IQWiG Reports – Commission No. A21-111

Tirbanibulin (actinic keratosis) –

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

Extract

[1] Translation of Sections 2.1 to 2.4 of the dossier assessment *Tirbanibulin (aktinische Keratose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2021). Please note: This document was translated by an external translator and 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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No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

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

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Table of contents

List of tables[2]

Page

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

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)

2 Benefit assessment

2.1 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 tirbanibulin. 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 31 August 2021.

Research question

The aim of this report is to assess the added benefit of tirbanibulin in field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) of the face or scalp in adults in comparison with the appropriate comparator therapy (ACT).

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of tirbanibulin

Therapeutic indication	**ACT**[a]
Field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) of the face or scalp in adults	Diclofenac/hyaluronic acid gel (3%) or 5-fluorouracil or imiquimod or (surgical) cryotherapy for the treatment of individual lesions
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company has designated diclofenac/hyaluronic acid gel (3%) or 5-fluorouracil or imiquimod as options for the ACT, thereby agreeing with the G-BA regarding these options. It has excluded (surgical) cryotherapy of individual lesion from the ACT. This benefit assessment was conducted in comparison with the ACT specified by the G-BA.

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

Results

No relevant study was identified for assessing the added benefit of tirbanibulin in comparison with the ACT.

Company's approach

The company likewise reports not having found any relevant studies. Nevertheless, it has submitted the RCTs KX01-AK-003 and KX01-AK-004 as well as a comparison with published

data on the drug options of the ACT; from its overall consideration of these results, the company has derived a non-quantifiable added benefit.

KX01-AK-003 and KX01-AK-004 are 2 phase III randomized, double-blind approval studies of identical study design comparing tirbanibulin versus vehicle.

Since the studies did not carry out a comparison with the ACT, they are unsuitable for assessing added benefit.

For the comparison with published data on the drug options of the ACT, the company has submitted a descriptive comparison of pooled data from the respective treatment arms of the tirbanibulin studies KX01-AK-003 and KX01-AK-004 as well as from published data on the drug options of the ACT. These data are likewise unsuitable since the data compilation in the dossier's Module 4 A fails to meet the requirements of the dossier templates, in part due to the absence of a similarity check.

No suitable data are available for assessing the added benefit of tirbanibulin in comparison with the ACT specified by the G-BA. Consequently, there is no hint of added benefit of tirbanibulin in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of tirbanibulin.

Table 3: Tirbanibulin – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) of the face or scalp in adults	Diclofenac/hyaluronic acid gel (3%) or 5-fluorouracil or imiquimod or (surgical) cryotherapy for the treatment of individual lesions	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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].

2.2 Research question

The aim of this report is to assess the added benefit of tirbanibulin in field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) of the face or scalp in adults in comparison with the ACT.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of tirbanibulin

Therapeutic indication	**ACT**[a]
Field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) of the face or scalp in adults	Diclofenac/hyaluronic acid gel (3%) or 5-fluorouracil or imiquimod or (surgical) cryotherapy for the treatment of individual lesions
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company has designated diclofenac/hyaluronic acid gel (3%) or 5-fluorouracil or imiquimod as the ACT. It bases its designation of the ACT on a consultation dated 12 June 2019, where ingenol mebutate was cited as an additional option. Since ingenol mebutate is no longer on the market, the company excluded it as an ACT option. This approach is appropriate. Ingenol mebutate is not listed in the current version of the ACT. The company has also excluded the ACT option of (surgical) cryotherapy for the treatment of individual lesions because tirbanibulin is approved for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) on the face or scalp. Said approach of the company remains inconsequential because no relevant data are available on this option for the present benefit assessment. This benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving any added benefit. This deviates from the company's inclusion criteria, which did not specify any minimum duration.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on tirbanibulin (as of 6 July 2021)
- Bibliographic literature search on tirbanibulin (most recent search on 6 July 2021)
- Search in trial registries / study results databases on tirbanibulin (most recent search on 6 July 2021)
- Search on the G-BA website on tirbanibulin (most recent search on 6 July 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on tirbanibulin (most recent search on 3 September 2021); see Appendix A of the full dossier assessment for search strategies.

Concurring with the company, the check of the study pool did not identify any study which would allow a direct comparison with the ACT specified by the G-BA.

For assessing the medical benefit and added benefit of tirbanibulin, the company therefore used 2 vehicle-controlled RCTs (KX01-AK-003 and KX01-AK-004 [3-5]). However, said 2 RCTs are unsuitable for deriving any added benefit of tirbanibulin because they did not involve a comparison with the ACT.

Evidence provided by the company

Studies KX01-AK-003 and KX01-AK-004

KX01-AK-003 and KX01-AK-004 are twin studies sharing an identical study design and were conducted in the United States. They are phase III randomized, double-blind approval studies comparing tirbanibulin versus vehicle. They included adult patients with clinically typical, visible, and discrete actinic keratosis lesions on the face or scalp. Patients had to exhibit 4 to 8 lesions within a contiguous 25 cm² treatment area. In both studies, a total of 702 patients were randomized in a 1:1 ratio to the tirbanibulin arm (KX01-AK-003: N = 175; KX01-AK-004: N = 178) or the vehicle arm (KX01-AK-003: N = 176; KX01-AK-004: N = 173). Randomization was stratified by treatment localization (face versus scalp) in a 2:1 ratio.

Tirbanibulin treatment was administered in accordance with the Summary of Product Characteristics [6]. In both study arms, tirbanibulin ointment (1%) or vehicle was applied by patients themselves to a marked treatment field once daily on 5 consecutive days, constituting 1 treatment cycle. Any concomitant treatment of actinic keratosis within the treatment field was disallowed, as was the use of additional topical (cosmetic) products. Outside the treatment field, only lesion-directed procedures (e.g. cryotherapy, biopsy) were allowed. Exposure to direct sunlight or ultraviolet radiation was to be avoided. The use of sunscreen was allowed from

Day 15. The maximum initial study duration was 8 weeks for all patients; any patients showing complete clearance of actinic keratosis by Day 57 were eligible for up to 12 additional months of treatment.

The primary outcome of the studies was complete clearance of clinically visible actinic keratosis lesions by Day 57. Patient-relevant outcomes on morbidity and adverse events (AEs) were additionally surveyed.

Since the studies did not involve a comparison with the ACT, they are unsuitable for assessing added benefit.

Inappropriate derivation of added benefit by the company

The company used the studies KX01-AK-003 and KX01-AK-004 for deriving added benefit. The company concedes that, due to the absence of a direct comparison with the ACT, the studies do not fulfil the G-BA's formal requirements for evidence used to prove added benefit. It concludes that the extent of added benefit of tirbanibulin cannot be quantified on the basis of the efficacy and safety data. The company argues that the available data on tirbanibulin can nevertheless be used to derive hints of added benefit.

In addition, the company has submitted a comparison of pooled data from the respective treatment arms of the tirbanibulin studies KX01-AK-003 and KX01-AK-004 versus published data on the drug options of the ACT [7-11]. In said comparison, the company submits descriptive details for the individual outcomes "complete clearance of clinically visible actinic keratosis" and various local skin reactions and derives distinct advantages with regard to the occurrence of local skin reactions and systemic side effects of tirbanibulin in comparison with the drug options of the ACT.

The company's approach is not appropriate. The studies KX01-AK-003 and KX01-AK-004 are unsuitable for assessing the added benefit of tirbanibulin because they do not involve a comparison with the ACT. Nor do the available data from the tirbanibulin studies lend themselves to deriving a non-quantifiable added benefit as postulated by the company. The descriptive comparison of data from the tirbanibulin studies versus published data on the drug options of the ACT are likewise unsuitable for assessing added benefit. The data compilation in the dossier's Module 4 A does not fulfil the requirements of the dossier templates, in part due to the absence of a similarity check. Therefore, taken together, the data presented by the company are unsuitable for the assessment of tirbanibulin in comparison with the ACT.

Results on added benefit

No suitable data are available for assessing the added benefit of tirbanibulin in field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) of the face or scalp in adults in comparison with the ACT specified by the G-BA. Consequently, there is no hint of added benefit of tirbanibulin in comparison with the ACT; an added benefit is therefore not proven.

2.4 Probability and extent of added benefit

Table 5 presents a summary of the results of the assessment of added benefit of tirbanibulin in comparison with the ACT.

Table 5: Tirbanibulin – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) of the face or scalp in adults	Diclofenac/hyaluronic acid gel (3%) or 5-fluorouracil or imiquimod or (surgical) cryotherapy for the treatment of individual lesions	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived a hint of non-quantifiable added benefit.

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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