IQWiG Reports – Commission No. A21-129

Solriamfetol (obstructive sleep apnoea) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Solriamfetol (obstruktive Schlafapnoe) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 3 March 2022). 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
Solriamfetol (obstructive sleep apnoea) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
5 October 2021

Internal Commission No.
A21-129

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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 Hartmut Rentmeister.

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment, and about treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Keywords: Solriamfetol, Disorders of Excessive Somnolence, Sleep Apnea – Obstructive, Benefit Assessment, NCT02348606

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AHI	apnoea-hypopnoea index
CPAP	continuous positive airway pressure
DGSM	Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (German Sleep Society)
EDS	excessive daytime sleepiness
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MWT	Maintenance of Wakefulness Test
OSA	obstructive sleep apnoea
PAP	positive airway pressure
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics+

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 solriamfetol. 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 5 October 2021.

Research question

The aim of the present report is to assess the added benefit of solriamfetol in comparison with optimized standard therapy of the underlying obstructive sleep apnoea (OSA) as the appropriate comparator therapy (ACT) to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).

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

Table 2: Research question of the benefit assessment of solriamfetol

Therapeutic indication	**ACT[a]**
Improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP[b, c]	Optimized standard therapy of the underlying OSA[d]
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the therapeutic indication also includes patients with a contraindication or for whom optimized standard therapy does not suffice. c. In accordance with the G-BA, patients in both study arms are assumed to receive optimal care. Standard therapy includes, in particular, CPAP. Standard therapy is assumed to be continued. Weight-reducing measures may represent add-on treatment strategies. d. Where optimization options are exhausted, the G-BA deems continuation of the existing OSA therapy to be acceptable. ACT: appropriate comparator therapy; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; G-BA: Federal Joint Committee; OSA: obstructive sleep apnoea	

The company followed the 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. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Study pool and study design

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of solriamfetol in comparison with the ACT. The company, in contrast, identified the RCT 14-003 and used it in its assessment. Under "other investigations", the company

additionally submitted the noncomparative solriamfetol 14-005 study as supplementary information.

The data presented by the company were unsuitable for drawing conclusions on added benefit of solriamfetol in comparison with the ACT.

Study 14-003

The 14-003 study is a randomized, double-blind, placebo-controlled study with solriamfetol. It included adults aged between 18 and 75 years with diagnosed OSA. In addition, patients had to be using at least minimal primary OSA therapy (i.e. positive airway pressure [PAP], oral pressure therapy, an oral appliance, or an upper airway stimulator at least 1 night/week) or have a history of at least 1 attempt of primary OSA therapy or 1 surgical intervention to treat OSA symptoms as well as EDS (operationalized as an Epworth Sleepiness Scale [ESS] score ≥ 10).

The study randomized a total of 476 patients, stratified by their adherence (compliance or non-compliance) to primary OSA therapy, at an allocation ratio of 1:1:2:2:2 to the study arms of solriamfetol 37.5 mg (N = 59), solriamfetol 75 mg (N = 61), solriamfetol 150 mg (N = 118), solriamfetol 300 mg (N = 119), and placebo (N = 119). Treatment was administered over a period of 12 weeks. During the study, patients were to additionally continue their existing primary OSA therapy at the same level as used at study start.

Unsuitability of the data submitted by the company from the 14-003 study for the benefit assessment

In the present therapeutic indication, its short treatment duration of 12 weeks already disqualifies the 14-003 RCT submitted by the company for the benefit assessment. OSA is a chronic disease. Since not only short-term effects, but particularly long-term effects are of interest, long-term studies are necessary to draw any conclusions on added benefit.

Furthermore, it is questionable whether the patients in the study's subpopulation taken into account by the company (compliant population) received OSA therapy which can be considered optimized, as required for the ACT. Moreover, contrary to Summary of Product Characteristics (SPC) recommendations, the study did not involve any individualized dosing of solriamfetol.

Study 14-005 used by the company as supporting evidence

The 14-005 study is an open-label, non-randomized extension study on solriamfetol, which enrolled patients with OSA or narcolepsy who had already completed a study on solriamfetol conducted by the company (14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202).

The 14-005 study is unsuitable for the present benefit assessment because, due to the absence of a comparator arm, no conclusions on added benefit of solriamfetol versus the ACT can be derived.

Results

In summary, no suitable data are available for the assessment of added benefit of solriamfetol in comparison with the ACT for improving wakefulness and reducing EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP. Hence, there was no hint of an added benefit of solriamfetol 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]

Based on the results presented, the probability and extent of added benefit of the drug solriamfetol in comparison with the ACT are assessed as follows:

Table 3 shows a summary of the probability and extent of added benefit of solriamfetol.

Table 3: Solriamfetol – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP[b, c]	Optimized standard therapy of the underlying OSA[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the therapeutic indication also includes patients with a contraindication or for whom optimized standard therapy does not suffice.
c. In accordance with the G-BA, patients in both study arms are assumed to receive optimal care. Standard therapy includes, in particular, CPAP. Standard therapy is assumed to be continued. Weight-reducing measures may represent add-on treatment strategies.
d. Where optimization options are exhausted, the G-BA deems continuation of the existing OSA therapy to be acceptable.

ACT: appropriate comparator therapy; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; G-BA: Federal Joint Committee; OSA: obstructive sleep apnoea

The G-BA decides on the added benefit.

[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 the present report is to assess the added benefit of solriamfetol in comparison with optimized standard therapy of the underlying OSA as the ACT to improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.

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

Table 4: Research question of the benefit assessment of solriamfetol

Therapeutic indication	**ACT[a]**
Improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP[b, c]	Optimized standard therapy of the underlying OSA[d]
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the therapeutic indication also includes patients with a contraindication or for whom optimized standard therapy does not suffice. c. In accordance with the G-BA, patients in both study arms are assumed to receive optimal care. Standard therapy includes, in particular, CPAP. Standard therapy is assumed to be continued. Weight-reducing measures may represent add-on treatment strategies. d. Where optimization options are exhausted, the G-BA deems continuation of the existing OSA therapy to be acceptable. ACT: appropriate comparator therapy; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; G-BA: Federal Joint Committee; OSA: obstructive sleep apnoea	

The company followed the 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 24 weeks were used for the derivation of added benefit. This did not concur with the inclusion criteria used by the company, which included RCTs with a minimum study duration of 12 weeks. The consequences resulting for the present benefit assessment of solriamfetol are explained in Section 2.3.

2.3 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 lists on solriamfetol (status: 4 August 2021)
- bibliographical literature search on solriamfetol (last search on 4 August 2021)
- search in trial registries / trial results databases for studies on solriamfetol (last search on 26 August 2021)
- search on the G-BA website for solriamfetol (last search on 4 August 2021)

To check the completeness of the study pool:

- search in trial registries for studies on solriamfetol (last search on 8 October 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any relevant studies for the assessment of added benefit of solriamfetol in comparison with the ACT. The company, in contrast, identified the RCT 14-003 [3-10] and used it for its assessment.

Under "other investigations", the company additionally presented as supplementary information the noncomparative solriamfetol study 14-005 [11-15].

The data presented by the company were unsuitable for drawing conclusions on added benefit of solriamfetol in comparison with the ACT. The reasons are explained below.

Evidence provided by the company

Study 14-003

The 14-003 study is a randomized, double-blind, placebo-controlled study with solriamfetol. It included adults aged between 18 and 75 years with diagnosed OSA. The diagnosis was established using the criteria of the International Classification of Sleep Disorders, 3rd edition (ICSD-3). In addition, patients had to be using at least minimal primary OSA therapy (i.e. PAP, oral pressure therapy, an oral appliance, or an upper airway stimulator at least 1 night/week) or have a history of at least 1 attempt of primary OSA therapy or 1 surgical intervention to treat OSA symptoms as well as EDS (operationalized as an ESS score ≥ 10). Furthermore, at baseline, patients were to have a mean sleep latency < 30 minutes in the first 4 of a total of 5 circles of the 40-minute Maintenance of Wakefulness Test (MWT) as well as a mean night-time sleep of ≥ 6 hours.

The study randomized a total of 476 patients, stratified by their adherence (compliance or non-compliance), to primary OSA therapy, at an allocation ratio of 1:1:2:2:2 to the study arms of solriamfetol 37.5 mg (N = 59), solriamfetol 75 mg (N = 61), solriamfetol 150 mg (N = 118), solriamfetol 300 mg (N = 119), and placebo (N = 119). Treatment was administered for a period of 12 weeks and deviated in part from the specifications of the SPC [16] (see dosing discussion below). During the study, patients were to additionally continue their existing primary OSA therapy at the same level they used at study start. Taking drugs for EDS was disallowed during the study. Where such drugs were taken before study start, they had to be washed out for a period of at least 5 half-lives before study start until patients had, in the investigator's opinion, returned to their baseline level of daytime sleepiness for at least 7 days before study start.

Coprimary outcomes of the study were change in ESS score and change in mean sleep latency in the 40-minute MWT, each from baseline to Week 12. Secondary outcomes were other morbidity outcomes as well as outcomes regarding health-related quality of life and side effects.

Further information on the 14-003 study can be found in Appendix B of the full dossier assessment.

Study 14-005 used by the company as supporting evidence

The 14-005 study is an open-label, non-randomized extension study on solriamfetol; eligible participants included patients with OSA or narcolepsy who had already completed a study on solriamfetol conducted by the company (14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202). During the first two weeks, the patients were individually titrated to the maximum tolerable dose of solriamfetol (75 mg, 150 mg, or 300 mg). Afterwards, a maximum of 3 dose modifications per study participant were allowed up to Week 14. Treatment was continued for up to 52 weeks. During the study, patients with OSA were to continue their existing primary OSA therapy at the same level they used at study start. The study also included a 2-week randomized and double-blind withdrawal phase after approximately half of the treatment period, during which patients either maintained their previously adjusted solriamfetol dose or received placebo. After these 2 weeks, patients in the placebo arm returned to their original solriamfetol dose.

For the benefit assessment, the company presents data from a subpopulation of OSA patients (compliant population). These results are disregarded in the present assessment because due to the lack of comparator arm, no conclusions on added benefit of solriamfetol versus the ACT can be derived.

Unsuitability of the data submitted by the company from the 14-003 study for the benefit assessment

Insufficient duration of the 14-003 study included by the company

Its short treatment duration of 12 weeks disqualifies the 14-003 RCT presented by the company for the benefit assessment in the therapeutic indication of OSA. OSA is a chronic disease requiring lifelong treatment. The IQWiG General Methods likewise state that in the assessment of therapeutic interventions for chronic diseases, short-term studies are not usually suitable to achieve a complete benefit assessment of the intervention [1]. This applies in particular when treatment is required for several years, or even lifelong. Conclusions on the added benefit thus require long-term studies, because not only short-term effects, but especially long-term effects are of interest. This applies not only to conclusions on benefit outcomes, but also to harm outcomes because it is possible that adverse events (AEs) do not manifest themselves until after prolonged use of the drug.

In its dossier, the company defined a minimum study duration of 12 weeks and deemed this period to be sufficient to achieve meaningful results on efficacy, tolerability, and quality of life. It argues that, while the European Medicines Agency (EMA) has not issued any specific guidelines regarding the development of medicinal products for EDS treatment, the EMA recommends a minimum study duration of 2 to 4 weeks for the treatment of insomnia [17]. The company deems a minimum study duration of 12 weeks to be an established design for proving

efficacy in the therapeutic indication and adds that this design has already been used in studies on armodafinil, modafinil, and pitolisant. The company adds that the G-BA has discussed directly comparative studies of 12-week duration as being acceptable in the therapeutic indication. However, the company fails to mention the G-BA's further discussion of the impossibility of deriving from such studies any conclusions on added benefit with regard to long-term symptom improvement, recurrences, or side effects [18]. For evidence of the long-term efficacy and safety of solriamfetol over a 52-week period, the company refers to long-term data from the single-arm study 14-005.

The company's rationale was not accepted. For the benefit assessment of solriamfetol versus the ACT in the therapeutic indication, comparing benefit and harm requires study durations of at least 24 weeks.

Questionable implementation of the ACT in study 14-003

The G-BA has specified as the ACT optimized standard therapy of the underlying OSA. In the 14-003 study, the primary OSA therapy was to be continued unchanged from enrolment in all treatment arms, including the placebo arm. The data on the outcome "use of primary OSA therapy", as presented in the company's Module 4 C, show that patients continued to use their primary therapy consistently throughout the course of the study. According to the G-BA, continuation of the existing OSA therapy is an acceptable ACT only if optimization options have been exhausted. However, the 14-003 study's inclusion criteria fail to ensure that patients' available optimization options had already been exhausted at study start and that, consequently, no such options were available to them any longer. They merely state that, to be enrolled, patients had to have a history of at least minimal use of primary OSA therapy (i.e. PAP therapy, oral pressure therapy, oral appliance, or upper airway stimulator at least 1 night/week) or at least 1 attempt of ≥ 1 primary OSA therapy for 1 month with at least 1 documented modification for optimization or a surgical intervention for the treatment of OSA symptoms. The company's dossier likewise provides no data on the existence and nature of any attempted treatment modifications received by study participants before enrolment.

According to national and international guidelines, CPAP therapy is the standard therapy. Various other OSA treatment options or optimizations are also available in this therapeutic indication [19-22]. They include, for instance, modification of the duration of PAP use as well as a switch of masks, pressure changes, or the use of humidifiers. In addition, changing the PAP therapy mode may be considered, such as automatic positive airway pressure (APAP) and bilevel techniques. Alternatively, treatment might be switched to a different method, such as an oral appliance. Another option is combination therapy consisting of PAP therapy and an oral appliance or possibly surgical interventions. In addition, add-on weight loss measures should be taken in overweight patients. In patients with positional OSA, positional therapy can be an option.

For the benefit assessment, the company primarily takes into account the subpopulation of patients deemed adherent/compliant with the primary OSA therapy (compliant population). For this purpose, the study plan defined the following criteria:

- PAP use for ≥ 4 hours/night in ≥ 70% of nights (≥ 5 of 7 days/week) if using an appliance which indicates the duration of use in number of hours, or ≥ 70% of nights (≥ 5 of 7 days/week, patient-reported with investigator concurrence) if using an appliance which does not indicate the duration of use or
- Use of an oral appliance (≥ 5 of 7 days/week) or
- Receipt of effective surgical intervention for OSA

This population included a total of 241 patients (solriamfetol 37.5 mg [n = 39], solriamfetol 75 mg [n = 42], solriamfetol 150 mg [n = 80], and placebo [n = 80]).

For this patient group, the company declares the optimization options available for primary OSA therapy to have been exhausted. The company justifies this assertion, firstly, by a minimal duration of use and the continuation of primary OSA therapy in accordance with inclusion criteria. Secondly, the company argues that this was demonstrated by a baseline apnoea-hypopnoea index (AHI) in the normal range, at a median of ≤ 2.2/hour, which did not substantially change throughout the treatment period. According to the company, the treatment goal for the underlying OSA had therefore been met in accordance with the criteria defined by the German Sleep Society (DGSM). In addition, the company expects that patients with primary therapy have already made lifestyle changes as part of optimized therapy.

While it is safe to assume that patients in the compliant population have received primary OSA therapy and have continued it for the defined duration of use, it remains questionable even for these patients whether they received optimized therapy at study start. The various national and international guidelines do not offer precise criteria defining optimized OSA therapy [19-22]. According to the DGSM's S3 guideline, the goal of OSA therapy is uninterrupted sleep characterized by AHI < 15/h and the absence of daytime sleepiness symptoms. However, despite their low AHI, patients in the compliant population exhibited an ESS score ≥ 10 at baseline, which represents a relevant level of daytime sleepiness [22]. In addition, more than half of the compliant population in the comparator arm still had an ESS score > 10 by Week 12. Overall, the available information fails to establish that the compliant population's therapy of the underlying OSA can be deemed optimized already at baseline.

Solriamfetol dosing in 14-003 study in violation of SPC specifications

According to the SPC, the daily dose of solriamfetol was to be adjusted within a defined range of possible dosages on an individual basis and depending on clinical response and tolerability [16]. However, the 14-003 study did not involve individualized dose titration:

During the study, no solriamfetol dose modification took place in the 37.5 mg arm or the 75 mg arm. Patients in the 150 mg arm received 75 mg solriamfetol in the first 3 days and were then force-titrated to 150 mg irrespective of clinical response. Patients in the 300 mg arm started with a 150 mg dose for 3 days and were then likewise titrated to 300 mg irrespective of clinical response. According to the SPC [16], the recommended starting dose is 37.5 mg/day. The dose can be titrated to a higher dose strength by doubling at intervals of at least 3 days. The recommended maximum daily dose is 150 mg. This decision should be based on the patients' clinical response. Thus, patients in the 37.5 mg and 75 mg arms were potentially underdosed, while patients in the 150-mg arm were force-titrated to the approved maximum dosage. A solriamfetol dose of 300 mg is in violation of approval, as are the starting doses of 75 mg and 150 mg.

Summary

All things considered, no data suitable for answering the research question of this benefit assessment are available. This is due, firstly, to the short treatment duration in the 14-003 RCT submitted by the company. Secondly, it is questionable whether the OSA therapy received by patients in the compliant population of RCT 14-003 can be considered optimized. Moreover, contrary to SPC recommendations, the study did not involve any individualized dosing of solriamfetol.

2.4 Results on added benefit

No suitable data are available for the assessment of added benefit of solriamfetol in comparison with the ACT for improving wakefulness and reducing EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP. Hence, there was no hint of an added benefit of solriamfetol in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of solriamfetol in comparison with the ACT.

Table 5: Solriamfetol – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP[b, c]	Optimized standard therapy of the underlying OSA[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the therapeutic indication also includes patients with a contraindication or for whom optimized standard therapy does not suffice.
c. In accordance with the G-BA, patients in both study arms are assumed to receive optimal care. Standard therapy includes, in particular, CPAP. Standard therapy is assumed to be continued. Weight-reducing measures may represent add-on treatment strategies.
d. Where optimization options are exhausted, the G-BA deems continuation of the existing OSA therapy to be acceptable.

ACT: appropriate comparator therapy; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; G-BA: Federal Joint Committee; OSA: obstructive sleep apnoea

The assessment described above deviates from that by the company, which derived minor added benefit for all patients in the therapeutic indication based on data from the 14-003 RCT's compliant population. For this purpose, the company used the 37.5 mg dose of solriamfetol. In addition, it claims that an analysis of the higher dose of 150 mg solriamfetol shows a considerable added benefit. The company did not draw an overall conclusion on the probability of added benefit.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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