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Solriamfetol (narcolepsy) –

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 (Narkolepsie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 August 2020). 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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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CGIc	Clinical Global Impression of Change
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESS	Epworth Sleepiness Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICSD	International Classification of Sleep Disorders
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (German Institute for Quality and Efficiency in Health Care)
MAO	monoamine oxidase
MSLT	Multiple-Sleep-Latency-Test
MWT	Maintenance of Wakefulness Test
OSA	obstructive sleep apnoea
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SOREM	sleep-onset rapid eye movement
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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 18 May 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of solriamfetol in comparison with the appropriate comparator therapy (ACT) for the improvement of the wakefulness and the reduction of excessive daytime sleepiness in adults with narcolepsy (with or without cataplexy).

In its specification of the ACT, the G-BA distinguished between different patient groups. This resulted in 2 research questions for the assessment; these are presented in Table 2.

Table 2: Research questions of the benefit assessment of solriamfetol

Research question	**Subindication**	**ACT[a]**
Improvement of the wakefulness and reduction of the excessive daytime sleepiness in adults with narcolepsy (with and without cataplexy)		
A	Narcolepsy without cataplexy	**Modafinil** or pitolisant
B	Narcolepsy with cataplexy	**Sodium oxybate** or pitolisant
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results of research question A and research question B

Evidence provided by the company

The company identified one RCT that compared solriamfetol with placebo (14-002). It additionally identified one RCT on the comparison of sodium oxybate with placebo

(OMC-SXB-15) and one RCT comparing both sodium oxybate and modafinil with placebo (OMC-SXB-15). Since there are no studies of direct comparison for the derivation of the added benefit of solriamfetol versus the ACT, the company presented one direct comparison for each of the two research questions (research question A: solriamfetol vs. modafinil; research question B: solriamfetol vs. sodium oxybate; each via the common comparator placebo) on the basis of the RCTs cited above.

The RCTs with solriamfetol as well as with modafinil or sodium oxybate presented by the company as well as the indirect comparisons based on these studies are unsuitable for the present benefit assessment. In particular, the duration of treatment with the respective drug compared with placebo was markedly less than 24 weeks in all 3 RCTs and therefore too short to derive conclusions on the added benefit of solriamfetol versus the ACT for research question A and research question B in the present therapeutic indication. In addition, the permitted prior and concomitant medication for the treatment of excessive daytime sleepiness and/or for the treatment of cataplexies was partially restricted in all 3 RCTs. Therefore, it is questionable whether the patients included in the studies received supportive treatment that is adequate in the German health care context to alleviate symptoms and improve the quality of life. Moreover, contrary to the recommendations of the respective Summary of Product Characteristics (SPCs), there were no individual dose adjustments of solriamfetol, modafinil or sodium oxybate in the studies. Irrespective of the lack of relevance of the studies used by the company for research question A and research question B, they are also not similar enough to enable an indirect comparison. This is particularly due to the different prior and concomitant therapies of the patients included in the studies.

Research question additionally investigated by the company

In Module 4 A of its dossier, the company addressed an additional research question: Determination of the extent of added benefit of solriamfetol for the total population of adult patients with narcolepsy (with or without cataplexy) and excessive daytime sleepiness in comparison with pitolisant. For this research question, the company presented an indirect comparison of the solriamfetol study 14-002 and the pitolisant studies Harmony I and Harmony Ibis using the common comparator placebo.

Based on the information available in the dossier, the data on the total population of patients with narcolepsy (with and without cataplexy) presented by the company are unsuitable to derive a conclusion on the added benefit of solriamfetol versus the ACT.

Adults with narcolepsy with or without cataplexy are comprised in the two above research questions of the present benefit assessment as subgroups. According to the G-BA's specification, the added benefit for the subpopulations specified by the G-BA has to be proven in comparison with the respective ACT. The company did not present such analyses for the comparison of solriamfetol versus pitolisant. Irrespective of this, the studies used by the company for this comparison are also not suitable for deriving the added benefit of solriamfetol as the study duration was 8 to 12 weeks and thus too short. Moreover, it is questionable whether

the patients included in the studies received supportive treatment which is adequate in the German health care context to alleviate symptoms and improve the quality of life.

Results

In its dossier, the company presented no data suitable to assess the added benefit of solriamfetol in comparison with the ACT in adult patients with excessive daytime sleepiness and narcolepsy (with and without cataplexy). This resulted in no hint of an added benefit of solriamfetol versus 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, probability and extent of the added benefit of the drug solriamfetol in comparison with the ACT are assessed as follows:

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

Table 3: Solriamfetol – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
Improvement of the wakefulness and reduction of excessive daytime sleepiness in adults with narcolepsy (with and without cataplexy)			
A	Narcolepsy without cataplexy	**Modafinil** or pitolisant	Added benefit not proven
B	Narcolepsy with cataplexy	**Sodium oxybate** or pitolisant	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

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 the assessment of the added benefit of solriamfetol in comparison with the ACT for the improvement of the wakefulness and the reduction of excessive daytime sleepiness in adults with narcolepsy (with or without cataplexy).

In its specification of the ACT, the G-BA distinguished between different patient groups. 2 research questions resulted from this for the assessment; these are presented in Table 4.

Table 4: Research questions of the benefit assessment of solriamfetol

Research question	**Subindication**	**ACT[a]**
Improvement of the wakefulness and reduction of the daytime sleepiness in adults with narcolepsy (with and without cataplexy)		
A	Narcolepsy without cataplexy	**Modafinil** or pitolisant
B	Narcolepsy with cataplexy	**Sodium oxybate** or pitolisant
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company followed the G-BA's specification of the ACT for both research questions. From the options mentioned by the G-BA, the company chose modafinil for research question A and sodium oxybate for research question B.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This did not concur with the inclusion criteria used by the company, which included RCTs with a minimum study duration of 8 weeks. The consequences resulting for the present benefit assessment of solriamfetol are explained in Section 2.3.1.

Research question additionally investigated by the company

In Module 4 A of its dossier, the company addressed an additional research question: Determination of the extent of added benefit of solriamfetol for the total population of adult patients with narcolepsy (with or without cataplexy) and excessive daytime sleepiness in comparison with pitolisant. For this purpose, it presented an adjusted indirect comparison due to the lack of studies of direct comparisons (see Section 2.3).

The company justified the investigation of the additional research question with the fact that the G-BA had specified pitolisant as an option for the ACT for both research questions. A comparison of the subpopulations relevant for research question A and research question B on the basis of the identified studies on pitolisant was impossible since the sources identified for these studies (Harmony I [3-10] und Harmony Ibis [7-9,11,12]) comprised no complete

analyses of the subpopulations specified by the G-BA. Moreover, the solriamfetol study (14-002) showed no effect modification by the characteristic "cataplexy (yes/no)" in the coprimary efficacy outcomes "Epworth Sleepiness Scale (ESS)" and "Maintenance of Wakefulness Test (MWT)". Against this background, the company considered it adequate to use a comparison of solriamfetol versus pitolisant for the total population of patients with narcolepsy (with and without cataplexy) for the benefit assessment of solriamfetol.

Based on the information provided in the dossier, the data presented by the company on the total population of patients with narcolepsy (with and without cataplexy) from the indirect comparison of solriamfetol versus pitolisant and the single-arm long-term study 14-005 [13-17] which is part of the solriamfetol study 14-002, are not suitable to derive a conclusion on the added benefit of solriamfetol. This is explained in more detail in Section 2.3.2.

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: 28 February 2020)
- bibliographical literature search on solriamfetol (last search on 2 April 2020)
- search in trial registries/trial results databases for studies on solriamfetol (last search on 19 February 2020)
- search on the G-BA website for solriamfetol (last search on 19 February 2020)
- bibliographical literature search on ACTs (last search on 23 April 2020)
- search in trial registries/trial results databases for studies on ACTs (last search on 20 February 2020)
- search on the G-BA website for ACTs (last search on 19 February 2020)

To check the completeness of the study pool:

- search in trial registries for studies on solriamfetol (last search on 27 May 2020)

The check did not identify any relevant studies for the assessment of the added benefit of solriamfetol in comparison with the ACT.

With its information retrieval, the company also identified no direct comparative RCTs on the comparison of solriamfetol with the ACTs. Since studies of direct comparison were lacking, the company presented indirect comparisons for both research questions, each using the common comparator placebo (see below).

The data presented by the company are not suitable to derive conclusions on the added benefit of solriamfetol in comparison with the ACT for research questions A and B and for the

additional research question addressed by the company (narcolepsy with and without cataplexy). This is explained in more detail below. At first, the evidence presented by the company is described. Then it is explained why the data presented permit no derivation of conclusions on the added benefit.

2.3.1 Research question A (narcolepsy without cataplexy) and research question B (narcolepsy with cataplexy)

Evidence provided by the company

In Module 4 A of its dossier, the company first presents the results of Study 14-002 [18-23], which compares solriamfetol with placebo, both for the total population (narcolepsy with and without cataplexy) and for the subpopulation of patients with narcolepsy without cataplexy (research question A). In Module 4 B, it only presents the results for the subpopulation of patients with narcolepsy with cataplexy (research question B) of study14-002.

To derive the added benefit for research question A (patients with narcolepsy without cataplexy), the company included study 14-002 for solriamfetol and study OMC-SXB-22 for modafinil [24-27] for the adjusted indirect comparison with the ACT. The comparison was conducted using placebo as the common comparator. For the comparison, the company used subpopulations corresponding to the research question from both studies.

To derive the added benefit for research question B (patients with narcolepsy with cataplexy), the company included study 14-002 for solriamfetol and the studies OMC-SXB-15 [28-33] and OMC-SXB-22 for sodium oxybate for the adjusted indirect comparison with the ACT. The comparison was also conducted using placebo as common comparator. For the comparison, the company considered subpopulations from 14-002 and OMC-SXB-22 corresponding to the research question, as well as the total population of study OMC-SXB-15.

In support of both research questions, the company presented the results of the single-arm long-term study 14-005, which is part of the solriamfetol study 14-002, but did not use them to derive the added benefit.

Because the company partly presented data from the same studies for the research questions, the evidence provided by the company is at first presented below in summarized form. Characteristics of the studies presented by the company, populations and subpopulations are presented in Table 9 to Table 12 in Appendix A of the full dossier assessment.

Study 14-002 (solriamfetol versus placebo, research question A and research question B)

14-002 is a 12-week randomized, double-blind, placebo-controlled approval study of solriamfetol. It included adults between 18 and 75 years of age with diagnosed narcolepsy (with or without cataplexy). The diagnosis was made according to the criteria of the International Classification of Sleep Disorders, 3rd edition (ICSD-3) or the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Moreover, at baseline patients were to have an ESS score ≥ 10 and an average sleep latency < 25 minutes in the first 4 of a total of 5 circles of the

40-minute MWT, as well as an average nocturnal sleep time of ≥ 6 hours. The patient population of the study corresponds to the therapeutic indication. Drugs that could affect the assessment of the excessive daytime sleepiness or the cataplexy were prohibited before and during the study, or the drugs had to be washed out within a period of at least 5 half-lives prior to the start of the study, until the patients had reached their baseline levels of daytime sleepiness or cataplexy for at least 7 days before the study started (see below and Table 10 of the full dossier assessment).

In the study, a total of 239 patients were randomly assigned to the study arms solriamfetol 75 mg (N = 59), solriamfetol 150 mg (N = 60), solriamfetol 300 mg (N = 60) and placebo (N = 60) in a 1:1:1:1 ratio. Stratification was based on the presence or absence of cataplexy. Due to the lack of approval of this dosage, the company did not include the study arm solriamfetol 300 mg in its benefit assessment. According to the cataplexy status, the company used subpopulations for research question A and research question B for the benefit assessment. Patients with narcolepsy without cataplexy were considered for research question A (solriamfetol 75 mg: n = 28, solriamfetol 150 mg: n = 29; placebo n = 30). Patients with narcolepsy with cataplexy were considered for research question B (solriamfetol 75 mg: n = 31, solriamfetol 150 mg: n = 31; placebo n = 30).

Coprimary outcomes of the study were the change in mean sleep latency in the 40-minute MWT from baseline to week 12 and the change in the ESS score from baseline to week 12. Secondary outcomes were further outcomes on morbidity, health-related quality of life and side effects.

OMC-SXB-15 (sodium oxybate versus placebo, research question B)

OMC-SXB-15 is an 8-week randomized, double-blind study, which compared different sodium oxybate dosages (4.5 g versus 6 g versus 9 g) were compared with placebo. It included adolescents and adults from 16 years of age with diagnosed narcolepsy with cataplexy. Diagnosis of narcolepsy had to be based on a polysomnography and a Multiple-Sleep-Latency-Test (MSLT) performed within the last 5 years. Moreover, patients had to show current symptoms of narcolepsy, including excessive daytime sleepiness, cataplexy and episodes of suddenly falling asleep recurring almost daily over the past 3 months. During the baseline phase (14 to 21 days), patients also had to have ≥ 8 cataplexy attacks per week to be included in the study. Thus, the included patient population does not fully correspond to the present research question B, since the study also included adolescents aged 16 years and older. However, sodium oxybate is only approved for adults [34]. There is no information on how many adolescents under 18 years of age were included in the study contrary to the approval of sodium oxybate. The permitted prior and concomitant medication for the treatment of cataplexies was limited in the study; the medication for the treatment of excessive daytime sleepiness was allowed to be continued at stable doses (see below and Table 10 of the full dossier assessment).

In the study, a total of 285 patients were randomly assigned to the study arms sodium oxybate 4.5 g (N = 75), sodium oxybate 6 g (N = 71), sodium oxybate 9 g (N = 68) and placebo (N = 71) in a 1:1:1:1 ratio. Information on a stratification is not available.

The study's co-primary outcomes were the change in ESS score from baseline to week 8 and the proportion of patients with strong and very strong improvement in Clinical Global Impression of Change (CGIc) from baseline to week 8. Secondary outcomes included further outcomes on morbidity, health-related quality of life and side effects.

OMC-SXB-22 (modafinil versus placebo, research question A; sodium oxybate versus placebo, research question B)

OMC-SXB-22 is an 8-week randomized, double-blind, placebo-controlled study comparing sodium oxybate, modafinil or a combination of the two drugs. It included adults ≥ 18 years of age with diagnosed narcolepsy. Narcolepsy was diagnosed according to the ICSD-2 criteria and patients had to be pretreated with modafinil (200 to 600 mg/day) for a period of at least 3 months prior to the start of the study, with stable doses administered for at least 1 month prior to the start of the study. A washout period was not mandated in the study. The permitted prior and concomitant medication was limited in the study (see below and Table 10 of the full dossier assessment).

In the study, a total of 231 patients were randomly assigned to the study arms sodium oxybate (N = 55), modafinil (N = 63), sodium oxybate plus modafinil (N = 57) and placebo (N = 56) in a 1:1:1:1 ratio. The combination of sodium oxybate and modafinil is not part of the ACT and will not be considered further. Information on a stratification in the study is not available. Presence of cataplexy was no explicit inclusion criterion for the study. Classification of the patient population into patients with narcolepsy with or without cataplexy was therefore done retrospectively. Patients with narcolepsy with cataplexy were identified based on the history of cataplexy, the use of anticataplectic drugs or the presence of a sleep-onset rapid eye movement (SOREM) phase in nocturnal polysomnography. All other patients were assigned to the subpopulation with narcolepsy without cataplexy. The company used the resulting subpopulations for research question A or research question B of the benefit assessment. For research question A (narcolepsy without cataplexy), it considered the study arms modafinil (n = 37) and placebo (n = 23), and for research question B (narcolepsy with cataplexy), it considered the study arms sodium oxybate (n = 14) and placebo (n = 32).

Primary outcome of the study was the change in mean sleep latency in the 20-minute MWT from baseline to week 8. Secondary outcomes were further outcomes on morbidity and side effects.

Study 14-005 used by the company as supporting evidence

The study 14-005 [13-17] was a 52-week open-label, non-randomized extension study on solriamfetol, which enrolled patients with narcolepsy (with or without cataplexy) or with obstructive sleep apnoea (OSA) who had already been included in a study of the company with solriamfetol (14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201 or ADX-N05 202). Patients were individually adjusted to the maximum tolerable dose of solriamfetol (75 mg, 150 mg or 300 mg). The study also included a 2-week randomized and double-blind withdrawal period after approximately half of the treatment period, during which patients either maintained

their previously adjusted solriamfetol dose or received placebo. After 2 weeks, patients in the placebo arm returned to their original dose of solriamfetol.

For research question A, the company presented the data of the patients with narcolepsy without cataplexy, and for research question B it presented the data of the patients with narcolepsy with cataplexy as supplementary information. The results were not considered in the present assessment, because due to the lack of the comparator arm no conclusions on the added benefit of solriamfetol versus the ACT can be derived for research question A or research question B.

Lack of suitability of the data presented by the company for the added benefit

Insufficient study duration of the studies included by the company

The RCTs presented by the company are not suitable for the benefit assessment in the therapeutic indication "narcolepsy", because their treatment duration was 8 to 12 weeks and thus too short. Narcolepsy is a chronic disease requiring lifelong treatment. The General Methods of IQWiG also describe that short-term studies for the evaluation of interventions for the treatment of chronic diseases are usually unsuitable to achieve a complete benefit assessment [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 does not only apply to statements on benefit outcomes, but also to harm outcomes, since adverse events (AEs) may possibly manifest themselves only after prolonged use of the drug.

In its dossier, the company included studies with a minimum study duration of 8 weeks and considered this period sufficient to achieve meaningful results on efficacy, tolerability and quality of life. There are no specific EMA guidelines for the development of medical products for the treatment of excessive daytime sleepiness. However, the company considered a minimum study duration of 8 weeks an established design for a proof of efficacy in the therapeutic indication, which had already been used in studies on modafinil, sodium oxybate and pitolisant. Moreover, the G-BA accepted a study duration of 7 weeks in the benefit assessment procedure on pitolisant to prove the added benefit [8]. For the proof of the long-term efficacy and the safety of solriamfetol over a period of 52 weeks, 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, studies with durations of at least 24 weeks are required for the comparison of benefit and harm.

Limitation of the concomitant medication in the studies

Narcolepsy is a lifelong disease with variable intensity of symptoms over the course of a lifetime. In addition to behaviour-modifying measures such as the improvement of coping strategies, sleep hygiene or the observance of individually adapted daytime sleep episodes, drug treatment is primarily aimed at the main symptoms of the disease. Excessive daytime sleepiness can be treated with various stimulants or wake-promoting agents, other drugs can alleviate the

cataplexies. However, in the studies included by the company (14002, OMC-SXB-15 and OMC-SXB-22), prior and concomitant drug therapy for the treatment of excessive daytime sleepiness and/or cataplexies in addition to the study medication was partially limited (see Table 10 of the full dossier assessment).

In study 14-002, any drugs that could affect the assessment of the excessive daytime sleepiness or the cataplexies were prohibited before and during the study, or the drugs had to be washed out within a period of at least 5 half-lives prior to the start of the study, until the patients, according to the investigator's assessment, had reached their initial levels of daytime sleepiness or cataplexies for at least 7 days before the start of the study. According to the SPC of solriamfetol, only the simultaneous application of monoamine oxidase inhibitors (MAO inhibitors) is contraindicated [35].

In the OMC-SXB-15 study, antidepressants or any other drugs for the treatment of cataplexy were to be tapered during the withdrawal phase (21 days) of the study and had to be washed out in the subsequent washout phase (5 to 18 days) of the study before randomization. Use of stimulants for the treatment of the excessive daytime sleepiness (e.g. modafinil) at stable doses was permitted before and during the study.

In the OMC-SXB-22 study, use of antidepressants at unchanged doses was permitted before and during the study. Further data pertaining to permitted or non-permitted prior and concomitant medication for the treatment of excessive daytime sleepiness or the cataplexy are lacking in the available study documents.

Due to the described restrictions of the concomitant symptomatic treatment in the studies, it is questionable whether the patients included in the studies received supportive treatment, which is adequate in the German health care context to alleviate symptoms and improve the quality of life.

Dosage of solriamfetol, sodium oxybate and modafinil

According to the SPC, the daily dose of solriamfetol, sodium oxybate and modafinil was to be adjusted within a given range of possible dosages on an individual basis and depending on clinical response and tolerability [34-36]. However, none of the studies involved individual dose titration.

In study 14-002, there was no dose adjustment of solriamfetol in the 75 mg arm, while patients in the 150 mg arm were forced to undergo titration from 75 mg to the approved maximum dose of 150 mg after 3 days, regardless of their clinical response. According to the SPC [35], the recommended initial dose is 75 mg/day and can be titrated to the recommended maximum daily dose of 150 mg/day after 3 days at the earliest. The decision on this should be based on the clinical response of the patients. Thus, patients in the 75 mg arm were potentially undersupplied, while patients in the 150 mg arm were forced to undergo titration to the approved maximum dosage.

In the OMC-SXB-15 study, no adjustment of the sodium oxybate dose took place in the 4.5 g arm during the study. During the study, patients in the other arms were forced to undergo titration to 6 g or 9 g sodium oxybate per day according to the scheme presented in Table 10 of the full dossier assessment, regardless of efficacy and tolerability. Here as well, patients were potentially undersupplied, whilst other patients were forced to undergo titration to the approved maximum dose. In the OMC-SXB-22 study, patients in the sodium oxybate arm were treated with an initial dose of 6 g sodium oxybate per day for 4 weeks. Subsequently, the dose of all patients was increased to the approved maximum dose of 9 g/day and treatment was continued for another 4 weeks. Contrary to the recommendation of the SPC of sodium oxybate [34], dose adjustments depending on efficacy and tolerability were not mandated in the studies. The patients thus had a potentially higher risk of side effects. The SPC, for instance, explicitly emphasises that sodium oxybate can cause respiratory depression.

In the OMC-SXB-22 study, patients in the modafinil arm continued to use their individual stable modafinil dose (200 to 600 mg) from the time before the study started on a blinded basis. Contrary to the recommendation of the SPC of modafinil [36], dose adjustments depending on the response were not mandated during the study. Moreover, patients who received a dose of 600 mg per day in the study were treated with too high a dose of modafinil, contrary to the approval. Information on how many patients in the modafinil arm were treated with 600 mg modafinil/day is not available.

Lack of similarity of the studies included by the company (research question A and research question B)

A prerequisite for conducting an adjusted indirect comparison is the sufficient similarity of the studies included. Irrespective of the lack of relevance of the studies regarding study duration and adequate concomitant symptomatic treatment as well as individual dose adjustment, the studies used by the company for research question A and research question B are also not similar enough for an indirect comparison. This is particularly due to the different prior and concomitant therapies of the patients included in the studies:

- Study 14-002: the included patients were treatment-naive (drugs for the treatment of the excessive daytime sleepiness and the cataplexies were not permitted and had to be washed out before the start of the study)
- OMC-SXB-15 study: the included patients were allowed to take stimulants during the study; anti-cataplectic drugs were not allowed and had to be washed out before the study started; the majority (78%) of the patients used stimulants during the study; 41% took modafinil during the study
- OMC-SXB-22 study: the patients included were pretreated with modafinil, with no washout phase; patients, particularly those in the placebo arm, were on modafinil withdrawal during the study

Due to their different prior and concomitant treatments, the patient populations included in the studies are not comparable and unsuitable for the conduction of an indirect comparison.

The different specifications in the studies with regard to the permitted and non-permitted prior and concomitant medications are also reflected in the initial scores of the disease characteristics ESS and MWT of the patients included. Thus, the treatment-naive patients of study 14-002 show both a shorter mean or median sleep latency measured using the MWT and a higher mean ESS score at baseline compared to the patients of the OMC-SXB-22 and OMC-SXB-15 studies (see Table 11 and Table 12 of the full dossier assessment).

Summary

Overall, there were no data suitable to answer research questions A and B of the present benefit assessment. On the one hand, this is due to the treatment durations that were too short in all presented RCTs. Moreover, it is questionable whether the patients included in the studies received supportive treatment that is adequate in the German health care context to alleviate symptoms and improve the quality of life. Moreover, contrary to the recommendations of the respective SPCs, there were no individual dose adjustments of solriamfetol, modafinil or sodium oxybate in the studies. Irrespective of this, the indirect comparisons presented for both research questions are not suitable for the assessment of the added benefit of solriamfetol due to the different prior and concomitant treatments in the studies.

2.3.2 Research question additionally investigated by the company (narcolepsy with and without cataplexy)

For its additional research question, the assessment of the added benefit of solriamfetol in the total population of adult patients with excessive daytime sleepiness with narcolepsy (with or without cataplexy) in comparison with pitolisant, the company presented an indirect comparison of the solriamfetol study 14-002 and the pitolisant studies Harmony I [3-10] and Harmony Ibis [7-9,11,12] using the common comparator “placebo”. The two latter studies were included in the indirect comparison as a meta-analysis. Based on this indirect comparison and taking into account the data on the long-term efficacy of solriamfetol from study 14-005 (see above), the company derived a hint of minor added benefit of solriamfetol in the total population of patients with excessive daytime sleepiness and narcolepsy with or without cataplexy.

Based on the information provided in the dossier, the data presented by the company on the total population of patients with narcolepsy (with and without cataplexy) from the indirect comparison of solriamfetol versus pitolisant and the long-term study 14-005, are not suitable to derive a conclusion on the added benefit of solriamfetol. This is explained in more detail below:

Additional research question of the company unsuitable for the derivation of the added benefit of solriamfetol

Adults with narcolepsy with or without cataplexy are comprised as subgroups in the research questions of the present benefit assessment shown in Table 4. As pitolisant was chosen as ACT

for both research questions and the pitolisant studies Harmony I and Harmony Ibis included no analyses on the subpopulations specified by the G-BA, the approach of the company to assess the added benefit of solriamfetol versus pitolisant based on the results of the total population of adult patients with narcolepsy with or without cataplexy, is at first comprehensible. As stated by the company, there are no effect modifications pertaining to the characteristic "cataplexy (yes/no)" for the primary efficacy outcomes ESS and MWT of the solriamfetol study 14-002. However, such information is not available for the comparative studies with pitolisant. Therefore, it cannot be ruled out that in the Harmony I and Harmony Ibis studies there is an effect modification for these outcomes due to the presence or absence of cataplexy. Moreover, an effect modification by the characteristic "cataplexy" cannot be ruled out for other relevant outcomes, e.g. "health-related quality of life" or "side effects". The comparison of solriamfetol versus pitolisant in the total population of patients with narcolepsy (with and without cataplexy) is therefore inadequate and is not considered for the assessment of the added benefit. In accordance with the GBA's specification, the added benefit in comparison with the respective ACT has to be proven separately for the subpopulations specified by the G-BA. The company did not present such analyses for the comparison of solriamfetol versus pitolisant.

Irrespective of this, the studies used by the company for this comparison are also not suitable for deriving the added benefit of solriamfetol:

- The study duration of 8 to 12 weeks is too short to permit conclusions on the added benefit of solriamfetol versus pitolisant for all 3 studies of the indirect comparison. The benefit assessment in the therapeutic indication requires studies with a duration of at least 24 weeks for the comparison of benefit and harm (see Section 2.3.1).
- In study 14-002, any medication used to treat excessive daytime sleepiness and cataplexies was to be discontinued before the start of the study. Also in the Harmony studies, any medication used to treat excessive daytime sleepiness and cataplexies was to be discontinued before the start of the study. However, patients with severe cataplexy were allowed to continue their anti-cataplectic medications (e.g. sodium oxybate) during the studies, but dose adjustment was not allowed. Therefore, it is questionable whether the patients included in the studies received supportive treatment, which is adequate in the German health care context to alleviate symptoms and improve the quality of life (see Section 2.3.1). Irrespective of this, the different specifications regarding the permitted or non-permitted concomitant medication challenge the similarity of the patient populations included in the solriamfetol study (14-002) and those included in the Harmony studies (Harmony I and Harmony Ibis).
- Treatment with solriamfetol in study 14-002 as well as treatment with pitolisant in the Harmony I and Harmony Ibis studies do not comply with the recommendations of the respective SPCs [35,37]. For study 14-002, this is explained in more detail in Section 2.3.1 of the present benefit assessment. For pitolisant, the daily dose (4.5 to 36 mg/day) can be individually adjusted at any time according to patient response and tolerability [37]. The doses used in the Harmony studies ranged between 5 and 20 mg/day (Harmony

Ibis) and between 10 and 40 mg/day (Harmony I). Individual dose titration was limited in both studies. After a forced dose increase from the respective lowest dosage (5 mg or 10 mg) to the next higher dosage (10 mg or 20 mg) after week 1, individual dose adjustment based on response and tolerability took place in both studies after week 2. After week 3, this dosage could be re-adjusted by a dose-reduction based on the individual tolerability. Dose increases were not permitted at this time. None of the two studies permitted subsequent dose adjustments within the next 5 weeks. Moreover, in the Harmony Ibis study it was not possible to reach the maximum dose (36 mg/day) specified in the SPC.

2.4 Results on added benefit

No suitable data are available for the assessment of the added benefit of solriamfetol in comparison with the ACT in adult patients with excessive daytime sleepiness and narcolepsy (with and without cataplexy). 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

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

Table 5: Solriamfetol – probability and extent of added benefit

Research question	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
Improvement of the wakefulness and reduction of the daytime sleepiness in adults with narcolepsy (with and without cataplexy)			
A	Narcolepsy without cataplexy	**Modafinil** or pitolisant	Added benefit not proven
B	Narcolepsy with cataplexy	**Sodium oxybate** or pitolisant	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

For both research questions, the assessment described above deviates from that of the company.

For research question A, the company stated that there was no added benefit due to the limitations of the methods of the indirect comparison of solriamfetol (study 14-002) with modafinil (study OMC-SXB-22), but not due to a lower efficacy. According to the company, this was also shown in the descriptive comparison of the outcome “ESS” of these studies. The company thus derived a non-quantifiable added benefit of solriamfetol in comparison with the ACT. From the company’s point of view, the results of the long-term study 14-005 should be included in the assessment.

For research question B, the company derived no proof of added benefit of solriamfetol on the basis of the indirect comparison of solriamfetol (study 14-002) with sodium oxybate (studies OMC-SXB-15 and OMC-SXB-22), taking into account the limitations of the indirect comparison and the prior and concomitant treatment of the patients included in the studies. From the company's point of view, the results of the long-term study 14-005 should be included in the assessment.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Bioprojet. Efficacy and safety study of BF2.649 in the treatment of excessive daytime sleepiness in narcolepsy (Harmony1): study details [online]. 11.06.2012 [Accessed: 13.07.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT01067222.

4. Bioprojet. Prospective, randomized, double-blind study, placebo-controlled, parallel-group, multi-center trial assessing the effects of BF2.649 in treatment of excessive daytime sleepiness in narcolepsy (HARMONY I) [online]. [Accessed: 13.07.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2008-007866-46.

5. Dauvilliers Y, Bassetti C, Lammers GJ et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol 2013; 12(11): 1068-1075. https://dx.doi.org/10.1016/s1474-4422(13)70225-4.

6. Kollb-Sielecka M, Demolis P, Emmerich J et al. The European Medicines Agency review of pitolisant for treatment of narcolepsy: summary of the scientific assessment by the Committee for Medicinal Products for Human Use. Sleep Med 2017; 33: 125-129. https://dx.doi.org/10.1016/j.sleep.2017.01.002.

7. Bioprojet Pharma. Pitolisant (Wakix): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2016 [Accessed: 19.05.2017]. URL: https://www.g-ba.de/informationen/nutzenbewertung/255/#tab/dossier.

8. Gemeinsamer Bundesausschuss. Pitolisant: Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Bewertung von Arzneimitteln für seltene Leiden nach § 35a Absatz 1 Satz 10 i.V.m. 5. Kapitel § 12 Nr. 1 Satz 2 VerfO [online]. 2016 [Accessed: 28.06.2017]. URL: https://www.g-ba.de/downloads/92-975-1657/2016-08-01_Nutzenbewertung-G-BA_Pitolisant-D-250.pdf.

9. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Pitolisant [online]. 2017. URL: https://www.g-ba.de/downloads/40-268-4159/2017-01-19_AM-RL-XII_Pitolisant_D-250_TrG.pdf.

10. Van der Heide A, Van Schie MK, Lammers GJ et al. Comparing treatment effect measurements in narcolepsy: the sustained attention to response task, epworth sleepiness scale and maintenance of wakefulness test. Sleep 2015; 38(7): 1051-1058. https://dx.doi.org/10.5665/sleep.4810.

11. Bioprojet. Randomized, double-blind, placebo and comparator-controlled, parallel-group, multi-center trial assessing the effects of BF2.649 in the treatment of excessive daytime sleepiness in narcolepsy [online]. [Accessed: 13.07.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-019687-36.

12. Bioprojet. Effects of BF2.649 in the treatment of excessive daytime sleepiness in narcolepsy: study details [online]. 31.01.2017 [Accessed: 13.07.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT01638403.

13. Jazz Pharmaceuticals. "A long-term safety study of JZP-110 in the treatment of excessive sleepiness in subjects with narcolepsy or OSA": study details [online]. 25.06.2019 [Accessed: 13.07.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02348632.

14. Jazz Pharmaceuticals. A long-term, safety and maintenance of efficacy study of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy or obstructive sleep apnea [online]. [Accessed: 13.07.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-005489-31.

15. Jazz Pharmaceuticals. "A long-term safety study of JZP-110 in the treatment of excessive sleepiness in subjects with narcolepsy or OSA": study results [online]. 25.06.2019 [Accessed: 13.07.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02348632.

16. Jazz Pharmaceuticals. A long-term, safety and maintenance of efficacy study of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy or obstructive sleep apnea: clinical trial results [online]. 23.12.2018 [Accessed: 13.07.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-005489-31/results.

17. Malhotra A, Shapiro C, Pepin JL et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. Sleep 2019. https://dx.doi.org/10.1093/sleep/zsz220.

18. Jazz Pharmaceuticals. "Twelve-week study of the safety and efficacy of JZP-110 in the treatment of excessive sleepiness in narcolepsy": study details [online]. 23.07.2019 [Accessed: 08.06.2020]. URL: https://ClinicalTrials.gov/show/NCT02348593.

19. Jazz Pharmaceuticals. A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy [online]. [Accessed: 08.06.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-005487-15.

20. Jazz Pharmaceuticals. A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy: clinical trial results [online]. 02.03.2018 [Accessed: 08.06.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-005487-15/results.

21. Jazz Pharmaceuticals. "Twelve-week study of the safety and efficacy of JZP-110 in the treatment of excessive sleepiness in narcolepsy": study results [online]. 23.07.2019 [Accessed: 08.06.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02348593.

22. Emsellem HA, Thorpy MJ, Lammers GJ et al. Measures of functional outcomes, work productivity, and quality of life from a randomized, phase 3 study of solriamfetol in participants with narcolepsy. Sleep Med 2020; 67: 128-136. https://dx.doi.org/10.1016/j.sleep.2019.11.1250.

23. Thorpy MJ, Shapiro C, Mayer G et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol 2019; 85(3): 359-370. https://dx.doi.org/10.1002/ana.25423.

24. Jazz Pharmaceuticals. Trial comparing effects of Xyrem taken orally and modafinil with placebo in treating daytime sleepiness in narcolepsy: study details [online]. 29.12.2011 [Accessed: 13.07.2020]. URL: https://clinicaltrials.gov/ct2/show/study/NCT00066170.

25. Jazz Pharmaceuticals. Trial comparing effects of Xyrem taken orally and modafinil with placebo in treating daytime sleepiness in narcolepsy: study results [online]. 29.12.2011 [Accessed: 13.07.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00066170.

26. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006; 29(7): 939-946.

27. Black J, Swick T, Bogan R et al. Impact of sodium oxybate, modafinil, and combination treatment on excessive daytime sleepiness in patients who have narcolepsy with or without cataplexy. Sleep Med 2016; 24: 57-62. https://dx.doi.org/10.1016/j.sleep.2016.07.010.

28. Orphan Medical. Safety and efficacy of Xyrem oral solution (sodium oxybate) compared with placebo in narcoleptic patients: study details [online]. 24.06.2005 [Accessed: 13.07.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT00049803.

29. Xu XM, Wei YD, Liu Y et al. Gamma-hydroxybutyrate (GHB) for narcolepsy in adults: an updated systematic review and meta-analysis. Sleep Med 2019; 64: 62-70. https://dx.doi.org/10.1016/j.sleep.2019.06.017.

30. Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005; 1(4): 391-397.

31. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. Sleep Med 2005; 6(5): 415-421. https://dx.doi.org/10.1016/j.sleep.2005.03.010.

32. Bogan R, Swick T, Mamelak M et al. Evaluation of quality of life in patients with narcolepsy treated with sodium oxybate: use of the 36-item Short-Form Health Survey in a clinical trial. Neurol Ther 2016; 5(2): 203-213. https://dx.doi.org/10.1007/s40120-016-0053-5.

33. Weaver TE, Cuellar N. A randomized trial evaluating the effectiveness of sodium oxybate therapy on quality of life in narcolepsy. Sleep 2006; 29(9): 1189-1194.

34. UCB. Xyrem 500 mg/ml Lösung zum Einnehmen: Fachinformation [online]. 02.2019 [Accessed: 13.07.2020]. URL: https://www.fachinfo.de.

35. Jazz Pharmaceuticals. Sunosi 75/150 mg Filmtabletten: Fachinformation [online]. 01.2020 [Accessed: 13.07.2020]. URL: https://www.fachinfo.de.

36. Teva. Vigil 100 mg/200 mg Tabletten: Fachinformation [online]. 02.2020 [Accessed: 13.07.2020]. URL: https://www.fachinfo.de.

37. Bioprojet Pharma. Wakix 4,5 mg/18 mg Filmtabletten: Fachinformation [online]. 04.2020 [Accessed: 13.07.2020]. URL: https://www.fachinfo.de.

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