IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Macitentan (pulmonary arterial hypertension) –

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

Extract

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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:

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment[2]:

- Susanne Haag
- Gertrud Egger
- Lisa Junge
- Ulrike Lampert
- Miriam Luhnen
- Katrin Nink
- Christoph Schürmann
- Anja Schwalm
- Beate Wieseler

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[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **4**
2.3 Information retrieval and study pool **4**
2.3.1 Information retrieval 4
2.3.2 Study pool of the company 5
2.4 Results on added benefit **7**
2.5 Extent and probability of added benefit **7**
2.6 List of included studies **8**
References for English extract **9**

List of tables[3]

Page

Table 2: Research questions of the benefit assessment of macitentan 1
Table 3: Macitentan – extent and probability of added benefit 3
Table 4: Research questions of the benefit assessment of macitentan 4
Table 5: Macitentan – extent and probability of added benefit 8

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ERA	endothelin receptor antagonist
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
PDE5	phosphodiesterase type 5
RCT	randomized controlled trial
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 macitentan. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 13 October 2016.

Research question

The aim of the present report was to assess the added benefit of macitentan, as monotherapy or in combination, in comparison with individually optimized drug treatment specified by the physician under consideration of the respective approval status as appropriate comparator therapy (ACT) in adult patients with pulmonary arterial hypertension (PAH) of World Health Organization (WHO) functional class II to III.

Table 2: Research questions of the benefit assessment of macitentan

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	As monotherapy or in combination, for the long-term treatment of PAH in adult patients of WHO functional class II to III	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; WHO: World Health Organization		

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 6 months were used for the derivation of the added benefit.

Results

The company identified no studies that allow a derivation of the added benefit of macitentan in comparison with the ACT specified by the G-BA. Nevertheless, the company presented the approval study SERAPHIN to show the medical benefit of macitentan. The presentation of the benefit of macitentan had no relevance for the assessment of the added benefit, however.

No implementation of the appropriate comparator therapy in the SERAPHIN study

The SERAPHIN study was a randomized, controlled, double-blind, 3-arm study on the comparison of macitentan (3 mg or 10 mg) with placebo. Adults and children (≥ 12 years of age) with symptomatic PAH of WHO functional class II to IV were included. A total of

742 patients were randomly assigned to treatment with macitentan 3 mg (250 patients), macitentan 10 mg (242 patients) or placebo (250 patients).

According to the G-BA's specification, the ACT was individually optimized drug treatment specified by the physician under consideration of the respective approval status. Drug (combinations) approved in the therapeutic indication of macitentan that have proven their worth in practical use were to be considered. Rigid prerequisites or restrictions of the physician's choice of drugs or of dose adjustments were inadequate.

The SERAPHIN study allows no comparison of macitentan versus the ACT and is therefore unsuitable for the derivation of an added benefit. This also concurs with the company's assessment.

However, the company explained that it is not possible to plan and conduct a study of direct comparison of macitentan versus individually optimized treatment. The company's rationale was not followed. The company's rationale is not comprehensible particularly because the company itself is currently conducting an (open-label) RCT in children with PAH, in which macitentan is compared with standard treatment (that is commonly used in the respective study centre).

Derivation of an added benefit by the company on the basis of "qualitative" advantages

Nonetheless, the company derived an added benefit for the total target population on the basis of "qualitative advantages of macitentan". For this purpose, it used the results of the placebo-controlled SERAPHIN study and referred to the "clinically relevant improvements in comparison with placebo". In addition, the company found "clinical and patient-relevant advantages" in comparison with individual components of the ACT (e.g. other endothelin receptor antagonists [ERAs]). For this purpose, it used the event rates of individual safety and efficacy outcomes of the macitentan arm of the SERAPHIN study and conducted a descriptive comparison with the results from individual study arms of other studies in the therapeutic indication (AMBITION, COMPASS-2). Furthermore, the company regarded the annual turnover achieved and the degree of market penetration of macitentan as a confirmation "that macitentan is considered to have a patient-relevant added benefit also in clinical practice". Overall, the data presented by the company to justify the "qualitative advantages" of macitentan are unsuitable to derive an added benefit of macitentan.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Table 3 presents a summary of the extent and probability of the added benefit of macitentan.

Table 3: Macitentan – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
As monotherapy or in combination, for the long-term treatment of PAH in adult patients of WHO functional class II to III	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. 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.

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in the framework of the market access in 2014. In this assessment, the G-BA had determined a minor added benefit of macitentan. However, the deviation was due to the special situation of the orphan assessment at the time. In this case, no ACT is specified by the G-BA, but the extent of added benefit is assessed exclusively on the basis of the approval studies, irrespective of whether the comparator therapy used in the respective approval study is appropriate.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report was to assess the added benefit of macitentan, as monotherapy or in combination, in comparison with individually optimized drug treatment specified by the physician under consideration of the respective approval status as ACT in adult patients with PAH of WHO functional class II to III.

Table 4: Research questions of the benefit assessment of macitentan

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	As monotherapy or in combination, for the long-term treatment of PAH in adult patients of WHO functional class II to III	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status
a: Presentation of the ACT specified by the G-BA. 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 of the ACT.

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 6 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

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 macitentan (status: 29 August 2016)
- bibliographical literature search on macitentan (last search on 12 September 2016)
- search in trial registries for studies on macitentan (last search on 25 August 2016)
- bibliographical literature search on ACTs (last search on 12 September 2016)
- search in trial registries for studies on ACTs (last search on 25 August 2016)

To check the completeness of the study pool:

- search in trial registries for studies on macitentan (last search on 19 October 2016)

No relevant study was identified from the check. This concurs with the approach of the company, which also identified no relevant study.

2.3.2 Study pool of the company

From the steps of information retrieval mentioned, the company identified no studies that would allow a derivation of the added benefit of macitentan in comparison with the ACT specified by the G-BA. The company itself described in its dossier that there was no study in which "the ACT defined by the G-BA is completely or even only approximately represented". As a result, no direct or indirect comparison of macitentan with the ACT is possible on the basis of RCTs.

Concurring with the company, there are therefore no relevant RCTs for the derivation of an added benefit of macitentan.

Description of the approval study SERAPHIN

Nevertheless, the company presented the approval study SERAPHIN [3-9] to show the medical benefit of macitentan.

The presentation of the benefit of macitentan had no relevance for the assessment of the added benefit. Nonetheless, the characteristics of the SERAPHIN are briefly presented below to show that the derivation of the added benefit is not possible on the basis of the SERAPHIN study.

The study characteristics of the SERAPHIN study and information on the intervention (including allowed/prohibited concomitant medication) in table format can be found in Appendix A of the full dossier assessment.

The SERAPHIN study was a randomized, controlled, double-blind, 3-arm study on the comparison of macitentan (3 mg or 10 mg) with placebo. Adults and children (≥ 12 years of age) with symptomatic PAH of WHO functional class II to IV were included. According to the Summary of Product Characteristics (SPC), however, macitentan is only approved in adult patients with PAH of WHO functional class II to III [10] so that individual patients may not have been treated in compliance with the approval. This only applied to 2.7% (< 18 years) and 1.9% (WHO functional class IV) of the study participants.

A total of 742 patients were randomly assigned to treatment with macitentan 3 mg[5] (250 patients), macitentan 10 mg (242 patients) or placebo (250 patients). In the study, macitentan 10 mg was administered once daily orally, which is in compliance with the approval [10]. The median treatment duration was 118.4 weeks in the macitentan arm (10 mg) and 101.3 weeks in the placebo arm.

No implementation of the appropriate comparator therapy in the SERAPHIN study

According to the G-BA's specification, the ACT was individually optimized drug treatment specified by the physician under consideration of the respective approval status. Drug

[5] A dosage of 3 mg/day is not approved in Germany and is therefore not considered further.

(combinations) approved in the therapeutic indication of macitentan that have proven their worth in practical use were to be considered. Rigid prerequisites or restrictions of the physician's choice of drugs or of dose adjustments were inadequate.

As presented by the company itself, the SERAPHIN study was a placebo-controlled study. At the start of the study, treatment in the intervention arm was expanded by administration of macitentan. No expansion was mandated in the control arm – only additional placebo was administered. Continuation of any ongoing PAH-specific treatment (e.g. with iloprost, oral phosphodiesterase type 5 [PDE5] inhibitors) was allowed in the study if the patients had received a stable dosage of these drugs for at least 3 months before randomization. Whereas 36.3% of the patients included in the study were receiving no PAH-specific medication at the start of the study, 63.7% of the patients were pretreated with PAH-specific therapy (mainly sildenafil monotherapy [57.6%]). The use of a new treatment for PAH in the absence of documented PAH worsening was strongly discouraged during the study. In addition, some drugs for the treatment of PAH were explicitly excluded in the study (e.g. ERAs, parenteral prostanoids; see Table 10 of the full dossier assessment) and their use was only allowed in case of worsening of the disease. The use of ERAs was only allowed after discontinuation of the study medication. In addition, worsening of the PAH in conjunction with a new treatment was defined as primary outcome event (see Table 9 of the full dossier assessment).

In summary, the study therefore allows no comparison of macitentan versus the ACT and is unsuitable for the derivation of an added benefit. This also concurs with the company's assessment.

Feasibility of a study of direct comparison of macitentan versus the ACT

In Module 4 A, Section 4.4.1, the company explained that it is not possible to plan and conduct a study of direct comparison of macitentan versus individually optimized treatment. The company's rationale was not followed (see Section 2.7.2.8.1 of the full dossier assessment).

The company's rationale is not comprehensible particularly because the company itself is currently conducting an (open-label) RCT in children with PAH, in which macitentan is compared with standard treatment (that is commonly used in the respective study centre) [11,12].

Derivation of an added benefit by the company

Although the company itself found that no proof of an added benefit of macitentan versus the ACT was possible in the indirect or in the direct comparison on the basis of RCTs, it still derived a hint of a non-quantifiable added benefit for the total target population on the basis of "qualitative advantages of macitentan".

In particular, it used the results of the placebo-controlled SERAPHIN study to justify the "qualitative advantages of macitentan" and referred to the "clinically relevant improvements

in comparison with placebo", which, from the company's point of view were shown for several outcomes of the SERAPHIN study in comparison with placebo treatment. As explained above, however, no conclusions on the added benefit of macitentan in comparison with the ACT can be derived from the placebo-controlled SERAPHIN study.

In addition, the company found "clinical and patient-relevant advantages" in comparison with individual components of the ACT (e.g. other ERAs). For this purpose, it used the event rates of individual safety and efficacy outcomes of the macitentan arm of the SERAPHIN study and conducted a descriptive comparison with the results from individual study arms of other studies in the therapeutic indication (AMBITION [13], COMPASS-2 [14]). These selective presentations of individual study results are not relevant for the benefit assessment, however. Furthermore, the company itself explained in Module 4 A, Section 4.4.1 that the studies AMBITION and COMPASS-2 deviated too far from the SERAPHIN study (e.g. regarding study population, study duration, definitions of outcomes) so that it was not possible to draw a "comparative conclusion on the efficacy and safety of two drugs" in the indirect comparison.

In addition, the company regarded the fact that macitentan had achieved an annual turnover of > 50 million euros already 2.5 years after market entry and was holding a total market share of endothelin receptor antagonists of 36% as a confirmation "that macitentan is considered to have a patient-relevant added benefit also in clinical practice". Both the annual turnover achieved and the degree of market penetration are not relevant for the assessment of the added benefit, however.

Overall, the data presented by the company to justify the "qualitative advantages" of macitentan are unsuitable to derive an added benefit of macitentan.

2.4 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of macitentan in its dossier. This resulted in no hint of an added benefit of macitentan in comparison with the ACT; an added benefit is therefore not proven.

2.5 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of macitentan in adult patients with PAH. Hence there was no hint of an added benefit of macitentan in comparison with the ACT. An added benefit for these patients is therefore not proven.

The result of the assessment of the added benefit of macitentan in comparison with the ACT is summarized in Table 5.

Table 5: Macitentan – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
As monotherapy or in combination, for the long-term treatment of PAH in adult patients of WHO functional class II to III	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; WHO: World Health Organization		

This approach deviates from that of the company. The company stated that it was not possible to prove an added benefit of macitentan in the direct or in the indirect comparison on the basis of RCTs. Nonetheless, it derived a hint of a non-quantifiable added benefit of macitentan without presenting suitable data for this.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in the framework of the market access in 2014 [15,16]. In this assessment, the G-BA had determined a minor added benefit of macitentan. However, the deviation was due to the special situation of the orphan assessment at the time. In this case, no ACT is specified by the G-BA, but the extent of added benefit is assessed exclusively on the basis of the approval studies, irrespective of whether the comparator therapy used in the respective approval study is appropriate.

2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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