Riociguat
(pulmonary arterial hypertension, children and adolescents)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Riociguat (Pulmonal arterielle Hypertonie, Kinder und Jugendliche) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the Federal Association for Children with Heart Disease e.V. (Bundesverband Herzkranke Kinder e.V., BVHK) for participating in the written exchange about how he/she experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
WHO	World Health Organization

I 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 (in combination with endothelin receptor antagonists). 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 26 June 2023.

Research question

The aim of the present report is to assess the added benefit of riociguat in combination with endothelin receptor antagonists (hereinafter referred to as riociguat + endothelin receptor agonists) in comparison with the appropriate comparator therapy (ACT) in children and adolescents under 18 years of age and weighing ≥ 50 kg with pulmonary arterial hypertension (PAH) of World Health Organization (WHO) functional classes II to III.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of riociguat + endothelin receptor antagonists

Therapeutic indication	**ACT[a]**
Treatment of children and adolescents under 18 years of age and weighing ≥ 50 kg with PAH of WHO functional classes II to III[b, c]	Individualized treatment[d, e, f] taking into account in particular the prior therapies, the severity and the underlying diseases choosing from ▪ endothelin receptor antagonists: bosentan, ambrisentan ▪ phosphodiesterase type 5 inhibitors: sildenafil, tadalafil

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients included in the study are not eligible for a lung transplant.
c. According to the G-BA, the recommendations of the guidelines 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 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. Therefore, it is assumed that the patients included in the study are not eligible for treatment with calcium channel blockers alone.
d. According to the G-BA, the available evidence contains recommendations for non-drug physiotherapeutic measures to improve symptoms and physical performance. Physiotherapeutic interventions can be indicated both in the sense of the "Heilmittel-Richtlinie", (Remedies Directive) (physical therapy, e.g. physiotherapy, exercise therapy, breathing therapy) and in the sense of targeted training therapy to improve performance (e.g. after surgical treatment). Only patients without significant limitations in their endurance are eligible for targeted training therapy to improve performance, while physiotherapeutic interventions in the sense of the "Heilmittel-Richtlinie" (Remedies Directive) (physical therapy, e.g. physiotherapy, exercise therapy, breathing therapy) might be suitable for all patients. If indicated, physiotherapy measures should be made available to patients in both arms of the study.
e. It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) was possible in both study arms.
f. For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; WHO: World Health Organization

The company followed the G-BA's specification on the ACT. The company notes that due to the availability of only a few specific approved treatment options in Germany, non-approved drugs are extensively used for the treatment of children with PAH. Although the company did not include the non-approved drugs macitentan, iloprost and selexipag in its benefit assessment, it did consider them when quantifying the costs of the ACT in Module 3 A of the dossier. In agreement with the company, the present benefit assessment is conducted in comparison with the G-BA's ACT.

The assessment is 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 are used for the derivation of added benefit.

Results

Concurring with the company, no direct comparative RCT on riociguat + endothelin receptor antagonists versus the ACT was identified for the benefit assessment. As the company did not identify any RCT on the direct comparison of riociguat + endothelin receptor antagonists versus the ACT, it conducted an information retrieval for further evidence on riociguat + endothelin receptor antagonists and identified the single-arm PATENT-CHILD study, which it used to assess the added benefit. However, as this study does not allow a comparison with the ACT, it is not suitable for assessing the added benefit of riociguat + endothelin receptor antagonists.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of riociguat + endothelin receptor antagonists 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 shows a summary of the probability and extent of added benefit of riociguat + endothelin receptor antagonists.

[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].

Table 3: Riociguat + endothelin receptor antagonists – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of children and adolescents under 18 years of age and weighing ≥ 50 kg with PAH of WHO functional classes II to III[b, c]	Individualized treatment[d, e, f] taking into account in particular the prior therapies, the severity and the underlying diseases choosing from ▪ endothelin receptor antagonists: bosentan, ambrisentan ▪ phosphodiesterase type 5 inhibitors: sildenafil, tadalafil	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients included in the study are not eligible for a lung transplant.
c. According to the G-BA, the recommendations of the guidelines 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 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. Therefore, it is assumed that the patients included in the study are not eligible for treatment with calcium channel blockers alone.
d. According to the G-BA, the available evidence contains recommendations for non-drug physiotherapeutic measures to improve symptoms and physical performance. Physiotherapeutic interventions can be indicated both in the sense of the "Heilmittel-Richtlinie, (Remedies Directive) (physical therapy, e.g. physiotherapy, exercise therapy, breathing therapy) and in the sense of targeted training therapy to improve performance (e.g. after surgical treatment). Only patients without significant limitations in their endurance are eligible for targeted training therapy to improve performance, while physiotherapeutic interventions in the sense of the "Heilmittel-Richtlinie", (Remedies Directive) (physical therapy, e.g. physiotherapy, exercise therapy, breathing therapy) might be suitable for all patients. If indicated, physiotherapy measures should be made available to patients in both arms of the study.
e. It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) was possible in both study arms.
f. For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; WHO: World Health Organization

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of riociguat in combination with endothelin receptor antagonists (hereinafter referred to as riociguat + endothelin receptor agonists) in comparison with the ACT in children and adolescents under 18 years of age and weighing ≥ 50 kg with PAH of WHO functional classes II to III.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of riociguat + endothelin receptor antagonists

Therapeutic indication	**ACT[a]**
Treatment of children and adolescents under 18 years of age and weighing ≥ 50 kg with PAH of WHO functional classes II to III[b, c]	Individualized treatment[d, e, f] taking into account in particular the prior therapies, the severity and the underlying diseases choosing from ▪ endothelin receptor antagonists: bosentan, ambrisentan ▪ phosphodiesterase type 5 inhibitors: sildenafil, tadalafil

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients included in the study are not eligible for a lung transplant.
c. According to the G-BA, the recommendations of the guidelines 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 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. Therefore, it is assumed that the patients included in the study are not eligible for treatment with calcium channel blockers alone.
d. According to the G-BA, the available evidence contains recommendations for non-drug physiotherapeutic measures to improve symptoms and physical performance. Physiotherapeutic interventions can be indicated both in the sense of the "Heilmittel-Richtlinie, (Remedies Directive) (physical therapy, e.g. physiotherapy, exercise therapy, breathing therapy) and in the sense of targeted training therapy to improve performance (e.g. after surgical treatment). Only patients without significant limitations in their endurance 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 therapy, breathing therapy) might be suitable for all patients. If indicated, physiotherapy measures should be made available to patients in both arms of the study.
e. It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) was possible in both study arms.
f. For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criterion (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; WHO: World Health Organization

The company followed the G-BA's specification on the ACT. With reference to [3,4], the company notes that due to the availability of only a few specific approved treatment options

in Germany, non-approved drugs are extensively used for the treatment of children with PAH. Although the company did not include the non-approved drugs macitentan, iloprost and selexipag in its benefit assessment, it did consider them when quantifying the costs of the ACT in Module 3 A of the dossier. In agreement with the company, the present benefit assessment is conducted in comparison with the G-BA's ACT.

The assessment is 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 are used for the derivation of added benefit. This departs from the inclusion criteria used by the company, which applied no restrictions of study duration and also considered non-randomized trials. This deviation is of no consequence for the present assessment, as the company did not present any data on the comparison of riociguat + endothelin receptor antagonists with the ACT (for reasons, see Chapter I 3).

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on riociguat (status: 3 April 2023)
- bibliographical literature search on riociguat (last search on 3 April 2023)
- search in trial registries/trial results databases for studies on riociguat (last search on 3 April 2023)
- search on the G-BA website for riociguat (last search on 3 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on riociguat (last search on 4 July 2023); for search strategies, see Appendix I A of the full dossier assessment

Concurring with the company, no direct comparative RCT on riociguat + endothelin receptor antagonists versus the ACT was identified from the check of the completeness of the study pool.

As the company did not identify any RCT for the direct comparison of riociguat + endothelin receptor antagonists versus the ACT, it conducted an information retrieval for further evidence on riociguat + endothelin receptor antagonists. In this information retrieval, the company identified the single-arm PATENT-CHILD study [5] and used this study to derive the added benefit. In its conclusion on the added benefit, the company also argues with comparable results of adults with children and adolescents. The company neither conducted an information retrieval nor presented data on the ACT. The completeness of the study pool for further investigations was not checked.

The data presented by the company are unsuitable for drawing any conclusions on the added benefit of riociguat + endothelin receptor antagonists in comparison with the ACT. This is justified below.

Evidence presented by the company – PATENT-CHILD study

The PATENT-CHILD study is a single-arm study investigating riociguat in children and adolescents aged 6 to < 18 years. The study included children and adolescents with PAH of WHO functional classes II to III. According to the study design, there was no restriction on the body weight of the children and adolescents included in the study. Children and adolescents with a body weight < 50 kg at baseline received riociguat in the form of an oral suspension, while tablets were administered orally if the body weight was ≥ 50 kg. According to the

inclusion criteria, pretreatment with endothelin receptor antagonists and/or prostacyclin analogues had to have taken place within the last 12 weeks before the start of the study, which was to be continued during the study. The use of phosphodiesterase inhibitors was not allowed during the study.

The study included a total of 24 children and adolescents aged 6 to < 17 years. Of these, 23 (96%) children and adolescents had PAH of WHO functional classes II and III. In addition to riociguat, all children and adolescents included in the study received endothelin receptor antagonists as concomitant treatment. In addition, 9 (38%) children and adolescents were also treated with prostacyclin analogues.

Treatment in the study was administered over a total of 24 weeks, whereby in the first 8 weeks the dosage was individually adjusted at the investigator's discretion as part of a dose titration phase depending on body weight and on the basis of monitoring of systolic blood pressure, well-being and clinical condition. This dosage was maintained for 16 weeks in the subsequent maintenance phase.

The aim of the study was to investigate the safety, tolerability and pharmacokinetics of riociguat in the treatment of children and adolescents aged 6 to < 18 years with PAH.

PATENT-CHILD study unsuitable for the benefit assessment

The PATENT-CHILD study is unsuitable for the derivation of an added benefit because, as a single-arm study, it does not permit a comparison with the ACT. Moreover, riociguat was not used in accordance with the specification of the Summary of Product Characteristics (SPC) [6] in a large proportion of the children and adolescents included in the study. According to the company's information in Module 4 A of the dossier, only 7 (29%) children and adolescents had a body weight of ≥ 50 kg according to the SPC. Furthermore, the titration algorithm for riociguat provided for in the study planning does not correspond to the specifications of the SPC. According to the SPC, dose increases are planned depending on the age group if certain systolic blood pressure thresholds are exceeded (≥ 90 mmHg in 6 to < 12-year-olds and ≥ 95 mmHg in 12 to < 18-year-olds), provided there are no signs or symptoms of hypotension. In the study, however, dose titration was at the discretion of the investigator. From the information provided by the company, it is not possible to assess whether and, if so, for what proportion of patients the dose titration in the study deviated from the specifications of the SPC.

Transferring the added benefit from adults to children is not possible

In its conclusion on the added benefit, the company argues with comparable results of adults with children and adolescents, but it does not present a processing of results for its reasoning. Furthermore, it should be noted that no suitable data were available for adults with PAH for the comparison of riociguat + endothelin receptor antagonists with the drugs of the ACT for

the benefit assessment; an added benefit is therefore not proven for adults [7]. Therefore, transferring the added benefit from adults to the population of children and adolescents is not possible in the present therapeutic indication.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of riociguat + endothelin receptor antagonists compared with the ACT for the treatment of children and adolescents under 18 years of age and weighing ≥ 50 kg with PAH of WHO functional classes II to III. This results in no hint of an added benefit of riociguat + endothelin receptor antagonists in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for riociguat + endothelin receptor antagonists in comparison with the ACT.

Table 5: Riociguat + endothelin receptor antagonists – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Treatment of children and adolescents under 18 years of age and weighing ≥ 50 kg with PAH of WHO functional classes II to III[b,c]	Individualized treatment[d, e, f] taking into account in particular the prior therapies, the severity and the underlying diseases choosing from ▪ endothelin receptor antagonists: bosentan, ambrisentan ▪ phosphodiesterase type 5 inhibitors: sildenafil, tadalafil	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
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ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; WHO: World Health Organization

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

I 6 References

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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-57.html.