Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Tirbanibulin (actinic keratosis, Olsen grade I)

of 17 February 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient tirbanibulin in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 September 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 26 August 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 December 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of tirbanibulin compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements

submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tirbanibulin.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Tirbanibulin (Klisyri) according to product information

Klisyri is indicated for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults.

Therapeutic indication of the resolution (resolution of 17.02.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Adults with non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp:</u>

- Diclofenac hyaluronic acid gel (3%) or 5-fluorouracil (5 FU) or (surgical) cryotherapy for the treatment of solitary lesions

<u>Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:</u>

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In the therapeutic indication for the treatment of actinic keratosis, the following active ingredients are generally approved:
- diclofenac in hyaluronic acid gel (topical)
- 5-fluorouracil (5-FU) (topical)
- 5-fluorouracil plus salicylic acid (topical)
- imiquimod (topical)
- aminolevulinic acid (as part of photodynamic therapy)
- methyl aminolevulinate (as part of photodynamic therapy)

on 2. In the present therapeutic indication of actinic keratosis, cryotherapy, curettage, surgical excision and chemical peeling are basically considered as non-medicinal treatment.

on 3. In the therapeutic indication considered here, a benefit assessment resolution according to Section 35a SGB V was adopted on 21 February 2019 for the active ingredient ingenol mebutate (based on new scientific knowledge). However, on 6 July 2020, the European Commission made a legally binding decision to revoke the marketing authorisation of the active ingredient ingenol mebutate, so that the benefit assessment resolution on ingenol mebutate was revoked by resolution of 20 August 2020.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

For the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults, diclofenac hyaluronic acid gel (topical) and 5-fluorouracil (topical) are available according to the respective approved therapeutic indication. When considering the body of evidence, 5-fluorouracil tended to be rated better than diclofenac hyaluronic acid based on available studies to determine recurrence rates. This has to be contrasted with the increased side effect potential of 5-fluorouracil compared to diclofenac hyaluronic acid gel (3%). Overall, both therapy options are therefore recommended for the treatment of actinic keratosis.

Medicinal products with the active ingredients 5-fluorouracil plus salicylic acid (topical), imiquimod (topical) as well as aminolevulinic acid and methyl aminolevulinate (each in the context of photodynamic therapy) are classified as lower-ranking therapy options compared to the active ingredients diclofenac hyaluronic acid and 5-fluorouracil.

Against the background that the treatment of multiple solitary lesions and field treatment cannot always be clearly distinguished from each other in clinical practice, the treatment of solitary lesions is also considered an option in the therapeutic indication to be assessed. Here, the G-BA considers non-medicinal (surgical) cryotherapy for solitary lesions to be an appropriate therapy option that has been proven in practical application.

In the overall assessment, diclofenac hyaluronic acid gel (3%) and 5-fluorouracil as well as (surgical) cryotherapy for solitary lesions are therefore considered relevant and equally appropriate treatment options.

Change of the appropriate comparator therapy

The originally named appropriate comparator therapy for adults with non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp also included the active ingredient imiquimod. The active ingredient imiquimod is approved for the treatment of clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratosis of the face or scalp in immunocompetent adults when the size or number of lesions limits the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate. Consequently, the active ingredient imiquimod is not a first-line therapy for the treatment of actinic keratosis according to the marketing authorisation. It also became clear in the course of the written statement procedure that imiquimod is to be regarded as a lower-ranking therapy option in care due to the side effects profile compared to a therapy with diclofenac hyaluronic acid or 5-fluorouracil.

For this reason, the G-BA considers it appropriate to adjust the appropriate comparator therapy and not to determine the active ingredient imiquimod as an appropriate comparator therapy in the present therapeutic indication.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of tirbanibulin is assessed as follows:

Adults with non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp

An additional benefit is not proven.

Justification:

No direct comparator studies are available for tirbanibulin versus the appropriate comparator therapy.

The pharmaceutical company presents data from the two marketing authorisation studies *KX01-AK-003* and *KX01-AK-004* in the dossier. These studies are randomised, double-blind phase III studies with identical study designs that investigated tirbanibulin versus active ingredient-free base (vehicle). Adults with clinically typical, visible and discrete actinic

keratosis of the face or scalp were enrolled, and patients had to have 4 to 8 lesions within a contiguous treatment area of 25 cm². In both studies, a total of 702 adults were randomised in a 1:1 ratio to the treatment arms tirbanibulin *(KX01-AK-003*: N = 175; *KX01-AK-004*: N = 178) and vehicle (*KX01-AK-003*: N = 176; *KX01-AK-004*: N = 173). Randomisation was stratified by treatment site (face or scalp) in a 2:1 ratio.

Treatment with tirbanibulin or vehicle was self-administered by patients in both study arms for a treatment cycle of 5 consecutive days, 1-time per day within a marked treatment area. Concomitant treatment to actinic keratosis therapy within the treatment area was not permitted. The maximum study duration after the start of treatment was 8 weeks. The primary endpoint of the studies was complete healing of clinically visible actinic keratosis at day 57. In addition, patient-relevant endpoints on morbidity and adverse events (AEs) were assessed.

As no active comparison was made in either study with the appropriate comparator therapy, they are not suitable for assessing an additional benefit of tirbanibulin. In addition, a study duration of 8 weeks is considered too short in the present therapeutic indication.

In addition, the pharmaceutical company therefore presents a descriptive comparison of pooled data of the respective treatment arms from the two tirbanibulin studies *KX01-AK-003* and *KX01-AK-004* in comparison to published data of medicinal products of the appropriate comparator therapy. These data are also not suitable for deriving an additional benefit, as the preparation of the data presented does not meet the methodological requirements, among other things, a similarity test is missing.

In the overall assessment, the pharmaceutical company thus does not present any relevant data for the benefit assessment. An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Klisyri with the active ingredient tirbanibulin. The active ingredient is approved for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) on the face or scalp in adults.

The G-BA determined diclofenac hyaluronic acid gel (3%) or 5-fluorouracil (5-FU) or (surgical) cryotherapy as appropriate comparator therapy in the treatment of solitary lesions.

For this patient group, the pharmaceutical company submits the two marketing authorisation studies *KX01-AK-003* and *KX01-AK-004*, in which tirbanibulin was investigated in each case against an active ingredient-free base (vehicle). However, direct comparator data of tirbanibulin versus the appropriate comparator therapy are missing.

The additionally presented descriptive comparison of data from the two tirbanibulin studies in comparison with published data from medicinal products of the appropriate comparator therapy are also not suitable for assessing the additional benefit, as the preparation of the data presented does not meet the methodological requirements.

In the overall assessment, the pharmaceutical company thus does not present any relevant data for the benefit assessment. An additional benefit is therefore not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the estimate of patient numbers derived by the pharmaceutical company in the dossier. However, the derivation of patient numbers is subject to uncertainty on the whole. This results in particular from the obsolete data on the prevalence of the relevant disease and the lack of valid data on the percentage of non-hyperkeratotic, non-hypertrophic actinic keratosis.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Klisyri (active ingredient: tirbanibulin) at the following publicly accessible link (last access: 29 November 2021):

https://www.ema.europa.eu/en/documents/product-information/klisyri-epar-product-information_en.pdf

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2022).

For cost representation, one treatment cycle is assumed for all medicinal products. This does not take into account the fact that treatment may be discontinued prematurely due to non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients must be taken into account when using the medicinal products.

Tirbanibulin ointment (Klisyri®) should be applied to the treatment area on the face or scalp 1-time daily for a treatment cycle of 5 consecutive days. The ointment should be applied in a thin layer to the treatment area of up to 25 cm^2.

The treatment of actinic keratosis with diclofenac hyaluronic acid gel 3% is usually intended for a period of 60 to 90 days with 0.5 g gel each twice daily; analogously, according to the product information, 5-fluorouracil cream (Tolak®) is used once daily for a treatment period of 4 weeks. The product information of diclofenac hyaluronic acid gel (3%) and 5-fluorouracil cream do not contain any information on the repetition of a treatment cycle.

Tirbanibulin, diclofenac hyaluronic acid and 5-fluorouracil are each applied topically. The size of the treatment area depends on the spread of the actinic keratosis. The annual treatment costs per patient are standardised for a treatment area of 25 cm^2 and one treatment cycle per year. This does not affect the treatment of larger or multiple areas or the implementation of multiple treatment cycles according to the respective product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirbanibulin	1 x daily	1	5	5
Appropriate comparator therapy				
Diclofenac hyaluronic acid gel (3%)	2 x daily	1	60 - 90	60 - 90
5-fluorouracil (Tolak®)	1 x daily	1	28	28
(Surgical) cryotherapy	No specification possible			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirbanibulin ointment	250 mg ointment ≙ 2.5 mg tirbanibulin (per sachet)	250 mg	1 x 250 mg	5	5 x 250 mg ointment
Appropriate comparator therapy					
Diclofenac hyaluronic acid gel (3%)	0.5 g gel ≙ 15 mg diclofenac	1 g	2 x 0.5 g	60 - 90	120 - 180 x 0.5 g gel
5-fluorouracil cream (Tolak®)	0.5 g cream ≙ 20 mg 5 FU	0.5 g	1 x 0.5 g	28	28 x 0.5 g cream
(Surgical) cryotherapy	No specification possible				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of usage. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tirbanibulin (ointment)	5 sachets (each 250 mg ointment)	€ 120.01	€ 1.77	€ 6.02	€ 112.22
Appropriate comparator therapy					
Diclofenac hyaluronic acid (gel, 3%)	90 g	€ 95.00	€ 1.77	€ 3.97	€ 89.26
5-Ffuorouracil (cream; Tolak®)	20 g	€ 80.47	€ 1.77	€ 3.28	€ 75.42
(Surgical) cryotherapy[2]	No specification possible				

LAUER-TAXE® last revised: 1 February 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

[2] Cryotherapy is covered by the basic flat rate for insured persons.

4. Process sequence

At its session on 12 June 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

Due to the withdrawal of the marketing authorisation for the active ingredient ingenol mebutate, the Subcommittee on Medicinal Products adapted the appropriate comparator therapy in its session on 25 February 2020.

On 26 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of tirbanibulin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 August 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient tirbanibulin.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2021. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 June 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	25 February 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 January 2022	Conduct of the oral hearing
Working group Section 35a	19 January 2022 2 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken