Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Riociguat (Reassessment of an Orphan Drug after Exceeding the € 50 Million Limit: PAH)

of 3 September 2020

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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient riociguat (Adempas®) was listed for the first time on 1 May 2014 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Adempas® for the treatment of pulmonary arterial hypertension (PAH) 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.

At its session on 16 October 2014, the G-BA passed a resolution on the benefit assessment of riociguat in the present therapeutic indication in accordance with Section 35a SGB V.

If the turnover of the orphan drugs with statutory health insurance at pharmacy sales prices as well as outside statutory medical care, including value added tax, exceeds € 50 million in the last twelve calendar months, the pharmaceutical company must, within three months of being requested to do so by the Federal Joint Committee, submit evidence in accordance with Section 5, paragraph 1 through 6 demonstrating the additional benefit compared with the appropriate comparator therapy.

In a letter dated 18 December 2019, the pharmaceutical company was requested to submit a dossier for a benefit assessment in accordance with Section 35a SGB V by 1 April 2020 because the € 50 million turnover limit had been exceeded between August 2018 and July 2019. The pharmaceutical company submitted the final dossier to the G-BA in due time 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 6 VerfO on 13 March 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 June 2020 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 came to a resolution on whether an additional benefit of riociguat compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG (A20-31), 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 assessed 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 arrived at 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, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity. Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III

Patient-individual optimised medicinal therapy, taking into account previous therapies and the patient's state of health, taking into account the following therapies:

- Endothelin receptor antagonists (ambrisentan, bosentan, macitentan)
- Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil)
- Prostacyclin analogues (iloprost)
- Selective prostacyclin receptor agonists (selexipag)

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], 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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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 active ingredient classes are approved in the therapeutic indication:

- Endothelin receptor antagonists (ambrisentan, bosentan, macitentan)
- Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil)
- Prostacyclin analogues (iloprost, treprostinil, epoprostenol)
- Selective prostacyclin receptor agonists (selexipag)

On 2. As a non-medicinal treatment option, a lung or heart-lung transplantation in this therapeutic indication is generally affordable at the expense of the statutory health insurance.

In the treatment of PAH, physiotherapeutic measures in the sense of the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) are generally considered as non-medicinal treatment.

On 3. Preference should be given to an appropriate comparator therapy for which a patient-relevant benefit has already been established by the G-BA. The G-BA has passed two resolutions on the benefit assessment in accordance with Section 35a SGB V for the active ingredients macitentan (dated 6 April 2017) and selexipag (dated 15 December 2016).

As a result of the benefit assessments, the resolution of 6 April 2017 on macitentan for the treatment of adult patients with pulmonary arterial hypertension (PAH) in the WHO/NYHA functional classes (WHO-FC) II to III as monotherapy or in combination found no additional benefit. For selexipag for the treatment of PAH in adult patients in WHO-FC Class II or III, either as a combination therapy or as monotherapy, no additional benefit was identified in the resolution of 15 December 2016.

On 4. The generally accepted state of medical knowledge on the appropriate comparator therapy in the therapeutic indication was represented by a search for systematic reviews and guidelines.

A standard therapy for the desired treatment situation cannot be derived from the available evidence. Rather, the patients should be treated in a patient-individual optimised way depending on the previous therapies and the respective health status. The comparator therapy consists of a patient-individual therapy with a given choice of different medicinal treatment options. These options also include dose optimisation of the existing therapy (if still indicated), a change of the active ingredient (if appropriate), or combination therapies of the different active ingredients (if approved and indicated). The formulation “patient-individual optimised medicinal therapy” means that the doctor can select the appropriate therapy for the individual patient from a range of approved medicinal therapy options, taking into account the authorisation status.

Although the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally only, are approved for WHO/NYHA Class III, it is assumed

that the continuous, subcutaneous, or intravenous use of prostacyclin analogues usually applies to advanced disease only. This option is therefore not considered an appropriate comparator therapy.

Furthermore, the evidence available includes recommendations for non-medicinal physiotherapeutic measures to improve symptomatology and physical performance. Physiotherapeutic interventions can be indicated in terms of both the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) and a targeted training therapy to improve performance (e.g. after a surgical treatment). For the specific training therapy to increase performance, only patients without significant limitations of resilience are considered. On the other hand, physiotherapeutic interventions in the sense of the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) may be suitable for all patients. Physiotherapeutic measures, if indicated, should be made available to patients in both arms of the study in addition to patient-individual medicinal therapy.

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

2.1.3 Extent and probability of the additional benefit

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

Adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of riociguat for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity, the pharmaceutical company presented the pivotal, randomised, double-blind, placebo-controlled parallel group study of the Phase III PATENT-1 study.

Patients were assigned to the treatment arms riociguat 1.0-–2.5 mg (n =2 54), placebo (n = 126) and riociguat 1.0–1.5 mg (n = 64) (non-approved dosage) at a ratio of 4:2:1.

The treatment and observation period of the PATENT-1 study is 12 weeks in total. Treatment with riociguat was carried out in accordance with the information given in the product information. Treatment with riociguat thus begins with an 8-week titration phase during which the dose is gradually increased every 2 weeks. This titration phase is also implemented in the study; the observation period under maintenance dose is therefore only 4 weeks.

The 12-week treatment phase chosen by the pharmaceutical company was considered sufficient for marketing authorisation to demonstrate the efficacy or the efficacy profile of riociguat and was used by the G-BA in the benefit assessment under orphan criteria for which an additional benefit is generally considered proven.

However for evaluating the effects on patient-relevant endpoints of a medicinal product that is now subject to an unrestricted benefit assessment, this study duration is too short in order to be able to make a valid assessment of the additional benefit for a chronic disease. In the therapeutic indication of PAH, short-term studies (with a treatment duration of less than 24 weeks) are unsuitable for the benefit assessment here.

Furthermore, in the PATENT-1 study, the appropriate comparator therapy of patient-individual optimised drug therapy was not implemented because there was no patient-

individual optimisation of the therapy for both therapy-naïve and therapy-experienced patients.

In the PATENT-1 study, the sub-population of patients receiving therapy received only a placebo in the control arm and no specific medicinal therapy or non-medicinal support for the treatment of PAH. Neither at the start of study nor during the course of the study was there a patient-individual optimisation of the therapy.

The PATENT-1 trial also included pretreated patients who were stable on an endothelin receptor antagonist (ERA) or prostacyclin analogue. The pre-treated patients continued this monotherapy unchanged in the control arm. In other words, any necessary escalation (change or addition of an active ingredient or change in dosage) did not occur in the control arm. In addition, only 2 of the 4 listed active ingredient classes were allowed.

Thus, for both therapy naïve and therapy experienced patients, the appropriate comparator therapy is not implemented in the PATENT-1 study.

The PATENT-1 study cannot be used for the benefit assessment because the study duration was too short and the appropriate comparator therapy was not implemented.

The pharmaceutical company also submitted the single-arm extension study of Phase III PATENT-2 study. This single-arm study is not relevant for the present benefit assessment because no data are available for an assessment of riociguat compared with the appropriate comparator therapy.

Thus, for this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of riociguat compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the active ingredient riociguat because the € 50 million turnover limit was exceeded. The present assessment refers to the therapeutic indication “for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity”.

Riociguat has received marketing authorisation as an orphan drug.

As an appropriate comparator therapy, the G-BA decided on a patient-individual optimised medicinal therapy, taking into account previous therapies and the patient’s health status, taking into account the following therapies: Endothelin receptor antagonists (ambrisentan, bosentan, macitentan), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), prostacyclin analogues (iloprost), and selective prostacyclin receptor agonists (selexipag).

For the assessment of the additional benefit of riociguat for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity, the pharmaceutical company presented the 12-week pivotal, randomised, double-blind, placebo-controlled parallel group study of the Phase III PATENT-1 study.

The 12-week PATENT-1 study cannot be used for the benefit assessment because the study duration was too short and the appropriate comparator therapy was not implemented.

The pharmaceutical company also submitted the single-arm extension study of Phase III PATENT-2 study. This single-arm study is not relevant for the present benefit assessment because no data are available for an assessment of riociguat compared with the appropriate comparator therapy.

Thus, for this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of riociguat compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

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

The patient numbers refer to the target population in the statutory health insurance (SHI).

The data are based on patient numbers, which are based on the information provided by the pharmaceutical company in the dossier, taking into account the most recent resolution (6 April 2017) on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication “Adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III”.

The number of patients in the SHI target population is of a plausible order of magnitude even if these figures are subject to uncertainties because the pharmaceutical company did not provide current prevalence data. Because the overall prevalence of the disease in the population is expected to remain stable, it can be assumed that there has been no fundamental change in the number of patients in the therapeutic indication. Also for reasons of consistency with the previous resolutions, the range indicated is considered appropriate.

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: 18 June 2020):

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

Treatment with riociguat should only be initiated and monitored by specialists who are experienced in the treatment of patients with PAH.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2020).

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 is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, time between individual treatments, and for maximum treatment duration if specified in the product information.

Treatment duration:

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	continuously, 3 × daily	365	1	365
Appropriate comparator therapy				
Endothelin receptor antagonists				

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Ambrisentan	continuously, 1 × daily	365	1	365
Bosentan	continuously, 2 × daily	365	1	365
Macitentan	continuously, 1 × daily	365	1	365
Phosphodiesterase type 5 inhibitors				
Sildenafil	continuously, 3 × daily	365	1	365
Tadalafil	continuously, 1 × daily	365	1	365
Prostacyclin analogues				
Iloprost	continuously, 6 - 9 × daily	365	1	365
Selective prostacyclin receptor agonists				
Selexipag	continuously, 2 × daily	365	1	365

Usage and 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					
Riociguat	1 mg –	3 mg –	3 × 1 mg	365	1095 × 1 mg –
	2.5 mg	7.5 mg	3 × 2.5 mg	365	1095 × 2.5 mg
Appropriate comparator therapy					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Endothelin receptor antagonists					
Ambrisentan	5 mg – 10 mg	5 mg – 10 mg	1 × 5 mg – 1 × 10 mg	365	365 × 5 mg – 365 × 10 mg
Bosentan	125 mg	250 mg	2 × 125 mg	365	730 × 125 mg
Macitentan	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
Phosphodiesterase type 5 inhibitors					
Sildenafil	20 mg	60 mg	3 × 20 mg	365	1095 × 20mg
Tadalafil	40 mg	40 mg	2 × 20 mg	365	730 × 20 mg
Prostacyclin analogues					
Iloprost	5 µg	30 µg – 45 µg	6 × 5 µg – 9 × 5 µg	365	2190 × 20 µg /ml – 3285 × 20 µg /ml
Selective prostacyclin receptor agonists					
Selexipag	200 µg – 1600 µg	400 µg – 3200 µg	2 × 200 µg – 2 × 1600 µg	365	730 × 200 µg – 730 × 1600 µg

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 Sections 130 and 130 a 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.

Costs of the medicinal product:

Designation of the therapy	Package 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	€ 2,546.94	€ 1.77	€ 0.00	€ 2,545.17
Riociguat 2.5 mg	294 FCT	€ 8,774.48	€ 1.77	€ 0.00	€ 8,772.71
Appropriate comparator therapy					
Ambrisentan 5 mg[2]	30 FCT	€ 2,011.79	€ 1.77	€ 0.00	€ 2,010.02
Ambrisentan 10 mg[2]	30 FCT	€ 2,049.41	€ 1.77	€ 0.00	€ 2,047.64
Bosentan 125 mg[2]	120 FCT	€ 4,001.55	€ 1.77	€ 330.23	€ 3,669.55
Macitentan 10 mg[2]	30 FCT	€ 2,039.44	€ 1.77	€ 0.00	€ 2,037.67
Sildenafil 20 mg[2]	300 FCT	€ 2,481.40	€ 1.77	€ 203.00	€ 2,276.63
Tadalafil 20 mg[2]	120 FCT	€ 1,294.07	€ 1.77	€ 104.13	€ 1,188.17
Iloprost 20 µg /ml	168 LOV	€ 4,120.40	€ 1.77	€ 238.13	€ 3,880.50
Selexipag 1600 µg	60 FCT	€ 3,054.22	€ 1.77	€ 0.00	€ 3,052.45
Selexipag 200 µg	140 FCT	€ 6,047.75	€ 1.77	€ 0.00	€ 6,045.98
Abbreviations: SFN = solution for a nebuliser; FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

In accordance with the product information, an inhaler is necessary for the application of iloprost. The following options for the 20 µg/ml are listed in the product information: Breelib and the I-Neb-AAD system. Breelib and the I-Neb-AAD system are both listed in the LAUER-TAXE®. However, price information is available only for the I-Neb-AAD system. This inhaler is therefore listed here as an example. The inhaler at a price of € 3,500 is charged and remains with the patient. The contract prices of the respective health insurance companies may differ.

[2] Fixed reimbursement rate

3. Bureaucratic costs

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 7 August 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 March 2020, 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 6 VerfO.

By letter dated 16 March 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient riociguat.

The dossier assessment by the IQWiG was submitted to the G-BA on 10 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 June 2020. The deadline for submitting written statements was 6 July 2020.

The oral hearing was held on 27 July 2020.

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 were discussed at the session of the subcommittee on 25 August 2020, and the proposed resolution was approved.

At its session on 3 September 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 August 2018	Determination of the appropriate comparator therapy
Working group Section 35a	22 July 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 July 2020	Conduct of the oral hearing
Working group Section 35a	5 August 2020 19 August 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 August 2020	Concluding discussion of the draft resolution
Plenum	3 September 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 3 September 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken