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)
Riociguat (new therapeutic indication: pulmonary arterial hypertension, < 18 years)

of 21 December 2023

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 start of the benefit assessment procedure of the active ingredient riociguat was on 1 July 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 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 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 VerfO on 26 June 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 October 2023 on the G-BA website (www.g-ba.de), 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 riociguat 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 riociguat.

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 Riociguat (Adempas) in accordance with the product information

Adempas is indicated for the treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged less than 18 years of age and body weight ≥ 50 kg with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists (see section 5.1b).

Therapeutic indication of the resolution (resolution of 21 December 2023):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Paediatric patients less than 18 years of age and body weight ≥ 50 kg with pulmonary arterial hypertension (PAH)

Appropriate comparator therapy for riociguat in combination with endothelin receptor antagonists:

Patient-individual therapy taking into account in particular previous therapies, severity grade and underlying diseases with selection of

- Endothelin receptor antagonists: Bosentan, ambrisentan
- phosphodiesterase-type-5 (PDE5) inhibitors: Sildenafil, tadalafil

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
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 patient-relevant benefit has already been determined by the G-BA 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. Active ingredients of the following product classes are approved in the therapeutic indication:

- Endothelin receptor antagonists (bosentan, abrisentan)
- phosphodiesterase-type-5 (PDE5) inhibitors (sildenafil, tadalafil)
- Prostacyclin analogues (treprostinil, epoprostenol)

on 2. As a non-medicinal treatment option, a lung or heart-lung transplant in this therapeutic indication can generally be covered by statutory health insurance.

Furthermore, physiotherapeutic measures within the meaning of the Remedies Directive (physical therapy, e.g. physiotherapy, exercise therapy, respiratory therapy) are generally considered as non-medicinal treatments in the treatment of PAH.

on 3. There are no resolutions for this therapeutic indication.

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 indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a, paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

A standard therapy for the intended treatment setting cannot be derived from the available evidence. Instead, patients should be treated on a patient-individual basis, depending on their previous therapies and the severity grade and underlying diseases. The comparator therapy consists of a patient-individual therapy with a given choice of various medicinal treatment options. This also includes the combined use of the aforementioned treatment options.

Although the prostacyclin analogues treprostinil and epoprostenol intended only for parenteral administration are approved for WHO/NYHA class III and III-IV, respectively, it is assumed that continuous, subcutaneous or intravenous administration of prostacyclin analogues is generally only used for advanced disease in patients at high risk (patients with severe (FC IV) and/or rapidly progressive PAH), so this option is not considered an appropriate comparator therapy.

The recommendations of the guidelines[2,3] state that treatment with calcium antagonists alone is indicated if the paediatric patients have a positive vasoreactivity test. However, targeted PAH therapy (e.g. with endothelin receptor antagonists, phosphodiesterase-type-5 (PDE5) inhibitors) is recommended for paediatric patients with a negative vasoreactivity test and for vasoreactive patients who no longer respond to treatment with calcium antagonists alone. It is therefore assumed that patients in the therapeutic indication are ineligible for treatment with calcium channel antagonists alone.

The available evidence contains recommendations for non-medicinal physiotherapy measures to improve symptomatology and physical performance. Physiotherapeutic interventions can be indicated both within the meaning of the Remedies Directive (physical therapy, e.g. physiotherapy, exercise therapy, respiratory therapy) and in the sense of targeted training therapy to improve performance (e.g. after surgical treatment). Only patients without significant limitations in their ability to exercise are eligible for targeted training therapy to improve performance, while physiotherapeutic interventions within the meaning of the Remedies Directive (physical therapy, e.g. physiotherapy, exercise treatment, respiratory therapy) may be suitable for all patients. Furthermore, it is assumed that patients in the therapeutic indication are ineligible for lung transplantation.

In the overall assessment, the G-BA therefore considers it appropriate in the present therapeutic indication to determine a patient-individual therapy as appropriate comparator therapy for riociguat in combination with endothelin receptor antagonists, taking into account in particular previous therapies, severity grade and underlying diseases, and selecting endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase-type-5 (PDE5) inhibitor (sildenafil, tadalafil).

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

[2] Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38(9):879-901.

[3] Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132(21):2037-2099.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of riociguat in combination with endothelin receptor antagonists is assessed as follows:

For paediatric patients ≥ 50 kg to < 18 years with pulmonary arterial hypertension (PAH), the additional benefit of riociguat, in combination with endothelin receptor antagonists, compared to the appropriate comparator therapy has not been proven.

Justification:

The pharmaceutical company did not submit any data for the assessment of the additional benefit of riociguat in combination with endothelin receptor antagonists compared with the appropriate comparator therapy.

The PATENT-CHILD study presented in the dossier is a single-arm study on treatment with riociguat in combination with endothelin receptor antagonists in children and adolescents aged 6 to < 18 years. Due to the lack of comparison with the appropriate comparator therapy, this study is not considered for the present benefit assessment.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient riociguat.

The therapeutic indication assessed here is as follows: "Adempas is indicated for the treatment of PAH in paediatric patients aged less than 18 years of age and body weight ≥ 50 kg with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists."

The G-BA determined the appropriate comparator therapy to be a patient-individual therapy, taking into account in particular previous therapies, severity grade and underlying diseases, and selecting endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase-type-5 (PDE5) inhibitors (sildenafil, tadalafil).

The single-arm PATENT-CHILD study was submitted by the pharmaceutical company for the assessment of the additional benefit of riociguat in combination with endothelin receptor antagonists for the treatment of PAH in paediatric patients aged less than 18 years of age and body weight ≥ 50 kg with WHO Functional Class (FC) II to III. However, due to the lack of comparison with the appropriate comparator therapy, this study is not considered for the present benefit assessment.

An additional benefit of riociguat in combination with endothelin receptor antagonists compared to the appropriate comparator therapy 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 resolution is based on the patient numbers specified by the pharmaceutical company.

The information provided by the pharmaceutical company is based on an analysis of registry data as well as a literature research.

When analysing the registry data, limitations arise, among other things, from the possible incomplete enrolment of all patients in Germany or a lack of mandatory reporting by the participating study sites. Due to the lack of a population reference, it can therefore be assumed that the lower limit is underestimated.

The conclusions drawn from the literature research are of uncertain significance due to uncertainties in the prevalence calculation of patients under the age of 18, uncertainties in the distribution of WHO functional classes in the course of the disease and other aspects.

Overall, the lower limit is assumed to be an overestimate, while the upper limit is fraught with uncertainties.

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 Adempas (active ingredient: riociguat) at the following publicly accessible link (last access: 20 September 2023):

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

Treatment with riociguat should only be initiated and monitored by doctors experienced in treating patients with PAH.

Reference is made to the information in the EPAR on safety aspects in children.

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 December 2023.

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 for the maximum treatment duration, if specified in the product information.

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

The dosage of bosentan is given as 2 mg/kg body weight according to the product information. Since this therapeutic indication includes children and adolescents with a minimum weight of 50 kg, a weight of 50 kg is used to calculate the lower range. The upper range for 17-year-olds with an average weight of 67 kg[4] is 134 mg, which is higher than the dosage for adults. For this reason, the maintenance dose of 125 mg twice daily for adults is used.

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				
Riociguat in combination with endothelin receptor antagonists[5]				
Riociguat	Continuously, 3 x daily	365.0	1	365.0
Bosentan	Continuously, 2 x daily	365.0	1	365.0
Ambrisentan	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Patient-individual therapy taking into account in particular previous therapies, severity grade and underlying diseases with selection of:				
Endothelin receptor antagonists (in monotherapy or combination therapy)				
Bosentan	Continuously, 2 x daily	365.0	1	365.0
Ambrisentan	Continuously, 1 x daily	365.0	1	365.0
Phosphodiesterase-type-5 (PDE5) inhibitor (in monotherapy or combination therapy)				
Sildenafil	Continuously, 3 x daily	365.0	1	365.0
Tadalafil	Continuously, 1 x daily	365.0	1	365.0

Consumption:

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.

[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

[5] For the combination of riociguat with an endothelin receptor antagonist, bosentan and ambrisentan are presented as possible concomitant active ingredients.

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:					
Riociguat in combination with endothelin receptor antagonists[5]					
Riociguat	1 mg – 2.5 mg	3 mg – 7.5 mg	3 x 1 mg – 3 x 2.5 mg	365.0 365.0	1,095 x 1 mg – 1,095 x 2.5 mg
Bosentan	2 mg/kg BW = 100 mg – 125 mg	200 mg – 250 mg	6 x 32 mg – 2 x 125 mg	365.0	2,190 x 32 mg – 730 x 125 mg
Ambrisentan	5 mg – 10 mg	5 mg – 10 mg	1 x 5 mg – 1 x 10 mg	365.0	365 x 5 mg – 365 x 10 mg
Appropriate comparator therapy					
Patient-individual therapy taking into account in particular previous therapies, severity grade and underlying diseases with selection of:					
Endothelin receptor antagonists (in monotherapy or combination therapy)					
Bosentan	2 mg/kg BW = 100 mg – 125 mg	200 mg – 250 mg	6 x 32 mg – 2 x 125 mg	365.0	2,190 x 32 mg – 730 x 125 mg
Ambrisentan	5 mg – 10 mg	5 mg – 10 mg	1 x 5 mg – 1 x 10 mg	365.0	365 x 5 mg – 365 x 10 mg
Phosphodiesterase-type-5 (PDE5) inhibitor (in monotherapy or combination therapy)					
Sildenafil	20 mg	60 mg	3 x 20 mg	365.0	1,095 x 20 mg
Tadalafil	40 mg	40 mg	2 x 20 mg	365.0	730 x 20 mg

Costs:

Costs of the medicinal products:

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.

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					
Riociguat 1 mg	84 FCT	€ 1,498.69	€ 2.00	€ 58.82	€ 1,437.87
Riociguat 2.5 mg	294 FCT	€ 5,104.45	€ 2.00	€ 205.87	€ 4,896.58
Bosentan 125 mg[6]	120 FCT	€ 3,857.33	€ 2.00	€ 310.00	€ 3,545.33
Bosentan 32 mg	56 TOS	€ 3,864.44	€ 2.00	€ 372.70	€ 3,489.74
Ambrisentan 5 mg[6]	60 FCT	€ 3,808.76	€ 2.00	€ 306.04	€ 3,500.72
Ambrisentan 10 mg[6]	60 FCT	€ 3,857.33	€ 2.00	€ 310.00	€ 3,545.33
Appropriate comparator therapy					
Bosentan 125 mg[6]	120 FCT	€ 3,857.33	€ 2.00	€ 310.00	€ 3,545.33
Bosentan 32 mg	56 TOS	€ 3,864.44	€ 2.00	€ 372.70	€ 3,489.74
Ambrisentan 5 mg[6]	60 FCT	€ 3,808.76	€ 2.00	€ 306.04	€ 3,500.72
Ambrisentan 10 mg[6]	60 FCT	€ 3,857.33	€ 2.00	€ 310.00	€ 3,545.33
Sildenafil 20 mg[6]	30 FCT	€ 94.95	€ 2.00	€ 6.62	€ 86.33
Tadalafil 20 mg[6]	28 FCT	€ 130.94	€ 2.00	€ 9.46	€ 119.48
Abbreviations: FCT = film-coated tablets; TOS = tablet for oral suspension					

LAUER-TAXE® last revised: 1 December 2023

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.

[6] Fixed reimbursement rate

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 need to be taken into account.

2.5 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 Riociguat

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:

Paediatric patients less than 18 years of age and body weight ≥ 50 kg with pulmonary arterial hypertension (PAH)

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 riociguat (Adempas); Adempas 0.5 mg/–1 mg/–1.5 mg/–2 mg/–2.5 mg film-coated tablets, last revised: May 2023

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

At its session on 10 March 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 May 2023.

On 26 June 2023 the pharmaceutical company submitted a dossier for the benefit assessment of riociguat to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 26 June 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 riociguat.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 September 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 October 2023. The deadline for submitting statements was 23 October 2023.

The oral hearing was held on 6 November 2023.

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 December 2023, and the proposed resolution was approved.

At its session on 21 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 March 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	23 May 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	31 October 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	6 November 2023	Conduct of the oral hearing
Working group Section 35a	14 November 2023 5 December 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 December 2023	Concluding discussion of the draft resolution
Plenum	21 December 2023	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 December 2023

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

Prof. Hecken