IQWiG Reports – Commission No. A22-105

Difelikefalin (pruritus) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Difelikefalin (Pruritus) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 20 December 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
UVB	ultraviolet B radiation
WI-NRS	Worst Itch Numeric Rating Scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug difelikefalin. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 4 October 2022.

Research question

The aim of the present report is to assess the added benefit of difelikefalin in comparison with individualized therapy as appropriate comparator therapy (ACT) in adult patients on haemodialysis with moderate-to-severe pruritus associated with chronic kidney disease.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of difelikefalin

Therapeutic indication	ACT[a]
Adult haemodialysis patients with moderate to severe chronic kidney disease–associated pruritus (CKD-aP)	Individualized therapy taking into account the respective prior therapies and the severity of the symptoms[b]

a. Presented is the ACT specified by the G-BA.
b. Adequate therapy of the underlying disease – in particular the implementation and optimization of haemodialysis – is assumed. With careful risk-benefit assessment, topical and/or systemic therapies may be considered as part of an individualized therapy: moisturizing and hydrating topicals, non-sedating systemic H1 antihistamines, UVB therapy, as well as gabapentin and pregabalin.

CKD: chronic kidney disease; CKD-aP: CKD-associated pruritus; G-BA: Federal Joint Committee; UVB: ultraviolet B radiation

The company did not follow the G-BA's specification of the ACT. It argued that no drugs were approved in the present therapeutic indication in Germany, that ultraviolet B radiation (UVB) therapy was the only option for non-drug treatment, and that there were no resolutions, assessments or recommendations of the G-BA as well as no generally valid or standardized therapy recommendations. Therefore, the company considered best supportive care as ACT.

Even though the current guideline on the diagnosis and therapy of chronic pruritus does not provide a generally valid, consistent treatment recommendation for pruritus, it provides various treatment options, which are oriented towards the underlying causes and the patient characteristics and thus represent individualized therapies. Overall, the company's deviation from the ACT specified by the G-BA is not sufficiently justified and therefore not appropriate. However, the approach of the company does not have any consequences for the content of the present benefit assessment, as there are neither suitable studies of difelikefalin in comparison with the comparator therapy chosen by the company nor suitable studies of difelikefalin in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of the added benefit.

Results

The check for completeness of the study pool for the present benefit assessment identified no RCT allowing a direct comparison of difelikefalin versus the ACT.

In the dossier, the company presented data from the 12-week randomized study phases of the studies KALM-1 and KALM-2. However, the studies KALM-1 and KALM-2 are unsuitable for the benefit assessment of difelikefalin versus the ACT. This is explained below.

Evidence presented by the company – studies KALM-1 and KALM-2

The 2 studies KALM-1 and KALM-2 each consist of a 12-week double-blind RCT phase followed by a 52-week open-label, single-arm extension phase. Both studies enrolled adults with end-stage renal disease who were treated by haemodialysis 3 to a maximum of 4 times a week and had moderate-to-severe pruritus prior to study entry.

From the time of randomization, patients in both studies received either difelikefalin in compliance with the Summary of Product Characteristics (SPC) or placebo as an intravenous bolus injection after each dialysis session during the 12-week treatment phase.

The primary outcome of both studies was the percentage of patients who had a $\geq$ 3-point improvement at week 12 in the weekly mean score on the Worst Itch Numeric Rating Scale (WI-NRS).

Data presented are unsuitable for the benefit assessment

Implementation of the appropriate comparator therapy

In the KALM-1 and KALM-2 studies, anti-pruritus therapies were only allowed if they had been used with stable doses for at least 14 days before the start of the study. During the double-blind RCT phase, initiation of new therapies for pruritus or adjustments to existing therapies were not allowed. More than half of the patients in the comparator arm received no anti-pruritus therapy in the course of the study. Hence, treatment in the comparator arms of the studies KALM-1 and KALM-2 does not correspond to individualized therapy taking into account the respective prior therapies and the severity of the symptoms, and thus does not correspond to the ACT specified by the G-BA.

Study duration

The treatment duration in the double-blind randomized study phases of the KALM-1 and KALM-2 studies was only 12 weeks. Since difelikefalin is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis, and the SPC does not contain any information on discontinuation of the therapy after a certain period of time, long-term treatment is assumed, in accordance with the statements

of the G-BA in the consultation. Consequently, the studies KALM-1 and KALM-2 are to be considered unsuitable for the benefit assessment, as the study duration of only 12 weeks is too short. For the benefit assessment of difelikefalin versus the ACT in the therapeutic indication, comparing benefit and harm requires study durations of at least 24 weeks.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of difelikefalin in comparison with the ACT; an added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of added benefit[3] of difelikefalin.

Table 3: Difelikefalin – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult haemodialysis patients with moderate to severe chronic kidney disease–associated pruritus (CKD-aP)	Individualized therapy taking into account the respective prior therapies and the severity of the symptoms[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Adequate therapy of the underlying disease – in particular the implementation and optimization of haemodialysis – is assumed. With careful risk-benefit assessment, topical and/or systemic therapies may be considered as part of an individualized therapy: moisturizing and hydrating topicals, non-sedating systemic H1 antihistamines, UVB therapy, as well as gabapentin and pregabalin.

CKD: chronic kidney disease; CKD-aP: CKD-associated pruritus; G-BA: Federal Joint Committee; UVB: ultraviolet B radiation

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of the present report is to assess the added benefit of difelikefalin in comparison with individualized therapy as ACT in adult patients on haemodialysis with moderate-to-severe pruritus associated with chronic kidney disease.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of difelikefalin

Therapeutic indication	ACT[a]
Adult haemodialysis patients with moderate to severe chronic kidney disease–associated pruritus (CKD-aP)	Individualized therapy taking into account the respective prior therapies and the severity of the symptoms[b]

a. Presented is the ACT specified by the G-BA.
b. Adequate therapy of the underlying disease – in particular the implementation and optimization of haemodialysis – is assumed. With careful risk-benefit assessment, topical and/or systemic therapies may be considered as part of an individualized therapy: moisturizing and hydrating topicals, non-sedating systemic H1 antihistamines, UVB therapy, as well as gabapentin and pregabalin.

CKD: chronic kidney disease; CKD-aP: CKD-associated pruritus; G-BA: Federal Joint Committee; UVB: ultraviolet B radiation

The company did not follow the G-BA's specification of the ACT. It argued that no drugs were approved in the present therapeutic indication in Germany, that UVB therapy was the only option for non-drug treatment, and that there were no resolutions, assessments or recommendations of the G-BA as well as no generally valid or standardized therapy recommendations. Therefore, the company considered best supportive care as ACT.

Even though the current guideline on the diagnosis and therapy of chronic pruritus [3] does not provide a generally valid, consistent treatment recommendation for pruritus, it provides various treatment options, which are oriented towards the underlying causes and the patient characteristics and thus represent individualized therapies. Overall, the company's deviation from the ACT specified by the G-BA is not sufficiently justified and therefore not appropriate. However, the approach of the company does not have any consequences for the content of the present benefit assessment, as there are neither suitable studies of difelikefalin in comparison with the comparator therapy chosen by the company nor suitable studies of difelikefalin in comparison with the ACT specified by the G-BA.

Consequently, the present benefit assessment is conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of the added benefit. The company initially followed the inclusion criterion of at least 24 weeks in its information retrieval, but also stated that if no RCT with a study

duration of at least 24 weeks was identified, it would select the RCT with the longest study duration as the best available evidence (see Chapter I 3).

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on difelikefalin (status: 6 July 2022)
- bibliographical literature search on difelikefalin (last search on 6 July 2022)
- search in trial registries/trial results databases for studies on difelikefalin (last search on 4 July 2022)
- search on the G-BA website for difelikefalin (last search on 4 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on difelikefalin (last search on 18 October 2022); for search strategies, see I Appendix A of the full dossier assessment

The check for completeness of the study pool for the present benefit assessment identified no RCT allowing a direct comparison of difelikefalin versus the ACT.

The company also did not identify any RCT with a duration of at least 24 weeks, but presented data from the 12-week randomized study phases of the studies KALM-1 [4] and KALM-2 [5]. However, the studies KALM-1 and KALM-2 are unsuitable for the benefit assessment of difelikefalin versus the ACT. This is explained below.

In addition, the company presented the results of the single-arm study phases of the studies KALM-1 and KALM-2 as well as the results of the single-arm CLIN3101 study [5]. The treatment duration in each of these studies (or study phases) was 52 weeks. These data are not suitable for the benefit assessment due to the lack of comparison.

Evidence presented by the company – studies KALM-1 and KALM-2

The 2 studies KALM-1 and KALM-2 each consist of a 12-week double-blind RCT phase followed by a 52-week open-label, single-arm extension phase. Both studies enrolled adults with end-stage renal disease who were treated by haemodialysis 3 to a maximum of 4 times a week. Patients were required to have moderate to severe pruritus (defined as a weekly mean score of > 4 on the WI-NRS questionnaire) prior to study entry.

From the time of randomization, patients in both studies received either difelikefalin in compliance with the SPC [6] or placebo as an intravenous bolus injection after each dialysis session during the 12-week treatment phase.

The primary outcome of both studies was the percentage of patients who had a ≥ 3-point improvement at week 12 in the weekly mean score on the WI-NRS. Outcomes on morbidity, health-related quality of life and side effects were additionally recorded.

Data presented are unsuitable for the benefit assessment

Implementation of the appropriate comparator therapy

According to the G-BA's specification of the ACT, with careful risk-benefit assessment, topical and/or systemic therapies, such as moisturizing and hydrating topicals, non-sedating systemic H1 antihistamines, UVB therapy, as well as gabapentin and pregabalin, may be considered as part of an individualized therapy.

In the KALM-1 and KALM-2 studies, anti-pruritus therapies, including antihistamines and corticosteroids, as well as therapy with opioids, gabapentin or pregabalin, were only allowed if they had been used with stable doses for at least 14 days before the start of the study. During the double-blind RCT phase, initiation of new therapies for pruritus or adjustments to existing therapies were not allowed. UVB therapy was not allowed in both studies. During the study, only 49.7% (KALM-1) and 38.6% (KALM-2) of patients in the comparator arm received anti-pruritus therapy. Thus, more than half of the patients in the comparator arm received no anti-pruritus therapy in the course of the study. Hence, treatment in the comparator arms of the studies KALM-1 and KALM-2 does not correspond to individualized therapy taking into account the respective prior therapies and the severity of the symptoms, and thus does not correspond to the ACT specified by the G-BA.

Study duration

The treatment duration in the double-blind randomized study phases of the studies KALM-1 and KALM-2 was only 12 weeks and was therefore too short for a benefit assessment in the present therapeutic indication. The company itself specified a study duration of at least 24 weeks as inclusion criterion, but used the studies KALM-1 and KALM-2 as the best available evidence for the benefit assessment. The company argued that a shorter study duration could also be sufficient to observe rapid treatment effects. To demonstrate the long-term efficacy and safety of difelikefalin over a period of 52 weeks, the company referred to long-term data from the single-arm study phases of the studies KALM-1 and KALM-2 as well as the single-arm CLIN3101 study, which it presented as supplementary information.

Since difelikefalin is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis, and the SPC does not contain any information on discontinuation of the therapy after a certain period of time, long-term treatment is assumed, in accordance with the statements of the G-BA in the consultation [7]. Consequently, the studies KALM-1 and KALM-2 are to be considered unsuitable for the benefit assessment, as the study duration of only 12 weeks is too short. Pruritus associated with chronic kidney disease is a chronic condition.

For the benefit assessment of difelikefalin versus the ACT in the therapeutic indication, comparing benefit and harm requires study durations of at least 24 weeks.

I 4 Results on added benefit

No suitable data are available to assess the added benefit in comparison with the ACT for difelikefalin in adult patients on haemodialysis with moderate-to-severe pruritus associated with chronic kidney disease. There is no hint of an added benefit of difelikefalin in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of difelikefalin in comparison with the ACT.

Table 5: Difelikefalin – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult haemodialysis patients with moderate to severe chronic kidney disease–associated pruritus (CKD-aP)	Individualized therapy taking into account the respective prior therapies and the severity of the symptoms[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Adequate therapy of the underlying disease – in particular the implementation and optimization of haemodialysis – is assumed. With careful risk-benefit assessment, topical and/or systemic therapies may be considered as part of an individualized therapy: moisturizing and hydrating topicals, non-sedating systemic H1 antihistamines, UVB therapy, as well as gabapentin and pregabalin.

CKD: chronic kidney disease; CKD-aP: CKD-associated pruritus; G-BA: Federal Joint Committee; UVB: ultraviolet B radiation

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit based on the data from the double-blind study phases of the studies KALM-1 and KALM-2.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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