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Riociguat (pulmonary arterial hypertension) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Riociguat (pulmonal arterielle Hypertonie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 June 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ERA	endothelin receptor agonist
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PAH	pulmonary arterial hypertension
PDE	phosphodiesterase
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO	Wold Health Organization

2 Benefit assessment

2.1 Extract of dossier assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug riociguat. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 March 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is to assess the added benefit of riociguat in adult patients with pulmonary arterial hypertension (PAH) of World Health Organization (WHO) functional class II to III to improve exercise capacity in comparison with individually optimized drug therapy as the appropriate comparator therapy (ACT). Riociguat can be used as monotherapy or in combination with endothelin receptor agonists (ERAs).

For the benefit assessment, 1 research question resulted, for which the G-BA specified the ACT presented in Table 2.

Table 2: Research question of the benefit assessment of riociguat (as monotherapy or in combination with ERAs)

Therapeutic indication	**ACT[a]**
Adult patients with PAH of WHO functional class II to III to improve exercise capacity	Individually optimized drug therapy, taking into account prior therapies and health status and considering the following therapies[b]: ▪ ERAs (ambrisentan, bosentan, macitentan) ▪ PDE5 inhibitors (sildenafil, tadalafil) ▪ Prostacyclin analogues (iloprost)[c] ▪ Selective prostacyclin receptor agonists (selexipag)

a. Presentation of the respective ACT specified by the G-BA.
b. As part of individualized therapy, the approval of the respective drugs as per SPC must be taken into account. It follows, for instance, that patients who are already receiving PDE5 inhibitor therapy are ineligible for simultaneous riociguat therapy. (Adempas SPC: Concomitant use of riociguat with PDE5 inhibitors [such as sildenafil, tadalafil, vardenafil] is contraindicated.)
c. Although prostacyclin analogues of treprostinil and epoprostenol, which are to be administered parenterally only, are approved for WHO/NYHA class III, it is assumed that the continuous subcutaneous or intravenous administration of prostacyclin analogues is typically used only in advanced disease; therefore, this option is not deemed an ACT.

ACT: appropriate comparator therapy; ERA: endothelin receptor agonist; G-BA: Federal Joint Committee; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PDE: phosphodiesterase; SPC: Summary of Product Characteristics; WHO: World Health Organization

The company used the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit. This deviates from the inclusion criteria of the company, which considered RCTs of any duration.

Results

Evidence presented by the company

In its information retrieval, the company identified 1 RCT (PATENT-1) and included this study in its benefit assessment. As supplementary evidence, the company resorted to the associated 1-arm extension study, PATENT-2.

PATENT-1

The PATENT-1 study is a double-blind RCT which compares riociguat with placebo in adult PAH patients, with a follow-up duration of 12 weeks. The patient population is appropriate for the therapeutic indication of riociguat as defined in the Summary of Product Characteristics (SPC). The study has 3 arms and was randomized in a 4:2:1 ratio:

1) riociguat 1.0 mg to 2.5 mg (n = 254)
2) placebo (n = 126)
3) riociguat 1.0 mg to 1.5 mg (n = 64)

In Arm 1 (1.0 to 2.5 mg), riociguat was administered as approved, which includes an 8-week up-titration phase until the individual optimal dose is reached. In the control arm, a sham titration with placebo was carried out. In Arm 3, an up-titration phase was carried out as well, but with a maximum dose of only 1.5 mg. Following the titration phase, all 3 study arms entered a 4-week maintenance phase with constant dosage.

The study's primary outcome was 6-minute walking distance after 12 weeks.

PATENT-2

PATENT-2 is a 1-arm extension study of PATENT-1. Patients from Arm 2 (placebo) and Arm 3 (riociguat 1.0 to 1.5) of the PATENT-1 study were, over the course of 8 weeks, switched while blinded to maintenance therapy with individually optimized dose of riociguat (up to a maximum of 2.5 mg). The company used PATENT-2-based supplementary analyses to investigate the robustness of results of PATENT-1.

For deriving any added benefit or harm, the company used neither the PATENT-2 study nor the associated supplementary analyses.

Unsuitability of the data presented by the company for the benefit assessment

Insufficient study duration of PATENT-1

Due to its short follow-up duration of only 12 weeks, PATENT-1 is unsuitable for the benefit assessment. Pulmonary arterial hypertension is a chronic condition requiring life-long treatment. Since not only short-term effects, but particularly long-term effects are of interest, long-term studies are necessary to draw any conclusions on added benefit. This applies not only to conclusions on benefit outcomes, but also to harm outcomes because adverse events may potentially manifest only after prolonged drug intake. Any benefit assessment in this therapeutic indication requires studies of at least 24 weeks in duration for weighing benefits and harms.

ACT not implemented in the PATENT-1 study

The study included patients who were symptomatic and required treatment. Patients could be either previously untreated or pretreated (each making up about 50% in riociguat Arm 1 and in the placebo arm). The control arm did not involve individualized optimization of drug therapy.

In the PATENT-1 control arm, the subpopulation of treatment-naive patients received only placebo and no specific anti-PAH drug therapy of any kind. Consequently, treatment was not individually optimized, neither at study start nor in the further course of the study. For this subpopulation, the ACT was therefore not implemented.

The study also included pretreated patients on stable doses of an ERA or a prostacyclin analogue. In the control arm, pretreated patients continued this monotherapy unchanged, i.e. the control arm did not receive any potentially necessary escalation (drug switch, added drug, or dose adjustment). Hence, even in the subpopulation of pretreated patients, there was no individualized optimization of therapy. Moreover, only 2 of the 4 drug classes listed by the G-BA were allowed. Overall, the ACT was therefore not implemented for this subpopulation either.

Aside from the above-described unsuitability of the PATENT-1 study due to its study duration and failure to implement the ACT, Arm 3 of the PATENT-1 study is irrelevant since the dose of 1.5 mg is not in full compliance with approval and might involve riociguat underdosage.

Relevance of the PATENT-2 study

Due to its lack of control arm, the 1-arm PATENT-2 study is irrelevant for the benefit assessment since no comparison with the ACT is available. The PATENT-2-based, supplementary robustness analyses are of no informative value with regard to potential treatment effects beyond 12 weeks; moreover, the company presents these analyses only selectively.

Consequence for the assessment

For the reasons cited above, no suitable data are available for assessing the added benefit of riociguat in comparison with the ACT in patients with PAH of WHO functional class II to III

with regard to improvement in exercise capacity. Consequently, there is no hint of an added benefit of riociguat in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of riociguat in the form of monotherapy or in combination with ERAs.

Table 3: Riociguat (as monotherapy or in combination with ERAs) – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with PAH of WHO functional class II to III to improve exercise capacity	Individually optimized drug therapy, taking into account prior therapies and health status and considering the following therapies: ▪ ERAs (ambrisentan, bosentan, macitentan) ▪ PDE5 inhibitors (sildenafil, tadalafil) ▪ Prostacyclin analogues (iloprost) ▪ Selective prostacyclin receptor agonists (selexipag)	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; ERA: endothelin receptor agonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PDE: phosphodiesterase; WHO: World Health Organization		

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the G-BA's assessment issued in the connection with the market launch in 2014. Back then, the G-BA established a minor added benefit of riociguat. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization on the basis of the special status of orphan drugs, regardless of the underlying data.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report is to assess the added benefit of riociguat in adult patients with PAH of WHO functional class II to III to improve exercise capacity in comparison with individually optimized drug therapy as the ACT. Riociguat can be used as monotherapy or in combination with ERAs.

For the benefit assessment, 1 research question resulted, for which the G-BA specified the ACT presented in Table 4.

Table 4: Research question of the benefit assessment of riociguat (as monotherapy or in combination with ERAs)

Therapeutic indication	**ACT**[a]
Adult patients with PAH of WHO functional class II to III to improve exercise capacity	Individually optimized drug therapy, taking into account prior therapies and health status and considering the following therapies[b]: ▪ ERAs (ambrisentan, bosentan, macitentan) ▪ PDE5 inhibitors (sildenafil, tadalafil) ▪ Prostacyclin analogues (iloprost)[c] ▪ Selective prostacyclin receptor agonists (selexipag)
a. Presentation of the respective ACT specified by the G-BA. b. As part of individualized therapy, the approval of the respective drugs as per SPC must be taken into account. It follows, for instance, that patients who are already receiving PDE5 inhibitor therapy are ineligible for simultaneous riociguat therapy. (Adempas SPC: Concomitant use of riociguat with PDE5 inhibitors [such as sildenafil, tadalafil, vardenafil] is contraindicated.) c. Although the prostacyclin analogues of treprostinil and epoprostenol, which are exclusively for parenteral administration, are approved for WHO/NYHA class III, it is assumed that continuous subcutaneous or intravenous administration of prostacyclin analogues is typically used only in advanced disease; therefore, this option is not deemed an ACT. ACT: appropriate comparator therapy; ERA: endothelin receptor agonist; SPC: Summary of Product Characteristics; G-BA: Federal Joint Committee; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PDE: phosphodiesterase; WHO: World Health Organization	

The company used the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit. This deviates from the inclusion criteria of the company, which considered RCTs of any duration.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on riociguat (status: 20 January 2020)

- Bibliographic literature search on riociguat (most recent search on 2 January 2020)
- Search in trial registries for studies on riociguat (most recent search on 3 January 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on riociguat (most recent search on 27 March 2020)

The check did not reveal any relevant study for assessing the added benefit of riociguat in comparison with the ACT.

The data presented by the company are unsuitable for deriving any added benefit of riociguat in comparison with the ACT. The reason is explained below: The data considered by the company and its approach are described first, followed by the reasons why the presented data are unsuitable for deriving any conclusions on added benefit.

Evidence presented by the company

In its information retrieval, the company identified 1 RCT (PATENT-1) [3] and included this study in its benefit assessment. As supplementary evidence, the company resorted to the associated 1-arm extension study, PATENT-2 [4].

PATENT-1

The PATENT-1 study is a double-blind RCT which compares riociguat with placebo in adult patients with PAH and has a follow-up duration of 12 weeks. The patient population is appropriate for the therapeutic indication of riociguat as defined in the SPC [5]. The study has 3 arms and was randomized in a 4:2:1 ratio:

1) riociguat 1.0 to 2.5 mg (n = 254)
2) placebo (n = 126)
3) riociguat 1.0 to 1.5 mg (n = 64)

In Arm 1 (1.0 to 2.5 mg), riociguat was administered asapproved. The initial dose of riociguat was 1 mg 3 times daily. An 8-week up-titration phase involved dose increases of 0.5 mg every 2 weeks until the patient's optimal dose was reached. The maximum dosage of riociguat was 2.5 mg 3 times daily. In the control arm, a sham titration with placebo was carried out. Arm 3 involved an up-titration phase as well. However, the maximum dose in this arm was only 1.5 mg, followed by sham titration with placebo. In all 3 study arms, the titration phase was followed by a 4-week maintenance phase under a constant dosage. Nevertheless, dose reduction due to adverse events, e.g. hypotension, was allowed.

The study's primary outcome was 6-minute walking distance after 12 weeks.

PATENT-2

PATENT-2 is an extension study of PATENT-1. Patients from Arm 2 (placebo) and Arm 3 (riociguat 1.0 to 1.5 mg) of the PATENT-1 study were, over the course of 8 weeks, switched to maintenance therapy with individualized dosing of riociguat (with a maximum of 2.5 mg). Thereafter, they were unblinded. The PATENT-2 study included 90.9% (N = 231) of patients of riociguat Arm 1 and 86.5% of the placebo arm (N = 109). Study participation and hence treatment within the study continued until riociguat was brought to market in the respective countries.

To confirm the 12-week data from PATENT-1, the company used results from the PATENT-2 study at the time point of 24 weeks after randomization, with the company pursuing 2 approaches:

1) Supplementary analysis of riociguat versus placebo at Week 24 with "conservative replacement":
   a) Benefit outcomes: analysis as "confirmed response"; i.e., in the intervention arm, an event is deemed present if a response at Week 12 was confirmed at Week 24; for all control arm patients with a response at Week 12, a response is assumed for Week 24.
   b) Harm outcomes: For the placebo group, no further patients with event are assumed to be found between Week 12 and Week 24.
2) Supplementary analysis for riociguat versus placebo at Week 24 ("as allocated"): The data of the riociguat arm at Week 24 are compared with those of the (original) control arm at Week 24; patients are compared as per their originally assigned arms (despite the fact that in Weeks 12 to 24, even patients in the control arm received riociguat).

The company presented these supplementary analyses only selectively. The analyses with "conservative replacement" (Approach 1) and the comparison at Week 24 ("as allocated", Approach 2) were submitted by the company only for benefit outcomes showing a statistically significant difference between treatment groups at Week 12 (in the PATENT-1 RCT). For harm outcomes, the company presented Approach 1 in all cases, regardless of the presence of any statistically significant effect; however, this was done only for the total rate of adverse events (AEs), SAEs, discontinuation due to AEs, hypotension, haemorrhage, and syncope – and not for further specific AEs.

Moreover, the company reported the 24-month results from PATENT-2, but again excluding further specific AEs.

For deriving any added benefit or harm, the company used neither the PATENT-2 study nor the associated supplementary analyses.

Unsuitability of the data presented by the company for the benefit assessment

Insufficient study duration of PATENT-1

Due to its short follow-up duration of only 12 weeks, PATENT-1 is unsuitable for the benefit assessment. Pulmonary arterial hypertension is a chronic condition requiring life-long treatment. Since not only short-term effects, but particularly long-term effects are of interest, long-term studies are necessary to draw any conclusions on added benefit. This applies not only to conclusions on benefit outcomes, but also to harm outcomes because AEs may potentially manifest only after prolonged drug intake.

In Module 4B, the company reports that the European Medicines Agency guideline on pulmonary arterial hypertension [6] recommends a treatment duration of 3 to 6 months when using stress tests (e.g. exercise capacity). The company's rationale is not acceptable. Any benefit assessment in this therapeutic indication requires study durations of at least 24 weeks for weighing benefits and harms. Furthermore, it must be noted that the first 8 weeks of the PATENT-1 study involved an up-titration phase to reach the patient's individual optimized dosage. Consequently, the treatment duration under the optimal dosage was only 4 weeks.

ACT not implemented in the PATENT-1 study

The PATENT-1 study included patients who were symptomatic and required treatment. About half of the patients (55.5% in riociguat Arm 1 versus 48.4% in the placebo arm) were in a WHO functional class of III or IV. In addition, 54.7% of patients in the riociguat Arm 1 as well as 42.1% in the placebo arm had a baseline value of less than 380 m in the 6-minute walking distance. Hence, these patients exhibit an intermediate or even high risk status. The overall treatment goal in patients with PAH is to reach a low-risk status [7,8]. For the majority of the patient population, this had not been achieved at study start, i.e. they were in need of treatment.

Patients in the PATENT-1 study were either treatment-naive (48.4% in the riociguat Arm 1 versus 52.4% in the placebo arm) or pretreated (51.6% in riociguat Arm 1 versus 47.6% in the placebo arm). The company reports that patients received riociguat or, in the control arm, placebo in addition to individualized therapy. However, an add-on design with placebo as a comparator is appropriate only if no further escalation or treatment optimization would be possible in the control arm. This is not the case for patients in the PATENT-1 control arm, as is described in more detail below.

Subpopulation of treatment-naive patients

In the PATENT-1 control arm, the subpopulation of treatment-naive patients received only placebo and no specific anti-PAH drug therapy of any kind. In other words, treatment was not individually optimized, neither at study start nor in the further course of the study. For this subpopulation, the ACT was therefore not implemented.

Subpopulation of pretreated patients

The study also included pretreated patients on stable doses of an ERA or a prostacyclin analogue. This means that in the 90 days before the 1st visit, no changes were made to either the drug itself or its dosage. This therapy had to be continued unchanged in the study, and no adjustments were allowed in the course of the study. For PAH therapy, the guidelines of the European Society of Cardiology and the European Respiratory Society as well as the Cologne Consensus Conference recommend primarily upfront or early sequential (initiated within the first 3 months after diagnosis) combination therapy or potentially monotherapy [7,8]. In case of inadequate clinical response, escalation with another drug is recommended.

In the PATENT-1 study, pretreated patients received merely continued, i.e., any needed escalation did not take place in this control arm. No drug switching or dose changes were allowed either. However, rigid guidelines or limitations regarding the physician's drug selection or dose adjustments are inappropriate in individualized therapy. Hence, even the subpopulation of pretreated patients did not receive individualized optimization of therapy.

The G-BA lists 4 drug classes as treatment options to be considered within the ACT. However, PATENT-1 allowed only ERAs or prostacyclin analogues for prior and continued treatment. This covers only 2 out of the 4 drug classes listed by the G-BA; hence, the ACT was not fully implemented. The company argues that the simultaneous use of riociguat and phosphodiesterase (PDE)-5-inhibitors is contraindicated according to the SPC, thus rendering it impossible to use PDE5 inhibitors in the study. The company's arguments regarding PDE5 inhibitors are not plausible. Riociguat is in fact contraindicated in patients simultaneously receiving PDE5 inhibitors [5], and the blinded design generally rules out the drug in PATENT-1 (to avoid a combination of riociguat and PDE5 donors in the intervention arm). Conversely, an open-label study design would have generally allowed the use of PDE5 inhibitors as part of the ACT in the control arm. Regarding selexipag, a representative of the 4th drug class defined in the ACT, the company points out that the drug had not been approved in the European Union until 2016, therefore making it unavailable in the study. Even so, the assessment of added benefit is conducted on the basis of the current treatment standard.

In summary, the ACT was not implemented in the PATENT-1 study.

Relevance of Arm 3 of the PATENT-1 study (riociguat 1.0 to 1.5)

Aside from the above-described unsuitability of the PATENT-1 study due to its study duration and the failure to implement the ACT, Arm 3 of the PATENT-1 study is irrelevant. At 1.5 mg, the maximum dosage specified in this arm fails to fully comply with the approval. Hence, riociguat treatment might possibly be underdosed. The company's approach of disregarding the study arm is therefore appropriate.

Relevance of the PATENT-2 study

Due to its lack of a control arm, the PATENT-2 study is irrelevant for the benefit assessment. Moreover, the supplementary analyses presented by the company are of no informative value concerning potential treatment effects beyond Week 12.

For all outcome categories, the analyses using a conservative replacement strategy (Approach 1) included patients of the intervention arm with an event at Week 24, while for the control arm, values at Week 12 were used. The company calls this the most conservative imputation possible. However, this designation is apt only for harm outcomes. The analysis of benefit outcomes (Approach 1) neglects the fact that further patients in the control arm might exhibit a response between Weeks 12 and 24. In Week 12, an improvement in the 6-minute walking test by at least 40 m was already observed in 23% of these patients. Consequently, an RCT duration of at least 24 weeks is necessary to record the disease course in the control arm from Week 12 to Week 24.

Further, the presented data are incomplete. For outcomes on specific AEs, the company presented no analyses from Approach 1.

All things considered, the presented analyses are therefore unsuitable for the benefit assessment of riociguat in comparison with the ACT. This is inconsistent with the company's approach. While the company likewise disregards the PATENT-2 study in its derivation of added benefit, it does present it as supplementary information and lists the supplementary analyses to support its conclusions.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of riociguat in comparison with the ACT in patients with PAH and WHO functional class II to III regarding the improvement of exercise capacity. Consequently, there is no hint of an added benefit of riociguat in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results of the benefit assessment of riociguat in comparison with the ACT.

Table 5: Riociguat (as monotherapy or in combination with ERAs) – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with PAH of WHO functional class II to III to improve exercise capacity	Individually optimized drug therapy, taking into account prior therapies and health status and considering the following therapies: ▪ ERAs (ambrisentan, bosentan, macitentan) ▪ PDE5 inhibitors (sildenafil, tadalafil) ▪ Prostacyclin analogues (iloprost) ▪ Selective prostacyclin receptor agonists (selexipag)	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; ERA: endothelin receptor agonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PDE: phosphodiesterase; WHO: World Health Organisation		

The assessment described above deviates from that of the company, which derives an indication of considerable added benefit on the basis of PATENT-1, supported by PATENT-2.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the G-BA's assessment issued in connection with the market launch in 2014. At the time, the G-BA established a minor added benefit of riociguat. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization on the basis of the special status of orphan drugs, regardless of the underlying data.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58.

3. Ghofrani HA, Galie N, Grimminger F, Grünig E, Humbert M, Jing ZC et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013; 369(4): 330-340.

4. Ghofrani HA, Grimminger F, Grünig E, Huang Y, Jansa P, Jing ZC et al. Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomised, long-term extension trial. Lancet Respir Med 2016; 4(5): 361-371.

5. MSD Sharp Dohme. Fachinformation Adempas Filmtabletten: Stand Februar. 2019.

6. Committee for Medicinal Products for Human Use. Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension [online]. 2009 [Accessed: 10.02.2020]. URL: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigations-medicinal-products-treatment-pulmonary-arterial-hypertension_en.pdf.

7. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016; 37(1): 67-119.

8. Hoeper MM, Apitz C, Grünig E, Halank M, Ewert R, Kaemmerer HJ et al. Gezielte Therapie der pulmonal arteriellen Hypertonie: Empfehlungen der Kölner Konsensuskonferenz 2016. Dtsch Med Wochenschr 2016; 141(S 01): S33-S41.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-31-riociguat-pah-benefit-assessment-according-to-35a-social-code-book-v.13051.html.