Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Solriamfetol (first dossier requirement: daytime sleepiness in obstructive sleep apnoea, after prior therapy)

of 18 March 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The medicinal product Sunosi with the active ingredient solriamfetol was approved on 16 January 2020 for the indications of daytime sleepiness in narcolepsy and daytime sleepiness in obstructive sleep apnoea after prior therapy. Sunosi was listed for the first time on 15 May 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

In its session on 15 April 2021, the G-BA decided on an amendment to Annex III number 44 (stimulants) of the Pharmaceuticals Directive. With the entry into force of the amendment on 30 June 2021, the medicinal product Sunosi became reimbursable for the first time for the indication of daytime sleepiness in obstructive sleep apnoea after prior therapy and thus falls within the scope of Section 35a paragraph 1 SGB V in analogous application of the regulation in Chapter 5, Section 1, paragraph 2, No. 4 of the Rules of Procedure (VerfO). Accordingly, the pharmaceutical company was requested to submit a dossier. The relevant date for the submission of a dossier was 1 October 2021 in analogous application of the regulation

according to Chapter 5, Section 8, paragraph 1, No. 3 of the Rules of Procedure (VerfO) and taking into account the process sequence of the amendment to Annex III of the Pharmaceuticals Directive due to the first-time procedure in this case design.

The pharmaceutical company submitted a dossier for the active ingredient solriamfetol for the therapeutic indication of daytime sleepiness in obstructive sleep apnoea after prior therapy in due time on 1 October 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 3 January 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of solriamfetol compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of solriamfetol.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Solriamfetol (Sunosi) according to product information

Sunosi is indicated to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose *EDS* has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).

Therapeutic indication of the resolution (resolution of 18 March 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with excessive daytime sleepiness (EDS) due to obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP

Appropriate comparator therapy for solriamfetol: An optimised standard therapy for the underlying obstructive sleep apnoea.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to solriamfetol, pitolisant is approved in the present therapeutic indication.

on 2. For obstructive sleep apnoea, non-medicinal treatments include continuous positive airway pressure therapy, mandibular advancement splints or surgical intervention.

on 3. There are no resolutions on the benefit assessment of medicinal products or non-medicinal procedures for the treatment of excessive sleepiness due to sleep apnoea. The evaluation procedure for pitolisant has not yet been completed at the time of the adoption of the resolution.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the “Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V”.

For the treatment of the underlying disease obstructive sleep apnoea, good efficacy is described in particular for continuous positive airway pressure therapy, which can also improve excessive daytime sleepiness. Further positive evidence is available for surgical interventions and mandibular advancement splints. Since it is the treatment of the underlying disease in each case, it cannot be directly determined as an appropriate comparator therapy for the treatment of sleepiness. However, no positive evidence was identified for therapies that explicitly address residual daytime sleepiness. Pitolisant is not determined as an appropriate comparator therapy because the benefit assessment has not yet been completed. Rather, optimised standard therapy of the underlying obstructive sleep apnoea is considered an adequate approach and an appropriate comparator therapy. Weight-reducing measures can be concomitant strategies. The unchanged continuation of the current therapy for obstructive sleep apnoea is acceptable for patients for whom the optimisation options have already been exhausted.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of solriamfetol is assessed as follows:

For adults with excessive daytime sleepiness (EDS) due to obstructive sleep apnoea (OSA) whose excessive daytime sleepiness has not been satisfactorily treated by primary OSA therapy, such as CPAP, an additional benefit is not proven.

Justification:

The pharmaceutical company submits the study 14-003. This is a randomised, double-blind, placebo-controlled study that enrolled adults aged 18-75 years diagnosed with OSA and was conducted at 59 study sites in Germany, France, Canada, the Netherlands and the USA. Study participants were required to have at least minimal administration of primary OSA therapy or at least one attempt at primary OSA therapy or surgery to treat OSA symptoms, and EDS (operationalised as Epworth Sleepiness Scale [ESS] score ≥ 10).

A total of 476 patients were randomised to the study arms solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg and placebo, stratified according to their adherence (compliance or non-compliance) to primary OSA therapy. The treatment took place over a period of 12 weeks. During the study, patients should also continue their existing primary OSA therapy at the same level as at the start of the study. In addition, at baseline, patients should have an average sleep latency of < 30 minutes in the first 4 of a total of 5 rounds of the 40-minute maintenance of wakefulness test (MWT) and an average nocturnal sleep time of ≥ 6 hours.

For the present benefit assessment, the pharmaceutical company assesses the sub-population (solriamfetol 37.5 mg (n = 39), solriamfetol 75 mg (n = 42), solriamfetol 150 mg (n = 80), placebo (n = 80)) that was compliant with its primary OSA therapy. This was defined as use of PAP therapy ≥ 70% of nights (≥ 5 of 7 days/week) and, if measurable, ≥ 4 hours/night, use of a UPS ≥ 70% of nights (≥ 5 of 7 days/week), or successful surgery to treat OSA. According to the marketing authorisation, the study arm with the dosage of 300 mg solriamfetol is not considered.

Due to the treatment duration of 12 weeks, it is not possible to make statements on patient-relevant endpoints in the present therapeutic indication with sufficient certainty on the basis of the study presented. OSA is a chronic disease that requires lifelong treatment. In the treatment of the symptom of excessive daytime sleepiness, a therapy lasting longer than 12 weeks should therefore also be assumed as a rule. For the assessment of the additional benefit, it is therefore not only necessary to consider short-term effects, which may be sufficient for proof of concept, but observations over a longer period of time are also necessary in order to be able to also record, for example adverse events that only become apparent after a longer period of taking the medicinal product. Uncertainties regarding the cardiovascular risk were pointed out in particular in the context of the marketing authorisation.[2]

[2] See EMA: EPAR Sunosi, 14.11.2019, Divergent Position, p. 128.

In addition, the dosing procedure in the study did not comply with the marketing authorisation: In the 37.5 mg and 75 mg arms, there was no dose adjustment of solriamfetol during the study. Patients in the 150 mg arm received 75 mg of solriamfetol for the first 3 days and were then forcibly dosed up to 150 mg, regardless of clinical response. In contrast, according to the product information, therapy should be started with an initial dose of 37.5 mg for all patients. Depending on the clinical response, the dose may be increased to a maximum of 150 mg. The procedure in the study leads to uncertainties, since patients in the 37.5 mg and 75 mg arms may have been under-treated on the one hand, and over-treatment in the 75 mg and 150 mg arms cannot be ruled out on the other.

In addition, uncertainties in the implementation of the appropriate comparator therapy must be taken into account. The study participants received primary OSA therapy, which was also used stably during the course of the study. This procedure corresponds to the optimised standard therapy for those cases of the appropriate comparator therapy in which the optimisation options have already been exhausted. However, it remains uncertain to what extent the therapy was already optimised at the start of the study (e.g. by adapting the previous procedure or switching to other methods). Overall, however, despite the uncertainties due to the median apnoea-hypopnoea index being in the normal range at the start of the study, it can at least be assumed that the therapy was sufficient.

The study 14-003 cannot be used for the assessment of the additional benefit for the reasons mentioned, in particular due to the short study duration and the lack of individual dosage. Therefore, there is no evaluation at endpoint level.

The pharmaceutical company submits a sub-population of the study 14-005 in substantiation. This is an open-label, non-randomised extension study in which patients with OSA or narcolepsy who had previously completed a study of the pharmaceutical company with solriamfetol (including the study 14-003) could be enrolled. Treatment was given for up to 52 weeks and included a 2-week randomised and double-blind withdrawal phase. The results of this study cannot be taken into account for the assessment of the additional benefit, as no statements on the additional benefit of solriamfetol compared to the appropriate comparator therapy can be derived due to the absence of a comparator arm.

Overall assessment

Overall, no appropriate data are available to allow an assessment of the additional benefit. The additional benefit for solriamfetol in the therapeutic indication of excessive daytime sleepiness (EDS) due to obstructive sleep apnoea (OSA) in adults whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP, is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the active ingredient solriamfetol in the therapeutic indication: To improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.

The G-BA determined an optimised standard therapy for the underlying obstructive sleep apnoea as an appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the RCT 14-003, in which different doses of solriamfetol were compared with placebo over 12 weeks. The patients also received primary OSA therapy.

The study duration of 12 weeks is not considered sufficient for an assessment in the present therapeutic indication. During this period, no long-term effects (especially adverse events) can be recorded that only occur after prolonged intake of solriamfetol. In addition, the dosing procedure in the study did not comply with the marketing authorisation, as no individual titration was carried out, but a fixed dosage was applied in each of the study arms. Depending on the dosage used, a potential over or under-treatment of patients cannot be ruled out.

For these reasons, the study is not suitable for the derivation of an additional benefit. In addition, uncertainties exist with regard to the implementation of the appropriate comparator therapy.

The single-arm study 14-005 submitted additionally cannot be considered, as no conclusions on the additional benefit of solriamfetol compared to the appropriate comparator therapy can be derived due to the absence of a comparator arm.

Overall, there are no assessable data. An additional benefit is therefore not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients (approx. 200,000 to 400,000) is based on the target population in statutory health insurance (SHI).

Due to the large discrepancy between the patient numbers submitted by the pharmaceutical companies in the present procedure and those in the currently ongoing benefit assessment procedure for pitolisant in a comparable therapeutic indication, IQWiG was commissioned to conduct a reassessment. The difference in the wording of the therapeutic indications of solriamfetol and pitolisant does not lead to a different assessment of patient numbers.

As uncertainties already have to be taken into account for the individual calculation methods of the pharmaceutical companies, these uncertainties also remain in IQWiG's estimate, which takes both methods into account (addendum G22-06 to mandate A21-129). This concerns in particular the data on prescriptions of CPAP therapy for obstructive sleep apnoea in Germany. There is also a lack of data on patients whose sleep apnoea is treated with another form of therapy (surgical interventions or mandibular advancement splints) and who also belong to the target population if daytime sleepiness remains.

The data on patient numbers must therefore be assessed as uncertain overall.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Sunosi (active ingredient: solriamfetol) at the following publicly accessible link (last access: 7 January 2022):

https://www.ema.europa.eu/en/documents/product-information/sunosi-epar-product-information_en.pdf

Treatment with solriamfetol may only be initiated and monitored by doctors experienced in treating patients with obstructive sleep apnoea.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs. The recommended dose of solriamfetol is between 37.5 mg and 150 mg once a day. A dose of 37.5 mg can be achieved by dividing a 75 mg tablet in half at the groove.

The appropriate comparator therapy "An optimised standard therapy for underlying obstructive sleep apnoea" includes continuous positive airway pressure (CPAP) therapies, surgical interventions and mandibular advancement splints. Weight-reducing measures can be concomitant strategies.

Since the optimised standard therapy of obstructive sleep apnoea is patient-individual, no specific costs for the appropriate comparator therapy can be mentioned here. In addition, the optimised standard therapy for the treatment of obstructive sleep apnoea is carried out both within the scope of the medicinal product to be assessed, solriamfetol, and within the scope of the appropriate comparator therapy.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Solriamfetol	Continuously, 1 x daily	365	1	365
Optimised standard therapy	Different from patient to patient			
Appropriate comparator therapy				
Optimised standard therapy	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Solriamfetol	37.5 mg - 150 mg	37.5 mg - 150 mg	0.5 x 75 mg - 1 x 150 mg	365	182.5 x 75 mg - 365 x 150 mg
Optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Solriamfetol 75 mg	28 FCT	€ 449.49	€ 1.77	€ 24.26	€ 423.46
Solriamfetol 150 mg	28 FCT	€ 594.08	€ 1.77	€ 32.27	€ 560.04
Optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	Different from patient to patient				
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 1 March 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 28 January 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 October 2021 the pharmaceutical company submitted a dossier for the benefit assessment of solriamfetol to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 3a VerfO.

By letter dated 5 October 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient solriamfetol.

The dossier assessment by the IQWiG was submitted to the G-BA on 21 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 January 2022. The deadline for submitting written statements was 24 January 2022.

The oral hearing was held on 7 February 2022.

On 4 March 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 03.03.2022 replaces version 1.0 of the dossier assessment dated 21.12.2021. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

By letter dated 9 March 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 16 March 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 9 March 2022, and the proposed resolution was approved.

At its session on 18 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	28 January 2020	Determination of the appropriate comparator therapy
Working group Section 35a	1 February 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	7 February 2022	Conduct of the oral hearing
Working group Section 35a	15 February 2022; 1 March 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 March 2022	Commissioning of the IQWiG with the supplementary assessment of documents, final consultation on the draft resolution
Plenum	18 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 18 March 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken