

IQWiG Reports – Commission No. A16-36

Selexipag (pulmonary arterial hypertension) –

Benefit assessment according to §35a Social Code Book V¹

Extract

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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
PDE-5	phosphodiesterase-5
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
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 selexipag. 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 14 June 2016.

Research question

The aim of the present report was to assess the added benefit of selexipag 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 World Health Organization (WHO) functional class II to III with pulmonary arterial hypertension (PAH). Selexipag is used as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase-5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Table 2: Research question of the benefit assessment of selexipag

Research question	Therapeutic indication	Appropriate comparator therapy ^a
1	Long-term treatment of PAH in adult patients with WHO functional class II to III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status
a: Presentation of the appropriate comparator therapy specified by the G-BA. ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase-5; WHO: World Health Organization		

The company formulated a different research question. The company initially stated to choose individual drug treatment specified by the physician and under consideration of the respective approval status. In contrast to the G-BA, however, the company did not include the additional criterion that this treatment was to be individually optimized and considered iloprost to be the only possible drug treatment option of an individual drug treatment. In addition, the company defined the subpopulations a and b. “Subpopulation a” comprised patients for whom also iloprost is not an option, and for whom therefore only watchful waiting until worsening of the PAH is available. “Subpopulation b” comprised patients for whom iloprost is an option.

The company’s limitation to use iloprost as the only option of individually optimized drug treatment and the subsequent division of the population was inadequate. The ACT specified

by the G-BA was used for the present assessment. No division into subpopulations was conducted in the present benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials with a minimum duration of 6 months were used for the derivation of the added benefit.

Results

The company identified the study GRIPHON as relevant study for its “subpopulation a” (patients for whom iloprost is not an option and for whom watchful waiting until worsening of the PAH is the only treatment option).

The GRIPHON study was a randomized, controlled, double-blind study on the comparison of selexipag with placebo. According to the inclusion criteria, adult patients 18 to 75 years of age with symptomatic PAH and a 6-minute walk distance of 50 m to 450 m at the start of the study were included. Patients with all WHO functional classes (I to IV) were included. The majority of the patients was allocated to the WHO functional class II (45.8%) or III (52.5%), and therefore did not correspond to the therapeutic indication of selexipag.

The study presented by the company was unsuitable to draw conclusions on the added benefit of selexipag in comparison with the ACT. The study was neither suitable to answer the research question defined by the company nor to answer the research question of the present benefit assessment:

- The GRIPHON study was unsuitable to investigate the company’s research question on patients for whom iloprost is unsuitable (“subpopulation a”). Half of the patients included in the study were patients with WHO functional class III. Iloprost is approved precisely for these patients. In addition, these patients could receive a PAH-specific treatment in case of worsening of the disease, i.e. when reaching a component of the composite primary outcome. This treatment was not restricted to certain drugs, and therefore also comprised iloprost. However, the treatment and observation period of the study ended with the expansion of the treatment.
- 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. All (combinations of) drugs in the therapeutic indication of selexipag were to be considered. Rigid prerequisites or restrictions of the physician’s choice of drugs and restrictions of dose adjustments were inadequate.

The GRIPHON study was a placebo-controlled study. At the start of the study, treatment in the intervention arm was expanded by administration of selexipag. No expansion was mandated in the control arm – only placebo was administered. In both treatment arms, it was not allowed to adjust the ongoing medication for treatment of the PAH. Hence the study only allowed a comparison of selexipag with placebo. The study design allowed

individual adjustment of the PAH-specific treatment in case of worsening of the PAH, but this was defined as primary outcome event and therefore ended the blinded and randomized treatment phase for the patient.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

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

Table 3: Selexipag – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy^a	Extent and probability of added benefit
Long-term treatment of PAH in adult patients with WHO functional class II to III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase-5; WHO: World Health Organization		

The G-BA decides on the added benefit.

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 selexipag in comparison with individually optimized drug treatment specified by the physician under consideration of the respective approval status as ACT in adult patients with WHO functional class II to III with PAH. Selexipag is used as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Table 4: Research question of the benefit assessment of selexipag

Research question	Therapeutic indication	Appropriate comparator therapy ^a
1	Long-term treatment of PAH in adult patients with WHO functional class II to III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status
a: Presentation of the appropriate comparator therapy specified by the G-BA. ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase-5; WHO: World Health Organization		

The company formulated a different research question. The company initially stated to choose individual drug treatment specified by the physician and under consideration of the respective approval status. In contrast to the G-BA, however, the company did not include the additional criterion that this treatment was to be individually optimized and considered iloprost to be the only possible drug treatment option of an individual drug treatment (see Section 2.7.1 of the full dossier assessment). In addition, the company defined the subpopulations a and b. “Subpopulation a” comprised patients for whom also iloprost is not an option, and for whom therefore only watchful waiting until worsening of the PAH is available. “Subpopulation b” comprised patients for whom iloprost is an option.

The company’s limitation to use iloprost as the only option of individually optimized drug treatment and the subsequent division of the population was inadequate. The ACT specified by the G-BA was used for the present assessment. No division into subpopulations was conducted in the present benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials with a minimum duration of 6 months were used for the derivation of the added benefit.

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 selexipag (status: 9 May 2016)
- bibliographical literature search on selexipag (last search on 4 May 2016)
- search in trial registries for studies on selexipag (last search on 9 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on selexipag (last search on 6 July 2016)

No relevant study was identified from the check. This deviates from the company's approach, which considered the randomized controlled trial (RCT) GRIPHON as relevant for the "subpopulation a" defined by the company. The company identified no studies for "subpopulation b".

2.3.2 Study pool of the company

From the steps of information retrieval mentioned, the company identified the RCT GRIPHON [3] as relevant study for its "subpopulation a" (patients for whom iloprost is not an option and for whom watchful waiting until worsening of the PAH is the only treatment option).

The study presented by the company was unsuitable to draw conclusions on the added benefit of selexipag in comparison with the ACT. The study was neither suitable to answer the research question defined by the company nor to answer the research question of the present benefit assessment. The GRIPHON study was unsuitable for the research question of the company because the administration of iloprost was not excluded for patients with worsening of their disease and iloprost was therefore principally suitable. The study was unsuitable for the research question of the present benefit assessment because the ACT was not implemented.

2.3.3 Assessment of the GRIPHON study presented by the company

Study description

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

The GRIPHON study was a randomized, controlled, double-blind study on the comparison of selexipag with placebo. Adult patients 18 to 75 years of age with symptomatic PAH and a

6-minute walk distance of 50 m to 450 m at the start of the study were included. Patients with all WHO functional classes (I to IV) were included. The majority of the patients was allocated to the WHO functional class II (45.8% [slight limitation of physical activity]) or III (52.5% [marked limitation of physical activity]), and therefore did not correspond to the therapeutic indication of selexipag.

A total of 1156 patients were randomly assigned to treatment with selexipag (574 patients) or to placebo (582 patients). In accordance with the approval, selexipag was up-titrated to the highest individually tolerated dose in the study [4].

The treatment phase ended with occurrence of an event of the primary outcome, premature discontinuation of treatment or the end of study. The median treatment duration was 70.7 weeks in the selexipag arm and 63.7 weeks in the placebo arm.

Lack of suitability of the GRIPHON study for the company's research question

It was not comprehensible that the company wanted to use the GRIPHON study to investigate the research question for patients for whom iloprost is unsuitable. The study description above shows that about half of the patients included in the study could be allocated to the WHO functional class III. Iloprost is approved precisely for these patients [5]. In addition, these patients could receive a PAH-specific treatment in case of worsening of the disease, i.e. when reaching a component of the composite primary outcome (see Table 10 of the full dossier assessment). This treatment was not restricted to certain drugs, and therefore also comprised iloprost. However, the treatment and observation period of the study ended with the expansion of the treatment.

Population of the GRIPHON study

It was assumed for the present benefit assessment that the pretreated patients included in the study were inadequately controlled with their PAH-specific treatment and were therefore treated in compliance with the approval.

Symptomatic patients were included in the GRIPHON study. The patients were allowed to continue their PAH-specific treatment consisting of ERA and/or PDE-5 inhibitor initiated before the start of the study as long as the dosage of the corresponding drug had been stable for the last 3 months. About 80% of the patients included were pretreated with such a PAH-specific treatment. 49.3% of the patients in the selexipag group had received monotherapy with an ERA or a PDE-5 inhibitor before the start of the study, and 44.9% in the placebo group; 31.2% and 33.8% had received a combination therapy.

About 20% of the patients included in the study were treatment-naïve at the start of the study and were receiving no PAH-specific concomitant medication. It was not clear from the inclusion and exclusion criteria of the GRIPHON study that treatment with ERA and/or PDE-5 inhibitor was not an option for them. Hence there was no approval-compliant use of selexipag for these patients.

No implementation of the appropriate comparator therapy in the GRIPHON 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. All (combinations of) drugs in the therapeutic indication of selexipag were to be considered. Rigid prerequisites or restrictions of the physician's choice of drugs and restrictions of dose adjustments were inadequate.

The GRIPHON study was a placebo-controlled study. At the start of the study, treatment in the intervention arm was expanded by administration of selexipag. No expansion was mandated in the control arm – only placebo was administered. In both treatment arms, it was not allowed to adjust the ongoing medication for treatment of the PAH. Hence the study only allowed a comparison of selexipag with placebo. The study design allowed individual adjustment of the PAH-specific treatment in case of worsening of the PAH, but this was defined as primary outcome event and therefore ended the blinded and randomized treatment phase for the patient (see Table 10 of the full dossier assessment).

The requirements for the PAH-specific concomitant medication in the GRIPHON study listed below show that it was a placebo comparison (see also Appendix A of the full dossier assessment):

- 1) It was strongly advised not to use a new therapy for the treatment of the PAH in the course of the study.
- 2) Initiation of prostanoid therapy (inhaled or parenteral) in the course of the study was not allowed.
- 3) The PAH-specific treatment – consisting of a PDE-5 inhibitor and/or an ERA – initiated already before the start of the study was not allowed to be changed until week 26 of the study treatment.
- 4) After worsening of the disease, treatment with parenteral prostanoids could be initiated, but was recorded as primary outcome event and therefore ended the blinded and randomized treatment phase for the patient.
- 5) Worsening of the disease and the necessity of additional PAH-specific treatment together with worsening of the 6-minute walk distance by $\geq 15\%$ in patients with WHO functional class III was also recorded as primary outcome event and therefore ended the blinded and randomized treatment phase for the patient.

2.4 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of selexipag in its dossier. This resulted in no hint of an added benefit of selexipag 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 selexipag in adult patients with PAH. Hence there was no hint of an added benefit of selexipag 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 selexipag in comparison with the ACT is summarized in Table 5.

Table 5: Selexipag – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy ^a	Extent and probability of added benefit
Long-term treatment of PAH in adult patients with WHO functional class II to III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase-5; WHO: World Health Organization		

This approach deviates from that of the company. On the basis of the GRIPHON study, the company derived an indication of considerable added benefit for patients in the therapeutic indication for whom the risk of treatment with iloprost outweighs its benefit due to the disease state (“subpopulation a”). For patients, for whom the benefit of treatment with iloprost outweighs its risk due to the disease state (“subpopulation b”), the company derived a hint of a non-quantifiable added benefit of selexipag without presenting data for this.

The G-BA decides on the added benefit.

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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