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
Pitolisant (daytime sleepiness in obstructive sleep apnoea, after prior therapy)

of 21 April 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 relevant date for the first placing on the (German) market of the medicinal product Ozawade with the active ingredient pitolisant in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentences 2 and 3 of the Rules of Procedure of the G-BA (VerfO) is 1 November 2021. 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 28 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 1 February 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 pitolisant compared to the appropriate comparator therapy could be determined on the basis of 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 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 pitolisant.

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 Pitolisant (Ozawade) according to product information

Ozawade 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, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP).

Therapeutic indication of the resolution (resolution of 21.04.2022):

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, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP)

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

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.

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

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 pitolisant, solriamfetol is approved in the present therapeutic indication.

on 2. For the treatment of the underlying disease, non-medicinal treatments include continuous positive airway pressure therapy, mandibular advancement splints or surgical intervention.

on 3. There is a resolution dated 18.03.2022 on the benefit assessment of solriamfetol in the treatment of excessive daytime sleepiness due to sleep apnoea according to Section 35a SGB V.

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 Section 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. Solriamfetol is not determined as an appropriate comparator therapy due to the only recently completed benefit assessment and the unproven additional benefit. 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 pitolisant is assessed as follows:

An additional benefit is not proven for adults with excessive daytime sleepiness (EDS) due to obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP).

Justification:

The pharmaceutical company states that no suitable studies are available for the assessment of the additional benefit of pitolisant, but additionally presents the HAROSA I and HAROSA II studies.

HAROSA I is a randomised, double-blind, placebo-controlled study that enrolled adults aged between 18 and 75 years and diagnosed with OSA. Study participants had to have regular CPAP therapy of at least four hours per day, an apnoea-hypopnoea index of ≤ 10/h, and EDS (operationalised as Epworth Sleepiness Scale [ESS] score ≥ 12). A total of 244 patients were randomised to the pitolisant or placebo treatment study arms. The treatment took place over a period of 12 weeks. During the study, other procedures (surgical or mandibular advancement splint) to treat the underlying OSA were prohibited. After the 12-week, double-blind study phase, treatment with pitolisant could be continued or initiated in an open-label, 40-week extension phase. Endpoints included change in ESS score, other morbidity endpoints and side effects.

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 HAROSA I 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.

In addition, the appropriate comparator therapy was not implemented. The study participants received CPAP therapy, but it remains unclear whether they continued this therapy during the study and whether optimisations such as adjustment of the time of use, pressure changes or humidifier use were planned or took place during the study. Also, other OSA primary therapies (surgical interventions and mandibular advancement splints), which represent further optimisation options, were not allowed in the study.

The HAROSA I study cannot be used for the assessment of the additional benefit for the reasons mentioned above.

The design of the HAROSA II study largely corresponds to that of the HAROSA I study, but patients who refused CPAP therapy and had an apnoea-hypopnoea index of ≥ 15/h were enrolled (n= 268) in the study. Further information on pretreatment is not available, so that it remains unclear to what extent the study participants received prior treatment. Since the therapeutic indication requires pretreatment with at least one OSA primary therapy, it is questionable whether the patients enrolled in the HAROSA II study correspond to the target population of the therapeutic indication. For this reason alone, the study cannot be used for the benefit assessment. For the study duration of 12 weeks, please refer to the comments on the HAROSA I study.

Overall assessment

Overall, no appropriate data are available to allow an assessment of the additional benefit. The additional benefit of pitolisant is therefore not proven 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, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP).

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the active ingredient pitolisant 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, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP).

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

The pharmaceutical company presents the RCT HAROSA I, in which pitolisant was compared with placebo over 12 weeks in patients whose underlying OSA was treated with CPAP.

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 (for example adverse events) can be recorded that only occur after prolonged intake of pitolisant.

Furthermore, the extent of optimisations of CPAP therapy is unclear. As no other therapies for the treatment of OSA (surgical interventions and mandibular advancement splints) were allowed in the study, the appropriate comparator therapy was not implemented. For these reasons, the study is not suitable for the derivation of an additional benefit.

The HAROSA II study, which was also presented, cannot be taken into account because it only enrolled patients who refused CPAP therapy and no further information on pretreatment was available. Since the therapeutic indication requires pretreatment with at least one OSA primary therapy, it is therefore questionable whether the enrolled patients correspond to the target population of the therapeutic indication. Therefore, this study cannot be used for the benefit assessment.

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 benefit assessment procedure for solriamfetol (resolution of 18.03.2022) in a comparable therapeutic indication, IQWiG carried out a new estimate (addendum G22-06 to mandate A21-129 in the benefit assessment procedure for solriamfetol), which takes both calculation methods into account.

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. 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 Ozawade (active ingredient: pitolisant) at the following publicly accessible link (last access: 4 April 2022):

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

Treatment with pitolisant should 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: 1 April 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 pitolisant is between 4.5 mg and 18 mg once a day. The upper limit of the annual treatment costs is reached when administering the medium dose level of 9 mg per day.

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, pitolisant, 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				
Pitolisant	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					
Pitolisant	4.5 mg 9 mg 18 mg	4.5 mg 9 mg 18 mg	1 x 4.5 mg 2 x 4.5 mg 1 x 18 mg	365 365 365	365 x 4.5 mg 730 x 4.5 mg 365 x 18 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					
Pitolisant 4.5 mg	30 FCT	€ 403.22	€ 1.77	€ 0.00	€ 401.45
Pitolisant 18 mg	90 FCT	€ 1,187.10	€ 1.77	€ 0.00	€ 1,185.33
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 April 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 had 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 8 September 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 October 2021, the pharmaceutical company submitted a dossier for the benefit assessment of pitolisant to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 November 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 pitolisant.

The dossier assessment by the IQWiG was submitted to the G-BA on 21 January 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 February 2022. The deadline for submitting written statements was 22 February 2022.

The oral hearing was held on 7 March 2022.

On 10 March 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 10 March 2022 replaces version 1.0 of the dossier assessment dated 20 January 2022. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 12 April 2022, and the proposed resolution was approved.

At its session on 21 April 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	8 September 2020	Determination of the appropriate comparator therapy
Working group Section 35a	1 March 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	7 March 2022	Conduct of the oral hearing
Working group Section 35a	15 March 2022 5 April 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	12 April 2022	Concluding discussion of the draft resolution

Plenum	21 April 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 April 2022

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

Prof. Hecken