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) Polihexanide (Acanthamoeba keratitis, ≥ 12 years)

of 20 March 2025

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Gemeinsamer Bundesausschuss

1. Legal basis

According to Section 35a paragraph 6 SGB V, the G-BA can initiate a benefit assessment according to paragraph 1 for a medicinal product with an active ingredient that is not a new active ingredient according to Section 35a paragraph 1, if a new marketing authorisation with new dossier protection is granted for the medicinal product. According to Chapter 5 Section 16, paragraph 1, sentence 3 of the Rules of Procedure of the G-BA, a benefit assessment according to Section 35a paragraph 6 SGB V can be initiated in particular for medicinal products whose therapeutic indication differs from the therapeutic indication of medicinal products with the same known active ingredients. According to Chapter 5 Section 16, paragraph 1, sentence 4 of the Rules of Procedure of the G-BA, a deviation may result in particular from changes in a therapeutic indication that are attributable to a different therapeutic indication compared to the therapeutic indication of the medicinal product with the same known active ingredient, by the fact that:

– the therapeutic indication relates to a different group of patients or

– the therapeutic area (treatment, diagnosis or prevention) differs.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis

for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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

At their session on 21 April 2022, the Federal Joint Committee (G-BA) decided to initiate a benefit assessment for the active ingredient polihexanide in the indication Acanthamoeba keratitis; ≥ 12 years according to Section 35a, paragraph 6 SGB V in conjunction with Chapter 5 Section 16, paragraph 1 VerfO.

The medicinal product Akantior, containing the active ingredient polihexanide, was first placed on the market on 1 October 2024. Relevant date according to Chapter 5, Section 8, paragraph 1, number 7 of the Rules of Procedure of the G-BA (VerfO) for the start of the assessment procedure for the active ingredient polihexanide is within three months of the request by the G-BA. If the medicinal product has not yet been placed on the market at that time, the procedure shall start on the date on which it is first placed on the market.

The final dossier was submitted to the G-BA in due time on 30 September 2024. On 1 October 2024, the assessment procedure started.

Polihexanide for the treatment of Acanthamoeba keratitis, ≥ 12 years is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 2 January 2025 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA adopted its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and

patient numbers and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of polihexanide.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Polihexanide (Akantior) in accordance with the product information

AKANTIOR is indicated for the treatment of Acanthamoeba keratitis in adults and children from 12 years of age.

Therapeutic indication of the resolution (resolution of 20 March 2025):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

For patients from 12 years of age with Acanthamoeba keratitis, there is a hint for a non-quantifiable additional benefit of polihexanide, since the scientific data does not allow a quantification.

Justification:

For the benefit assessment, the pharmaceutical company submitted the data from the intervention arm of the label-enabling 043/SI study. They also present an indirect comparison in the dossier based on historical control data.

043/SI study

The 043/SI study is a randomised, double-blind, phase III study investigating the efficacy, safety and tolerability of polihexanide (0.8 mg/ml) versus polihexanide (0.2 mg/ml) and propamidine (1 mg/ml) as combination therapy in subjects with Acanthamoeba keratitis.

Adults and adolescents from 12 years of age who were diagnosed with Acanthamoeba keratitis by clinical and confocal microscopic findings were enrolled. Patients with extensive-stage Acanthamoeba keratitis and indication for urgent surgical intervention were excluded.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

A total of 135 subjects were enrolled in the study, 69 of them in the intervention arm and 66 in the control arm. Acanthamoeba keratitis was subsequently confirmed by laboratory diagnosis in 66 of the subjects in the intervention arm and 61 in the control arm.

The primary endpoint of the study was the clinical cure rate within 12 months of randomisation.

Analysis of the uncontrolled data from the intervention arm of the 043/SI study

With reference to the marketing authorisation justification of the *European Medicines Agency* (EMA), the pharmaceutical company only presented the uncontrolled results of the intervention arm of the 043/SI study in the dossier.

The EMA considered the limitations of the study design of the 043/SI study to be so far-reaching, particularly due to the choice of treatment in the comparator arm, that the proof of efficacy of the intervention by means of the randomised controlled trial (RCT) was not considered to have been provided (see European Public Assessment Report [EPAR][2]). Criticism of the comparator is based in particular on the fact that it is a non-approved therapy whose clinical effects and relevance in medical care are unclear. In addition, no rationale was provided for the dosage regimen used. Ultimately, the uncontrolled results of the intervention arm of the 043/SI study were taken into account for the decision on the marketing authorisation.

In the overall assessment, the comparator data of the 043/SI study do not provide any additional information for assessment of the additional benefit, so that the RCT is not presented in the benefit assessment.

Against this background, only the data based on the intervention arm of the 043/SI study were considered for the present benefit assessment.

Indirect comparison

In the dossier, the pharmaceutical company presented an indirect comparison based on historical control data and the intervention arm of the 043/SI study for the primary endpoint "clinical cure rate within 12 months".

For the comparator arm of the indirect comparison, data based on historical case reports of 56 patients with Acanthamoeba keratitis who did not receive amoebicidal treatment were included. It is unclear how this data was identified. Inclusion and exclusion criteria were not described. According to the EPAR, the case reports were collected between 1970 and 1998. Apart from information on age and sex, there is no information on essential baseline characteristics such as disease severity or time to diagnosis. However, it can be assumed on the basis of the available information on surgical interventions that the population in the comparator arm was at a more advanced stage of the disease than in the intervention arm of the indirect comparison. Overall, sufficient comparability between the study population to be compared and the historical control population cannot therefore be assumed.

Other serious shortcomings are the lack of concurrence, the unclear operationalisation of the endpoint presented in the comparator arm, the lack of basic information on the propensity score model presented and the inappropriate selection of confounders. The length of the

[2] Akantior - EPAR of 25.07.2024, available at: https://www.ema.europa.eu/en/documents/assessment-report/akantior-epar-public-assessment-report_en.pdf [last revised 13.03.2025]

follow-up period in the comparator arm is also unclear. If the follow-up period is too short, the percentage of subjects with a cure without amoebicidal treatment may be underestimated and cannot be compared with the clinical cure rate within 12 months in the 043/SI study.

In the overall assessment, the indirect comparison is therefore not used for the benefit assessment.

Mortality

Overall mortality was assessed as part of the safety assessment. There was no death in the 043/SI study.

Morbidity

Clinical cure rate

In the 043/SI study, the "clinical cure rate within 12 months" was defined as the primary endpoint as follows: Percentage of subjects who were cured 30 days after discontinuation of all study therapies within 12 months of enrolment in the study. A subject was considered cured when the disappearance or absence of all of the following clinical signs was confirmed by a slit lamp examination performed by study personnel:

- No corneal inflammation requiring treatment (including subepithelial infiltrates, stromal infiltrates and oedema) with healed corneal epithelium and minimal dot discolouration (10 dots or less, corresponding to grade 1 on the Oxford scale)
- Mild conjunctivitis or none (including bulbar injection, bulbar oedema, tarsal hyperaemia): Mild conjunctivitis is acceptable if it is associated with other concomitant diseases such as blepharitis.
- No limbitis, scleritis or inflammation of the anterior chamber of the eye.
- No recurrence within 30 days after discontinuation of all topical and systemic therapy for Acanthamoeba keratitis.

Against the background of the curative therapeutic approach, the percentage of patients who achieve a cure for Acanthamoeba keratitis is considered to be patient-relevant.

However, the present operationalisation of the composite endpoint only represents a partial aspect of clinical cure, i.e. essentially, the eradication in association with the clinical remission of inflammation and healing of the corneal epithelium corresponding to a clinical response rate. This is a primary therapeutic goal with significant clinical relevance.

In order to be able to comprehensively assess the clinical cure of affected subjects, data on the remission of inflammation in the eye and healing of the corneal epithelium, as well as results on the restoration of visual function, are required in addition to data collected using imaging procedures. This is considered to be particularly significant in view of the fact that more than half of the patients had corneal scarring at the end of the study. Against the background of the symptomatic course of the disease, effects should also be reflected in the assessment of symptoms such as pain, burning or itching.

In addition, the observation of recurrences over a period of 30 days is considered too short for a conclusive assessment of the clinical cure rate. In this regard, the pharmaceutical company however stated during the oral hearing that no recurrences occurred during the 3-month follow-up after the end of treatment.

In the overall assessment, no statement on the extent of additional benefit can be made based on the present operationalisation of the endpoint "clinical cure rate within 12 months". The endpoint is therefore only presented additionally.

In the present analysis, only the data of those subjects with confirmed Acanthamoeba keratitis were taken into account ("efficacy population"; n = 66). Analyses including the intention-to-treat (ITT) population (n = 69) are not available.

In the intervention arm of the 043/SI study, the "clinical cure rate" was 84.8%.

Health status

Health status was assessed using the visual analogue scale (VAS) of the European Quality of Life 5-Dimension (EQ-5D) and the subscale of the Visual Function Questionnaire-25 (VFQ-25) on general health status (see explanations below).

As no MMRM or responder analyses and no analyses with the ITT population were submitted, the change in the mean value from baseline to the end of the study for the efficacy population specified by the pharmaceutical company was presented in the resolution.

The time of the end of the study is different for each participating subject who has achieved a cure. Patients who did not achieve a clinical cure of the underlying infection were followed up for the full duration of the study.

The mean value of the EQ-5D VAS was 69.8 at baseline and improved by 17.9 at the end of the study. In the VFQ-25 subscale of general health status, the mean value at baseline was 61.7 and changed by 12.9 at the end of the study. In both instruments, a score of 100 represents the best possible health status and a score of 0 the worst possible.

Overall, no statements on the extent of the additional benefit of polihexanide in the morbidity category can be made due to a lack of comparator data.

Quality of life

In the 043/SI study, the "Visual Function Questionnaire-25" (VFQ-25) was used to assess the impact of potential corneal events on function and health-related quality of life.

The VFQ-25 is a questionnaire for self-assessment of visual acuity-related quality of life, consisting of a total of 26 items and 12 subscales. Of these, 25 items (11 subscales) ask about vision and 1 item (1 subscale) about general health. The subscale on general health status is assigned to the morbidity category (see further above). The reference period is undetermined.

The values of all items are transformed to a score from 0 to 100 and a score averaged over the items of the subscale is calculated for each subscale. The summary score finally results from the mean of the averaged scores of the subscales. The general health subscale is not included here. The summary score of the VFQ-25 can take values between 0 and 100 points, with higher values indicating a better visual acuity-related quality of life.

As no MMRM or responder analyses and no analyses with the ITT population were submitted, the change in the mean value from baseline to the end of the study for the efficacy population was presented in the resolution.

At baseline, the mean value of the VFQ-25 summary scale was 64.9 points and improved by 23.5 points at the end of the study.

Due to the lack of comparison, no statement can however be made on the extent of the additional benefit for health-related quality of life.

Side effects

In the 043/SI study, adverse events (AEs) were collected until the end of the study for each participating subject. The median treatment duration is 120 days (min: 10; max: 387). The AEs were analysed without taking into account the events of the underlying diseases.

AEs occurred in 45% of patients in the intervention arm. The results were only presented additionally. One severe AE (CTCAE grade ≥ 3) occurred in 6% of the study participants in the intervention arm and no serious AE occurred in any of them. Overall, 10% of the ITT population discontinued the study due to an AE.

Due to the single-arm data basis, it is not possible to assess the extent of the additional benefit for the side effects category.

Overall assessment

The present benefit assessment is based on the label-enabling data of the intervention arm of the blinded, controlled, multicentre phase III 043/SI study. The comparator data from this study do not provide any additional information for assessment of the additional benefit.

Results on mortality, health status, health-related quality of life and side effects are available. However, due to the lack of comparison, it is not possible to quantify the extent of the additional benefit on the basis of these data.

The indirect comparison presented in the dossier for the endpoint "clinical cure rate within 12 months" is not used for the present benefit assessment. The main reason for this is that sufficient similarity between the study population and the control population used cannot be assumed on the basis of the available data. For the comparator arm, important information in particular on disease severity at the start of treatment and other baseline characteristics, on the observation period, on the propensity score model used and on the operationalisation of the endpoint assessed is missing. Moreover, the lack of concurrence is another critical aspect.

Overall, a non-quantifiable additional benefit of polihexanide is derived since the scientific data does not allow quantification.

Significance of the evidence

Only single-arm data could be considered for the benefit assessment. The risk of bias of the single-arm study data is estimated to be high at study and endpoint level. In addition, results-driven reporting cannot be ruled out against the background that a randomised controlled trial was planned, but only the intervention arm was considered in the present study.

The significance of the evidence is classified as 'hint'.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Akantior with the active ingredient polihexanide. Akantior was approved as an orphan drug for the treatment of Acanthamoeba keratitis in patients from 12 years of age.

The present benefit assessment is based on the label-enabling data of the intervention arm of the blinded, controlled, multicentre phase III 043/SI study.

The indirect comparison presented by the pharmaceutical company for the endpoint "clinical cure rate within 12 months" is not used for the present benefit assessment. The main reason for this is that sufficient similarity between the study population and the control population used cannot be assumed on the basis of the available data. For the comparator arm, important information in particular on disease severity at the start of treatment and other baseline characteristics, on the observation period, on the propensity score model used and on the operationalisation of the endpoint assessed is missing. Moreover, the lack of concurrence is another critical aspect.

Data on mortality, health status and health-related quality of life collected using the Visual Function Questionnaire-25 (VFQ-25) and on side effects are available for the intervention arm of the 043/SI study. However, due to a lack of comparison, it is not possible to quantify the extent of the additional benefit on the basis of these data.

In the overall assessment, the G-BA classifies the extent of the additional benefit as non-quantifiable since the scientific data does not allow quantification.

Against the background of uncontrolled results and possible results-driven reporting, the reliability of data is assessed as a hint.

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 patient numbers stated by the pharmaceutical company in the dossier are underestimated for the lower limit and subject to uncertainty for the upper limit. The main reasons for this are an underestimated incidence rate for the lower limit in comparison with other sources, the limitation to incidence as well as uncertainties regarding the percentage of contact lens wearers.

The resolution is therefore based on the calculations by IQWiG from the dossier assessment (mandate G24-26). The calculation was based on a current systematic review[3], but without limitation to the age of 12 years and above. However, it is assumed that the limitation to the age of 12 years and above according to the therapeutic indication will not lead to a significant reduction in the number of patients.

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 Akantior (active ingredient: polihexanide) at the following publicly accessible link (last access: 4 December 2024):

[3] Aiello F, Gallo Afflitto G, Ceccarelli F et al. Perspectives on the Incidence of Acanthamoeba Keratitis; A Systematic Review and Meta-Analysis; Article in Press. Ophtalmology 2024. https://doi.org/10.1016/j.ophtha.2024.08.003.

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

Treatment with polihexanide should only be initiated and monitored by doctors experienced in the therapy of Acanthamoeba keratitis.

Akantior must be discontinued in patients who are not cured within 12 months of starting treatment.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2025).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Treatment of Acanthamoeba keratitis with polihexanide is a therapy limited to a maximum of 12 months. Initially, intensive treatment is given over a period of 19 days. Follow-up treatment is then carried out until cure or the maximum treatment duration is reached. As the treatment duration with polihexanide differs from patient to patient, a range of minimum treatment durations from a total of 20 days (one day of subsequent therapy) to a maximum treatment duration of 365 days (346 days of subsequent therapy) is shown. According to the product information, the 19-day intensive treatment phase can be resumed in the event of deterioration or exacerbation of the ocular inflammation during the follow-up treatment and the Acanthamoeba culture is negative. Actual consumption may therefore also be higher patient-individually.

The costs for the treatment of one eye are taken into account.

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: Polihexanide				
Initial treatment phase (19 days)				
Day 1 - 5	16x daily for 5 weeks	1	5	5
Day 6 - 12	8x daily for 7 weeks	1	7	7
Day 13 - 19	6x daily for 7 weeks	1	7	7
Follow-up treatment (duration differs from patient to patient)				
	4x daily for 1 day up to 346 days	1	1 - 346	1 - 346

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: Polihexanide					
Initial treatment phase					
Day 1 - 5	0.025 mg	0.4 mg	16 x 0.025 mg	5	80 x 0.025 mg
Day 6 - 12	0.025 mg	0.2 mg	8 x 0.025 mg	7	56 x 0.025 mg
Day 13 - 19	0.025 mg	0.15 mg	6 x 0.025 mg	7	42 x 0.025 mg
Follow-up treatment					
	0.025 mg	0.1 mg	4 x 0.025 mg	1 - 346	4 x 0.025 mg - 1384 x 0.025 mg

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 consumption. 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Patients from 12 years of age with Acanthamoeba keratitis

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					
Polihexanide	120 Egtts	€ 34,843.02	€ 1.77	€ 1,986.60	€ 32,854.65
Polihexanide	30 Egtts	€ 8,754.00	€ 1.77	€ 496.65	€ 8,255.58
Abbreviations: Egtts = eye drops					

LAUER-TAXE® last revised: 1 March 2025

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.

No additionally required SHI services are taken into account for the cost representation.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1

SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients from 12 years of age with Acanthamoeba keratitis

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for polihexanide (Akantior); Akantior 0.8 mg/ml eye drops, solution in a single-dose container; last revised: August 2024

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.

4. Process sequence

On 30 September 2024, the pharmaceutical company submitted a dossier for the benefit assessment of polihexanide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 7, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 2 January 2025 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 23 January 2025.

The oral hearing was held on 10 February 2025.

An amendment to the benefit assessment with a supplementary assessment (here only if aspects actually submitted in written statement were reassessed: from data submitted in the written statement procedure) was submitted on 27 February 2025.

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 11 March 2025, and the draft resolution was approved.

At its session on 20 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	17 December 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	5 February 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 February 2025	Conduct of the oral hearing
Working group Section 35a	19 February 2025 5 March 2025	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 March 2025	Concluding discussion of the draft resolution
Plenum	20 March 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 March 2025

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

Prof. Hecken