IQWiG Reports – Commission No. A20-30

Riociguat (chronic thromboembolic pulmonary 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 (chronisch thromboembolische pulmonale 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Riociguat (chronic thromboembolic pulmonary hypertension) – Benefit assessment according to §35a Social Code Book V

Commissioning agency

Federal Joint Committee

Commission awarded on

17 March 2020

Internal Commission No.

A20-30

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

Due to the corona pandemic, no external experts were involved.

IQWiG employees involved in the dossier assessment

- Michael Köhler
- Nadia Abu Rajab
- Ulrich Grouven
- Tatjana Hermanns
- Sabine Ostlender
- Daniela Preukschat
- Min Ripoll
- Beate Wieseler

Keywords: Riociguat, Hypertension – Pulmonary, Benefit Assessment

Table of contents

Page

List of tables[2]

Page

[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
BSC	best supportive care
CTEPH	chronic thromboembolic pulmonary hypertension
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NO	nitric oxide
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO	World Health Organization

2 Benefit assessment

2.1 Executive summary of the benefit 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 comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) with regard to improving exercise capacity in adult patients of World Health Organization (WHO) functional class II to III with chronic thromboembolic pulmonary hypertension (CTEPH). Patients included must exhibit inoperable CEPTH or persistent/recurrent CEPTH after surgical treatment.

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of riociguat

Therapeutic indication	**ACT**[a]
Adult patients of WHO functional class II to III with ▪ inoperable CTEPH ▪ persistent/recurrent CTEPH after surgical treatment to improve exercise capacity	BSC[b]
a. Presentation of the respective ACT specified by the G-BA. b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. Supportive measures (e.g. anticoagulation, treatment of cardiovascular symptoms) are understood to be performed in both study arms. ACT: appropriate comparator therapy; BSC: best supportive Care; CTEPH: chronic thromboembolic pulmonary hypertension; G-BA: Federal Joint Committee; 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 (CHEST-1) and included this study in its benefit assessment. As supplementary evidence, the company considered the associated 1-arm extension study, CHEST-2. Neither of the studies presented by the company are suitable for the benefit assessment.

CHEST-1 is an RCT with a total treatment and follow-up duration of 16 weeks. The study included 262 patients. The patient population of the study fits the therapeutic indication. Riociguat treatment was administered in compliance with the Summary of Product Characteristics (SPC). Accordingly, riociguat treatment starts with an 8-week up-titration phase, during which time the dose is incrementally increased every 2 weeks. This up-titration phase was implemented in the study; therefore, the follow-up period under maintenance dose was only 8 weeks in duration.

CHEST-2 is a 1-arm extension study of CHEST-1. In CHEST-2, 155 patients from the riociguat arm of CHEST-1 each received continued treatment with their individual maintenance dose, while 82 patients from the control arm underwent an 8-week blinded dose-adjustment phase to establish riociguat maintenance therapy. Rather than using CHEST-2 to derive any added benefit or harm, the company relied on CHEST-2-based supplementary analyses to determine the robustness of CHEST-1 results.

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

Due to its short follow-up duration of only 16 weeks, CHEST-1 is unsuitable for the benefit assessment in the therapeutic indication of pulmonary hypertension. Pulmonary hypertension is a chronic condition requiring life-long treatment. Short-term studies cannot be used to draw any conclusions on the longer-term persistence of any short-term effects. Further, these studies are unsuitable for observing any effects which arise at a later point, particularly adverse events (AEs). Any benefit assessment in this therapeutic indication requires studies of at least 24 weeks in duration for weighing benefits and harms.

Further, it is questionable whether the ACT of BSC was adequately implemented in the CHEST-1 study since a number of therapies which might be of patient benefit in the given therapeutic indication were not approved. This includes NO donors (including in the study's control arm) as well as concomitant physical therapy.

CHEST-2 data are of no informative value with regard to any potential treatment effects arising after 16 weeks since for these data, no randomized comparison with the ACT is available. Moreover, in its various robustness analyses, the company engages in selective reporting of study data.

For the above reasons, no suitable data are available for the assessment of riociguat in the treatment of adult patients with inoperable CEPTH or persistent/recurrent CEPTH after surgical treatment. 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 added benefit of riociguat.

Table 3: Riociguat – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients of WHO functional class II to III with ▪ inoperable CTEPH ▪ persistent/recurrent CTEPH after surgical treatment to improve exercise capacity	BSC[b]	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. Supportive measures (e.g. anticoagulation, treatment of cardiovascular symptoms) are understood to be performed in both study arms. ACT: appropriate comparator therapy; BSC: best supportive Care; CTEPH: chronic thromboembolic pulmonary hypertension; G-BA: Federal Joint Committee; 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 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.

[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 comparison with BSC as the ACT with regard to improving exercise capacity in adult patients of WHO functional class II to III with CTEPH. Patients included must exhibit inoperable CEPTH or persistent/recurrent CEPTH after surgical treatment.

Table 4 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of riociguat

Therapeutic indication	**ACT[a]**
Adult patients of WHO functional class II to III with ▪ inoperable CTEPH ▪ persistent/recurrent CTEPH after surgical treatment to improve exercise capacity	BSC[b]
a. Presentation of the respective ACT specified by the G-BA. b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. Supportive measures (e.g. anticoagulation, treatment of cardiovascular symptoms) are understood to be performed in both study arms. ACT: appropriate comparator therapy; BSC: best supportive Care; CTEPH: chronic thromboembolic pulmonary hypertension; G-BA: Federal Joint Committee; 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. 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 BSC.

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

CHEST-1

CHEST-1 is an RCT with a total treatment and follow-up duration of 16 weeks. The study included 262 patients (riociguat: 174, out of which 1 patient received no study drug; placebo: 88). The patient population of the study fits the therapeutic indication. Riociguat treatment was administered in accordance with the SPC [5]. The administration of riociguat requires an 8-week up-titration phase with dose increases every 2 weeks. After individual adjustment to establish the optimal dose, riociguat therapy is taken continuously 3 times daily. This up-titration phase was implemented in the study; therefore, the follow-up period under maintenance dose was only 8 weeks in duration. The study was blinded and compared to placebo. The primary outcome was change in 6-minute walking distance after 16 weeks. The study was completed in June 2012.

CHEST-2

CHEST-2 is a 1-arm extension study of CHEST-1. In CHEST-2, 155 patients from the riociguat arm of CHEST-1 received continued treatment with their individual maintenance dose, while 82 patients from the control arm underwent an 8-week blinded up-titration phase to establish riociguat maintenance therapy.

To confirm the 16-week data from CHEST-1, the company used results from the CHEST-2 study at the time point of 24 weeks after randomization. This time point marks the completion of the up-titration phase in patients who were originally in the control arm, 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 16 was confirmed at Week 24; for all control arm patients with a response at Week 16, a response is assumed for Week 24.

b) Harm outcomes: For the placebo group, it is assumed that no further patients with event are observed between Week 16 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 16 to 24, even patients in the control arm received riociguat).

The company presented these supplementary analyses only selectively. The analyses using "conservative replacement" (Approach 1) and the comparison at Week 24 ("as allocated", Approach 2) were submitted by the company only for the benefit outcomes showing a statistically significant difference between treatment groups at Week 16 (in the CHEST-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 AEs, serious adverse events (SAEs), discontinuation due to AEs, hypotension, haemorrhage, and syncope – and not for further specific AEs.

Moreover, the company reported the 28-month results from CHEST-2 (riociguat arm), but again excluding further specific AEs.

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

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

CHEST-1: Study duration of 16 weeks insufficient for the benefit assessment

Due to its short follow-up duration of only 16 weeks, CHEST-1 is unsuitable for the benefit assessment in the therapeutic indication of pulmonary hypertension. Pulmonary hypertension is a chronic condition requiring life-long treatment. On the basis of short-term studies, it is impossible to draw any conclusions on the longer-term persistence of any short-term effects. Further, these studies are unsuitable for observing any effects which arise at a later point, particularly AEs.

In Module 4A, the company states that a minimum study duration of 3 to 6 months is sufficient for outcomes intended to demonstrate improved exercise capacity, referring to the Guideline on Pulmonary Arterial Hypertension of the European Medical Agency (EMA) [6]. The company's rationale is not persuasive. Any benefit assessment in this therapeutic indication requires studies of at least 24 weeks in duration for weighing benefits and harms.

CHEST-1: Incomplete implementation of the ACT

It is questionable whether the CHEST-1 study adequately implemented the ACT. In CTEPH, BSC primarily involves the treatment of cardiovascular symptoms (arrhythmia, dyspnoea, angina pectoris, etc.) and the prevention of renewed thromboembolic events. Alongside the study drug, both CHEST-1 study arms received several concomitant therapies which, as

adjunctive treatment of CTEPH and its complications, can be deemed components of BSC. These therapies include, in particular, oral anticoagulants (used by > 95% of patients), diuretics (61% to 76%), calcium channel blockers (20%), digitalis preparations (10%), and oxygen (22%). The CHEST-1 study, however, disallowed the concomitant administration of nitric oxide (NO) donors (e.g. nitrates) [3]. This exclusion may potentially violate the appropriate standards of care. For instance, the current national disease management guideline on chronic coronary heart disease recommends rapid-acting and slow-acting nitrates for the acute and long-term therapy of angina pectoris [7-9].

In this context, the company asserts that all measures performed as part of BSC would have to be allowed in both study arms. This view is misguided. Riociguat is in fact contraindicated in patients simultaneously receiving NO donors [5], and the blinded design rules out NO donors (to avoid a combination of riociguat and NO donors in the intervention arm). Conversely, an open-label study design (e.g. where investigators are not blinded) could certainly have allowed the use of NO donors as part of BSC in the control arm.

Further, the CHEST-1 study disallowed any concomitant physical therapy measures (exercise therapy and rehabilitation). Yet European guidelines on the treatment of pulmonary hypertension recommend these measures since RCT data suggest that they can contribute to the improvement in exercise capacity [10,11].

All things considered, the CHEST-1 study fails to fully implement BSC.

One-arm extension study CHEST-2 of no informative value for the benefit assessment

Due to its lack of a comparator arm, the CHEST-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 16.

For all outcome categories, the analyses using a conservative replacement strategy (Approach 1) included patients observed with an event at Week 24 in the intervention arm, while values at Week 16 were used in the control arm. The company calls this the most conservative analysis possible. However, this designation is apt only for harm outcomes. The analysis of benefit outcomes (Approach 1) disregards the fact that further patients in the control arm might exhibit a response between Weeks 16 and 24. At Week 16, 24% of these patients already exhibited an improvement in the 6-minute walking test by at least 40 m. Consequently, an RCT duration of at least 24 weeks is necessary to record the disease course in the control arm from Week 16 to Week 24.

Moreover, the presented data are incomplete. The company did not submit any analyses as per Approach 1 for outcomes on specific AEs, particularly on those already exhibiting a disadvantage of riociguat after 16 weeks (e.g. System Organ Class [SOC] gastrointestinal disorders, SOC nervous system disorders). Further, the analyses using a conservative

replacement strategy do indeed suggest some potential disadvantages of riociguat, e.g. regarding the outcome of SAEs.

Hence, the supplementary analyses presented by the company on the CHEST-2 study are not only incomplete, but also highlight the necessity of observing even effects which might manifest only in the longer term (e.g. SAEs) by selecting a sufficient study duration. These are prerequisites for adequately weighing benefits and harms.

All things considered, the presented analyses are 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 CHEST-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

No suitable data are available for assessing the added benefit of riociguat in patients with CTEPH of WHO functional classes II to III with regard to the 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.

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 – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients of WHO functional class II to III with ▪ inoperable CTEPH ▪ persistent/recurrent CTEPH after surgical treatment to improve exercise capacity	BSC[b]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.

b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. Supportive measures (e.g. anticoagulation, treatment of cardiovascular symptoms) are understood to be performed in both study arms.

ACT: appropriate comparator therapy; BSC: best supportive Care; CTEPH: chronic thromboembolic pulmonary hypertension; G-BA: Federal Joint Committee; WHO: World Health Organization

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit on the basis of the presented data.

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, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013; 369(4): 319-329.

4. Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Hoeper MM, Jansa P et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur Respir J 2015; 45(5): 1293-1302.

5. MSD. Adempas 0,5 mg/–1 mg/–1,5 mg/–2 mg/–2,5 mg Filmtabletten: Fachinformation [online]. 02.2019 [Accessed: 15.04.2020]. URL: https://www.fachinfo.de/.

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. Gomez A, Bialostozky D, Zajarias A, Santos E, Palomar A, Martinez ML et al. Right ventricular ischemia in patients with primary pulmonary hypertension. J Am Coll Cardiol 2001; 38(4): 1137-1142.

8. Galie N, Saia F, Palazzini M, Manes A, Russo V, Bacchi Reggiani ML et al. Left main coronary artery compression in patients with pulmonary arterial hypertension and angina. J Am Coll Cardiol 2017; 69(23): 2808-2817.

9. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Chronische KHK: Langfassung; Version 1 [online]. 04.2019 [Accessed: 15.04.2020]. URL: https://www.leitlinien.de/mdb/downloads/nvl/khk/khk-5aufl-vers1-lang.pdf.

10. Grunig E, Eichstaedt C, Barbera JA, Benjamin N, Blanco I, Bossone E et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. Eur Respir J 2019; 53(2): 1800332.

11. Wilkens H, Konstantinides S, Lang IM, Bunck AC, Gerges M, Gerhardt F et al. Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol 2018; 272(Suppl): 69-78.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-30-riociguat-cteph-benefit-assessment-according-to-35a-social-code-book-v.13052.html.