the first treatment approved for the treatment of chronic kidney disease associated pruritus.  Research indicates that EQ-5D is not sensitive to changes in some psychological disorders and conditions affecting sensory functions. Improvements in, for example, sleep and skin irritation are not adequately captured by changes to EQ-5D index scores. Therefore, the use of difelikefalin may result in significant health related benefits that are unlikely to be included in the QALY calculation.	Thank you for your comment. The committee will consider the innovative nature of difelikefalin when it makes recommendations. No change to scope required.
Questions for consultation	The Renal Association UK	How does difelikefalin compare with gabapentin in the treatment of uraemic pruritus in ESKD patients on haemodialysis?	Thank you for your comment. Please see response to comment in section on relevant comparators, above.

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Heart UK

National Kidney Federation