

Justification



to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Solriamfetol (Narcolepsy with and without Cataplexy)

of 5 November 2020

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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 based on 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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient solriamfetol in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 May 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 15 May 2020.

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 17 August 2020, 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 based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit based on their therapeutic relevance (qualitative) according to the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in

accordance with the General Methods¹ was not set aside 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 arrived at 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®) in accordance with the product information

Sunosi is indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with narcolepsy without cataplexy

Appropriate comparator therapy:

Modafinil or pitolisant

b) Adult patients with narcolepsy and cataplexy

Appropriate comparator therapy:

Sodium oxybate or pitolisant

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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.

¹ General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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

On 1. The active ingredients pitolisant, modafinil, sodium oxybate (only narcolepsy with cataplexy), methylphenidate, and clomipramine (only for sleep paralysis, cataplexy, hypnagogic hallucinations in narcolepsy) are approved for the therapeutic indication narcolepsy.

On 2. Non-medicinal treatment is not indicated for daytime sleepiness because of narcolepsy.

On 3. For the active ingredient pitolisant, a resolution on the benefit assessment according to Section 35a SGB V of 19 January 2017 is available. A non-quantifiable additional benefit was determined.

On 4. The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in this indication.

Based on the aggregated evidence, the active ingredients modafinil, sodium oxybate, and pitolisant have a comparably good efficacy in reducing daytime sleepiness in narcolepsy; however, an effect on cataplexies can be derived only for sodium oxybate and pitolisant. There are currently no guidelines for the indication narcolepsy with or without cataplexy. Taking into account the International Classification of Sleep Diseases (ICSD-3), the evidence available, and the respective authorisation status, a division into two patient groups is considered appropriate. Modafinil or pitolisant is thus determined as an equally appropriate comparator therapy for adults with narcolepsy without cataplexy (Patient group a) and sodium oxybate or pitolisant for adults with narcolepsy and cataplexy (Patient group b) .

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

2.1.3 Extent and probability of the additional benefit

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

For adult patients with narcolepsy with or without cataplexy, the additional benefit of solriamfetol compared with the appropriate comparative therapy is not proven.

Justification for patient group a (Adult patients with narcolepsy without cataplexy):

In the dossier for the assessment of the additional benefit of solriamfetol, the pharmaceutical company does not present any directly comparative studies compared with the appropriate comparator therapy.

Indirect comparison: solriamfetol vs modafinil

In the absence of directly comparative studies, the pharmaceutical company presents an indirect comparison (patient group a: solriamfetol vs modafinil via the bridge comparator placebo) based on RCTs with solriamfetol and modafinil. However, the RCTs on solriamfetol and modafinil as well as the indirect comparisons based on these studies are not suitable for the present benefit assessment.

Thus, the pre-medication and concomitant medication allowed in the RCTs for the treatment of excessive daytime sleepiness and/or cataplexies were restricted to varying degrees. Furthermore, there was no patient-specific dose setting of solriamfetol and modafinil depending on the response according to the recommendations of the respective product

information. Furthermore, the RCTs considered for the indirect comparisons by the pharmaceutical company had a study duration of 8 weeks in the comparator arm. They are therefore too short to derive statements on the additional benefit in the present therapeutic indication. Irrespective of the aforementioned aspects, the studies presented by the pharmaceutical company for patient group a are also not similar enough for an indirect comparison (e.g. different pre- and concomitant treatment of the patients included in the studies).

Indirect comparison: solriamfetol vs pitolisant

Furthermore, in the dossier for the total population of adult patients with excessive daytime sleepiness in narcolepsy with or without cataplexy included in patient groups a and b, the pharmaceutical company also addressed another common issue compared with the alternative appropriate comparator therapy pitolisant. Similar to the justification for the indirect comparison of solriamfetol vs modafinil, the indirect comparison of solriamfetol (Study 14-002) and pitolisant (HARMONY I and HARMONY Ibis studies) via the bridge comparator placebo is also not suitable (study duration too short; no patient-specific dose setting of solriamfetol or pitolisant according to the recommendations of the respective product information; no formal separation into the patient groups a and b specified by the appropriate comparator therapy). Furthermore, the studies used by the pharmaceutical company are not sufficiently similar with regard to the patient group to be examined for an indirect comparison.

Summary for patient group a:

In the dossier, the pharmaceutical company has not submitted any relevant data for the assessment of the additional benefit of solriamfetol compared with the appropriate comparator therapy for adult patients with narcolepsy without cataplexy. Overall, the G-BA does not consider the indirect comparisons presented to be suitable for deriving patient-relevant effects on the additional benefit of solriamfetol. The additional benefit compared with the appropriate comparator therapy is therefore not proven for adult patients with narcolepsy without cataplexy.

Justification for patient group b (Adult patients with narcolepsy and cataplexy):

In the dossier for the assessment of the additional benefit of solriamfetol, the pharmaceutical company does not present any directly comparative studies compared with the appropriate comparator therapy.

Indirect comparison: solriamfetol vs sodium oxybate

In the absence of directly comparative studies, the pharmaceutical company makes an indirect comparison analogous to patient group a (patient group b: solriamfetol vs sodium oxybate via the bridge comparator placebo) based on RCTs with solriamfetol and sodium oxybate. However, the RCTs on solriamfetol and sodium oxybate as well as the indirect comparisons based on these studies are not suitable for the present benefit assessment.

Thus, the pre-medication and concomitant medication allowed in the RCTs for the treatment of excessive daytime sleepiness and/or cataplexies were restricted to varying degrees. Furthermore, there was no patient-specific dose setting of solriamfetol and sodium oxybate depending on the response according to the recommendations of the respective product information. Furthermore, the RCTs considered for the indirect comparisons by the pharmaceutical company had a study duration of 8 weeks in the comparator arm. They are

therefore too short to derive statements on the additional benefit in the present therapeutic indication. Irrespective of the aforementioned aspects, the studies presented by the pharmaceutical company for patient group b are also not similar enough for an indirect comparison (e.g. different pre- and concomitant treatment of the patients included in the studies).

Indirect comparison: solriamfetol vs pitolisant

As described for patient group a, in the dossier for the total population of adult patients with excessive daytime sleepiness in narcolepsy with or without cataplexy included in patient groups a and b, the pharmaceutical company also addressed another common issue compared with the alternative appropriate comparator therapy pitolisant. As already justified for patient group a, this indirect comparison of the solriamfetol (Study 14-002) and pitolisant (HARMONY I and HARMONY Ibis studies) via the placebo bridge comparator is also not suitable for the benefit assessment (study duration too short; no patient-specific dose setting of solriamfetol or pitolisant according to the recommendations of the respective product information; no formal separation into the patient groups a and b specified by the appropriate comparator therapy). Furthermore, the studies used by the pharmaceutical company are not sufficiently similar with regard to the patient group to be examined for an indirect comparison.

Summary for patient group b:

In the dossier, the pharmaceutical company has not submitted any relevant data for the assessment of the additional benefit of solriamfetol compared with the appropriate comparator therapy for adult patients with narcolepsy and cataplexy. Overall, the G-BA does not consider the indirect comparisons presented to be suitable for deriving patient-relevant effects on the additional benefit of solriamfetol. The additional benefit compared with the appropriate comparator therapy is therefore not proven for adult patients with narcolepsy and cataplexy.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the medicinal product Sunosi[®] with the active ingredient solriamfetol. The therapeutic indication assessed here is as follows: “to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy)”.

For the benefit assessment, the following patient groups were distinguished:

- a) Adult patients with narcolepsy without cataplexy
- b) Adult patients with narcolepsy and cataplexy

Patient group a

Modafinil or pitolisant was determined as an appropriate comparator therapy by the G-BA. For this patient group, the pharmaceutical company does not present any direct comparative data compared with the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Because of methodological limitations, the indirect comparisons presented are not suitable for addressing the question of benefit assessment. There are thus no suitable data for assessing the additional benefit of solriamfetol. In the overall view, for adult patients with narcolepsy without cataplexy, the additional benefit of solriamfetol compared with the appropriate comparator therapy is not proven.

Patient group b

Sodium oxybate or pitolisant was determined as an appropriate comparator therapy by the G-BA. For this patient group, the pharmaceutical company does not present any direct comparative data compared with the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Because of methodological limitations, the indirect comparisons presented are not suitable for addressing the question of benefit assessment. There are thus no suitable data for assessing the additional benefit of solriamfetol. In the overall view, for adult patients with narcolepsy and cataplexy, the additional benefit of solriamfetol compared with the appropriate comparator therapy is not proven.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

These are based on the data from the dossier of the pharmaceutical company. The figures are based on prevalence and incidence data from diagnosed patients. The overall calculation of the number is subject to uncertainties. Thus, the lower limit for patient group a (narcolepsy without cataplexy) can be assumed to be an overestimation because of the proportion of patients without cataplexy being overestimated by the pharmaceutical company; the lower limit for patient group b (narcolepsy with cataplexy) is considered to be plausible overall. For both patient groups, the upper limit of the range is assumed to be underestimated in each case; this is due, in particular, to the lack of consideration of indications of a higher prevalence.

The information provided by the pharmaceutical company does not call into question the range (14,920 to 29,840 adults with narcolepsy) stated in the dossier on pitolisant and assessed as plausible in terms of magnitude. A breakdown of this range is possible using the proportions 18.1% (patient group a) and 81.9% (patient group b); however, it should be noted that these proportions are subject to uncertainties because their transferability to the German healthcare context is unclear.

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: 26 August 2020):

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

Treatment with solriamfetol should only be initiated and monitored by specialists who are experienced in the treatment of patients with narcolepsy.

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 October 2020).

Treatment duration:

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 different for each

individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

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
Appropriate comparator therapy				
a) Adult patients with narcolepsy without cataplexy				
Modafinil	continuously, 1–2 x daily	365	1	365
Pitolisant	continuously, 1 x daily	365	1	365
b) Adult patients with narcolepsy and cataplexy				
Sodium oxybate	continuously, 2 x daily	365	1	365
Pitolisant	continuously, 1 x daily	365	1	365

Usage and 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	75–150 mg	75–150 mg	1 x 75 mg – 1 x 150 mg	365	365 x 75 mg – 365 x 150 mg
Appropriate comparator therapy					
a) Adult patients with narcolepsy without cataplexy					
Modafinil	200 – 400 mg	200 – 400 mg	1 x 200 mg – 2 x 200 mg	365	365 x 200 mg – 730 x 200 mg
Pitolisant	4.5 – 36 mg	4.5 – 36 mg	1 x 4.5 mg – 2 x 18 mg	365	365 x 4.5 mg – 730 x 18 mg
b) Adult patients with narcolepsy and cataplexy					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/patient/year	Average annual consumption by potency
Sodium oxybate	2.25 g – 4.5 g	4.5 g – 9 g	2 × 2.25 g – 2 × 4.5 g	365	730 × 2.25 g – 730 × 4.5 g
Pitolisant	4.5 – 36 mg	4.5 – 36 mg	1 × 4.5 mg – 2 × 18 mg	365	365 × 4.5 mg – 730 × 18 mg

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 Sections 130 and 130 a 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 product:

Designation of the therapy	Package 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	545.64	€ 1.77	30.38	€ 513.49
Solriamfetol 150 mg	28 FCT	866.57	€ 1.77	48.61	€ 816.19
Appropriate comparator therapy					
Modafinil 200 mg	100 TAB	€ 388.93	€ 1.77	€ 22.58	€ 450.28
Pitolisant 4.5 mg	30 FCT	€ 392.82	€ 1.77	€ 0.00	€ 391.05
Pitolisant 18 mg	90 FCT	€ 1,156.94	€ 1.77	€ 0.00	€ 1,155.17
Sodium oxybate 500 mg/ml	180 LSE	€ 405.13	€ 1.77	€ 19.20	€ 384.16

FCT = film-coated tablets, OSL = oral solution

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 October 2020

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 assessed 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 standard

expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

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 May 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 15 May 2020, 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 1, sentence 2.

By letter dated 18 May 2020 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 13 August 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 17 August 2020. The deadline for submitting written statements was 7 September 2020.

The oral hearing was held on 21 September 2020.

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 were discussed at the session of the subcommittee on 27 October 2020, and the proposed resolution was approved.

On 5 November 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	28 May 2019	Determination of the appropriate comparator therapy
Working group Section 35a	16 September 2020	Information on written statements received; preparation of the oral hearing

Subcommittee on Medicinal Products	21 September 2020	Conduct of the oral hearing
Working group Section 35a	29 September 2020 13 October 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	27 October 2020	Concluding discussion of the draft resolution
Plenum	5 November 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 5 November 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken