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
Sirolimus (facial angiofibroma associated with tuberous sclerosis complex, ≥ 6 years)

of 21 March 2024

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.

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 German Social Code, Book Five (SGB V). 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 its session on 16 February 2023, the G-BA decided to initiate a benefit assessment for the active ingredient sirolimus in the indication "Treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and children aged 6 years and older" in accordance with Section 35a paragraph 6 SGB V in conjunction with Chapter 5 Section 16 paragraph 1 VerfO.

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient sirolimus on 1 October 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 17 August 2023.

Sirolimus for the treatment of facial angiofibroma associated with tuberous sclerosis complex is approved as a medicinal product for the treatment of rare diseases in accordance with 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 evaluate 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 2024 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 made 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 (IQWiG G23-28) 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 approval 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 sirolimus.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Sirolimus (Hyftor) in accordance with the product information

Hyftor is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older.

Therapeutic indication of the resolution (resolution of 21.03.2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex

For sirolimus for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older, there is a hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

Justification:

The benefit assessment is based on the pivotal approval study NPC-12G-1, the dose escalation study OSD-001-001 and the single-arm long-term study NPC-12G-2.

The NPC-12G-1 study is a multicentre, stratified, randomised, double-blind, placebo-controlled phase III study in a parallel-group design in children and adults with angiofibroma associated with TSC. The study was only conducted in study sites in Japan. The study participants had to have a confirmed diagnosis of tuberous sclerosis complex (TSC) according to Northrup and Krueger and have 3 or more reddish angiofibroma papules on the face at screening. In addition, patients may either not be eligible for laser therapy or surgery or may not want these therapy options. A total of 62 patients were enrolled in the study, who were randomised in a 1:1 allocation ratio stratified by age group. The treatment took place over a period of 12 weeks. The primary endpoint of the study was the combined improvement in angiofibromas by means of photographs at week 12 according to the IRC (Independent Review Committee).

The OSD-001-001 study is a single-centre, stratified, randomised, double-blind, placebo-controlled dose escalation study in parallel group design in children and adults with angiofibroma associated with TSC. The study was only conducted in a study site in Japan. The study participants had to have a confirmed diagnosis of tuberous sclerosis complex (TSC) according to the guidelines of the Japanese Dermatological Association and have 3 or more reddish angiofibroma papules on the face at screening. In addition, patients may either not be eligible for laser therapy or surgery or may not want these therapy options. A total of 36 patients were enrolled in the study, of which 8 study participants received the dosage of sirolimus in accordance with the product information (12 participants received placebo). The treatment took place over a period of 12 weeks. The primary endpoint of the study was the combined improvement in angiofibromas at week 12 according to the principal investigator.

The NPC-12G-2 study is an open-label, uncontrolled, multicentre, single-arm, long-term study in which both study participants from the NPC-12G-1 study after the end of study and newly registered subjects were enrolled. The inclusion and exclusion criteria essentially correspond to those of the NPC-12G-1 study. A total of 94 patients were enrolled in the study. The treatment took place over a period of 52 weeks.

The results of the 12-week randomised double-blind phase of the approval study NPC-12G-1 and the OSD-001-001 study were used for the benefit assessment. The data from the long-term study NPC-12G-2 are presented additionally.

Mortality

No deaths occurred in any of the studies.

Morbidity

The improvement in angiofibromas on the face is generally a patient-relevant endpoint. In the dossier, the pharmaceutical company presents endpoint surveys with different operationalisations "combined improvement in angiofibromas" and "improvement in angiofibromas according to IFA".

Combined improvement in angiofibromas (presented additionally)

The "combined improvement in angiofibromas" was the primary endpoint in the NPC-12G-1 and OSD-001-001 studies. This endpoint was also collected in the single-arm long-term study NPC-12G-2.

The combined improvement in angiofibromas was assessed at week 12 in the NPC-12G-1 and OSD-001-001 studies and at week 52 in the NPC-12G-2 study. The composite endpoint consists of the individual components "improvement in the size of the angiofibromas" and "improvement in the redness of the angiofibromas, assessed using the Pantone colour scale".

In the NPC-12G-1 and NPC-12G-2 studies, the improvement in angiofibromas was assessed on the basis of photographs. The photographs of each lesion are recorded together with a colour scale with a scale bar for the planned study visits. If possible, the photographs should be taken by the same person at the respective study visits. The camera as well as the training in handling are provided by the sponsor.

In the NPC-12G-1 and NPC-12G-2 studies, the photographs are assessed by an independent review committee (IRC). The members of the IRC consist of dermatologists who were blinded with regard to treatment allocation and were not involved in the treatment or implementation process of the studies. The improvement in the size of the angiofibromas and the reddening of the angiofibromas is assessed by the IRC. Only the skin areas on which the test preparation was applied were assessed.

In the dossier, the pharmaceutical company specifies post hoc that an improvement compared to the start of study is defined as achieving a score of 2 (improved) or 3 (significantly improved).

In the OSD-001-001 study, the combined improvement in angiofibromas at week 12 was assessed by the investigators. The fact that the assessment should be carried out by investigators is reported exclusively in the dossier. The endpoint comprises the same individual components as in the NPC-12G-1 and NPC-12G-2 studies. However, the assessment is based exclusively on the 3 largest tumours at separated sites from isolated papules with a longitudinal diameter of at least 2 mm. The assessment of the improvement in the size of the

angiofibromas and the reddening of the angiofibromas is carried out by the investigators according to defined criteria. A score for the combined improvement in angiofibromas is calculated by adding up both individual components. Positive values indicate an improvement in the angiofibromas. According to the information in the dossier, module 4, a maximum improvement value of 4 (significantly improved in size and redness) and a minimum value of -2 (exacerbated in size and redness) can be achieved based on the criteria pre-specified in the study documents. In the dossier, the pharmaceutical company specifies post hoc that the improvement at week 12 compared to the start of study is defined as achieving a score of 1.5 (improved) or higher.

The operationalisation of the endpoint is not fully comprehensible in the NPC-12G-1 and NPC-12G-2 studies as well as in the OSD-001-001 study. The assessment and evaluation of the size and redness of facial angiofibromas is based on different defined criteria. However, there is no information on the validation of these criteria or the assigned categories and scores.

The measurement instrument of combined improvement in angiofibromas has limitations in the different operationalisations in the NPC-12G-1, NPC-12G-2 and OSD-001-001 studies. Overall, the measurement instrument is therefore not considered in the benefit assessment, but is presented additionally.

Improvement in angiofibromas according to IFA (Index for facial angiofibromas)

The post hoc evaluated endpoint "improvement in angiofibromas according to IFA" is defined in the NPC-12G-1 study as an assessment of angiofibromas using the "Index for Facial Angiofibromas" (IFA). The assessment is carried out retrospectively by an independent evaluation committee (IEC) on the basis of photographs (3 per visit) taken for the primary endpoint. The members (n = 3) were assessed independently of each other and blinded to the treatment and only for the visits at baseline and week 12 (randomised allocation). Finally, an overall IFA value was generated as the mean value of the individual IEC assessments. The IFA was developed to assess minor changes and improvement in facial angiofibromas in a numerical value. The size, redness and extent of angiofibromas are assessed using a 20-point scoring system distributed among 8 items. The total value is calculated by adding the individual values and can be between 0 and 20 points, with higher values indicating a severe disease burden. Only the skin areas on which the test preparation was applied were assessed.

An improvement is defined as any improvement in the IFA total score at week 12 compared to baseline. All evaluations for this endpoint were performed post hoc after the final data cut-off.

The endpoint was not collected in the NPC-12G-2 and OSD-001-001 studies.

The endpoint was defined and evaluated post hoc after the final data cut-off. The assessment is based on the photographs taken for the assessment of the primary endpoint. If possible, these photographs should be taken by a person trained in advance for each study site. The exact and always equal distance to the affected skin area appears to be of particular relevance here. Exact details of the training (distance to the lesions, light) were not identified, but it can be assumed that the photographs were taken in a standardised manner and that there was uniformity between the study sites due to the training. Overall, the IFA score is subject to uncertainty as it was validated within the pivotal study. No other validation studies were identified.

No information is available on the development of instruments. Although the instrument has good internal consistency, which was demonstrated by high intrarater and interrater reliability, this investigation was not carried out in an external validation study, but as part of

the pivotal study NPC-12G-1 using the study population. According to the information provided by the authors, there was a visible improvement due to a reduction in the IFA score by ≥ 2 points. Due to a lack of information on the development of the instrument, possible floor/ ceiling effects cannot be assessed. Studies on the sensitivity of the index to change and on construct validity are also not available.

The responder analysis improvement by ≥ 3 points (15% of the scale range) shows a statistically significant advantage of sirolimus. The response was seen in more than 2/3 of patients in the sirolimus arm, while the response in the comparator arm was almost non-existent. Due to the effect size, the results of this endpoint are considered for the benefit assessment despite the stated significant uncertainties with regard to the validity of the measurement instrument. However, it is not possible to quantify this treatment effect due to the uncertainties described.

Quality of life

In the NPC-12G-1 and NPC-12G-2 studies, the DLQI (Dermatology Life Quality Index) and the CDLQI (Children's Dermatology Life Quality Index) were collected. The DLQI was used for children and adults aged 16 years and older and the CLDQI for children aged 15 years and under.

The DLQI (≥ 16 years) and CDLQI (< 16 years) are validated questionnaires for determining the disease-specific health-related quality of life in patients with dermatological diseases. 10 items for 6 domains are recorded: Symptoms and well-being, daily activities, leisure time, work and school, personal relationships and treatment; the questionnaire is completed by the patient. Each item has 4 response categories ranging from 0 (not at all) to 3 (very strongly). A total score is then formed (values from 0 to 30). The lower the score, the better is the health-related quality of life.

The DLQI/CDLQI survey instruments are generally estimated to be valid in this therapeutic indication.

The mean total score was low in both treatment arms of the NPC-12G-1 study for both the DLQI and the CLDQI, which indicates a good quality of life already at baseline. There is no statistically significant difference between the treatment groups in the change in the CDLQI/DLQI total score at week 12.

In the NPC-12G-2 study presented additionally, there was no difference in the change in the CDLQI total score at week 52 compared to baseline. The DLQI also showed only a slight improvement in the total score of -0.5 points. Notwithstanding this, due to the single-arm study design, a comparative assessment of the data on quality of life is not possible in the NPC-12G-2 study.

Side effects

Meta-analyses from the NPC-12G-1 and OSD-001-001 studies are available for the safety endpoints. In the meta-analysis of the NPC-12G-1 and OSD-001-001 studies, there were no significant differences between the treatment groups in the endpoints of severe AEs and SAEs. In the endpoint of discontinuation due to AEs, no events occurred in either study.

For the pre-specified AE of special interest (AESI) "symptoms of skin irritation", the NPC-12G-1 and OSD-001-001 studies each showed a statistically significant effect to the disadvantage of sirolimus.

In the NPC-12G-2 study presented additionally, severe AEs occurred in 6.4% of the study participants. SAEs occurred in 9.6% of the study participants. AEs that led to discontinuation of the study medication occurred in 2.1% of the study participants. Due to the single-arm study design, a comparative assessment of side effects is not possible for this study.

Overall assessment/ conclusion

Data from the pivotal approval study NPC-12G-1, the dose escalation study OSD-001-001 and the single-arm long-term study NPC-12G-2 are available for the benefit assessment.

The results of the 12-week randomised double-blind phase of the approval study NPC-12G-1 and the OSD-001-001 study were used for the benefit assessment. The data from the long-term study NPC-12G-2 are presented additionally.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects.

There were no deaths in the studies There were therefore no differences in the endpoint category of mortality.

In the endpoint category of morbidity, the pharmaceutical company presents surveys with different operationalisations for the patient-relevant endpoint of improvement in angiofibromas on the face. The survey "improvement in angiofibromas according to IFA" in the NPC-12G-1 study is used for the benefit assessment despite significant limitations in the operationalisation. There is a statistically significant difference in favour of sirolimus for the endpoint of improvement in angiofibromas by ≥ 3 points according to IFA at week 12. Due to the effect size, the results of this endpoint are considered for the benefit assessment despite the stated significant uncertainties with regard to the validity of the measurement instrument. However, it is not possible to quantify this treatment effect in view of the uncertainties described.

Health-related quality of life is assessed in the NPC-12G-1 study using the DLQI or CDLQI. In the NPC-12G-1 study, there is no statistically significant difference between the treatment groups in the change in the CDLQI/DLQI total score at week 12.

In the meta-analysis of the NPC-12G-1 and OSD-001-001 studies, regarding side effects, there are no significant differences between the treatment groups in the endpoints of severe AEs and SAEs. In the endpoint of discontinuation due to AEs, no events occurred in either study. In detail, there is a disadvantage of sirolimus for the specific AE "symptoms of skin irritation".

In the overall assessment, an additional benefit of sirolimus was identified for adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex based on the endpoint of improvement in angiofibromas according to the IFA. However, the extent of the additional benefit cannot be quantified, as the magnitude of the treatment effect cannot be conclusively assessed, in particular due to insufficient information on the development and the associated unclear validity of the measurement instrument.

Significance of the evidence

This assessment is based on the results of the randomised, controlled, double-blind, multicentre NPC-12G-1 and OSD-001-001 studies.

The risk of bias in the NPC-12G-1 and OSD-001-001 studies is considered to be low during the blinded treatment phase of 12 weeks.

Uncertainties arise due to the study duration of the direct comparator studies, which at 12 weeks is too short for the present therapeutic indication of a chronic disease, as well as the significant uncertainties regarding the measurement instrument used.
In the overall assessment, the significance of the evidence is classified as a hint.

2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Hyftor with the active ingredient sirolimus.

Sirolimus is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older.

For the benefit assessment, the pharmaceutical company submitted data from the pivotal approval study NPC-12G-1, the dose escalation study OSD-001-001 and the single-arm long-term study NPC-12G-2.

In the endpoint category of morbidity, an additional benefit of sirolimus was identified based on the endpoint of improvement in angiofibromas according to IFA. However, the extent of the additional benefit cannot be quantified, as the magnitude of the treatment effect cannot be conclusively assessed, in particular due to insufficient information on the development of the measurement instrument and the associated unclear validity. Uncertainties remain due to limitations in the operationalisation of the endpoint of improvement in angiofibromas according to IFA and due to the study duration of the direct comparator studies, which is considered short for the present therapeutic indication. In the overall assessment, a hint for a non-quantifiable additional benefit is concluded.

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 resolution is based on the information from the dossier assessment of the IQWiG (G23-28). Overall, an underestimation of the patient numbers for the lower limit can be assumed. This is mainly due to an underestimation of the percentage of facial angiofibromas. The upper limit, on the contrary, is subject to uncertainty.

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 Hyftor (active ingredient: sirolimus) at the following publicly accessible link (last access: 13 March 2024):

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

If there is no effect of treatment, the use of sirolimus must be discontinued after 12 weeks.

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 2024).

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

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Sirolimus	Continuously, 2 x daily	365.0	1	365.0

Consumption:

Consumption is calculated for the relevant age groups (children aged 6 to below 11 years, adolescents aged 12 years and older and adults) according to the product information.

For the calculation of the lower cost limit, the dose amount for lesion surface area of 50 cm^2 specified in the product information is used. The maximum daily dose (for the corresponding age group) specified in the product information was used to calculate the upper cost range.

Based on the shelf life after the 1st opening (4 weeks), a minimum consumption of 13 tubes per year is calculated even for smaller doses.

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					
Children aged 6 to 11 years					
Sirolimus	125 mg – 300 mg	250 mg – 600 mg	2 x 125 mg – 2 x 300 mg	365.0	730 x 125 mg – 730 x 300 mg
Adolescents aged 12 years and above and adults					
Sirolimus	125 mg – 400 mg	250 mg – 800 mg	2 x 125 mg – 2 x 400 mg	365.0	730 x 125 mg – 730 x 400 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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Sirolimus 2 mg/g	10 g GEL	€ 694.04	€ 2.00	€ 37.80	€ 654.24

LAUER-TAXE® last revised: 1 March 2024

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 information 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:

Adults and paediatric patients aged 6 years and older with facial angiofibroma associated with tuberous sclerosis complex

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.

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 13 October 2023, the pharmaceutical company submitted a dossier for the benefit assessment of sirolimus to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 2 January 2024 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 2024.

The oral hearing was held on 5 February 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 13 February 2024.

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 12 March 2024, and the proposed resolution was approved.

At its session on 21 March 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 December 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	30 January 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	5 February 2024	Conduct of the oral hearing
Working group Section 35a	13 February 2024 5 March 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	12 March 2024	Concluding discussion of the draft resolution
Plenum	21 March 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 March 2024

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

Prof. Hecken