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Pitolisant (obstructive sleep apnoea) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pitolisant (obstruktive Schlafapnoe) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 10 March 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Boris A. Stuck, Clinic for Otorhinolaryngology, University Hospital of Marburg, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Hartmut Rentmeister.

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

IQWiG employees involved in the dossier assessment

- Selver Altin
- Charlotte Guddat
- Florina Kerekes
- Ulrike Lampert
- Regine Potthast
- Volker Vervölgyi
- Carolin Weigel
- Pamela Wronski

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CPAP	continuous positive airway pressure
EDS	excessive daytime sleepiness
EPAR	European Public Assessment Report
ESS	Epworth Sleepiness Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICSD-2	International Classification of Sleep Disorders, second edition
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
nCPAP	nasal continuous positive airway pressure
OSA	obstructive sleep apnoea
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
UPPP	uvulopalatopharyngoplasty

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 pitolisant. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 November 2021.

Research question

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

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

Table 2: Research question of the benefit assessment of pitolisant

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

The company specified as the ACT optimized standard therapy of the underlying OSA and thereby follows the G-BA's specification.

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.

Study pool and study design

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of pitolisant in comparison with the ACT.

The company explains that no suitable studies are available for assessing the added benefit of pitolisant in comparison with the ACT. In its Module 4 A, the company presents, as supplementary information, the HAROSA I and HAROSA II studies with treatment durations of 12 weeks each.

The data presented by the company as supplementary information are unsuitable for drawing conclusions on the added benefit of pitolisant in comparison with the ACT.

HAROSA I study

The HAROSA I study is a randomized, double-blind, placebo-controlled study with pitolisant. It included adult patients with diagnosed OSA. Patients had to have an apnoea-hypopnoea index (AHI) of ≤ 10 events/h during sleep, as measured within the past 12 months or 2 weeks before randomization by means of polysomnography with nasal CPAP (nCPAP). Before study start, patients had to have received nCPAP therapy for ≥ 3 months and still suffer from EDS despite prior efforts to establish efficient nCPAP therapy. At the time of study inclusion, nCPAP therapy was to be used for ≥ 4 h/day, and daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS) had to be at a score ≥ 12.

The HAROSA I study comprises a 12-week double-blind study phase and a subsequent optional open-label extension phase. The double-blind study phase included 244 patients, randomized in a 3:1 ratio either to treatment with pitolisant (N = 183) or to placebo (N = 61).

The primary outcome of the HAROSA I study was a change in ESS score between baseline and treatment end. Secondary outcomes included outcomes from the morbidity and side effects categories.

HAROSA II study

The HAROSA II study is a randomized, double-blind, placebo-controlled study with pitolisant. It included adult patients with diagnosed OSA who have refused nCPAP therapy and whose daytime sleepiness score as measured by ESS was ≥ 12. Patients had to have an AHI ≥ 15 events/h during sleep as measured by means of polysomnography within the past 12 months or 2 weeks before randomization.

Like the HAROSA I study, HAROSA II comprises a double-blind study phase and an extension phase. The double-blind study phase included a total of 268 patients, randomized in a 3:1 ratio either to treatment with pitolisant (N = 201) or to placebo (N = 67).

The primary outcome in the HAROSA II study was a change in ESS score between baseline and treatment end. Secondary outcomes included outcomes from the morbidity and side effects categories.

Unsuitability of data presented by the company from the HAROSA I and HAROSA II studies for the benefit assessment

Their short treatment duration of 12 weeks in the double-blind study phase already disqualifies the HAROSA I and HAROSA II studies presented by the company for the benefit assessment in the present therapeutic indication. OSA is a chronic disease. Since not only short-term effects, but particularly long-term effects are of interest, long-term studies are necessary to draw any conclusions on added benefit.

In addition, both studies inadequately implemented the ACT, and the HAROSA II study population may not correspond to the approval population of pitolisant.

Results

In summary, no suitable data are available for the assessment of added benefit of pitolisant in comparison with the ACT for improving wakefulness and reducing excessive daytime sleepiness in adult patients with OSA whose EDS has not been satisfactorily treated by, or who have not tolerated, primary OSA therapy, such as CPAP. Hence, there is no hint of an added benefit of pitolisant in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

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

[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].

Table 3: Pitolisant – probability and extent of added benefit

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

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, patients in both study arms are assumed to receive optimal care. Standard therapy includes, in particular, CPAP. Standard therapy is assumed to be continued. Weight-reducing measures may represent add-on treatment strategies.
c. For patients who refuse or do not tolerate CPAP therapy, the reasons for refusal or intolerance to CPAP should be documented.
d. Where optimization options are exhausted, the G-BA deems continuation of the existing OSA therapy to be acceptable.

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

The G-BA decides on the added benefit.

2.2 Research question

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

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

Table 4: Research question of the benefit assessment of pitolisant

Therapeutic indication	ACT[a]
Improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by, or who have not tolerated, primary OSA therapy, such as CPAP[b, c]	Optimized standard therapy of the underlying OSA[d]

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, patients in both study arms are assumed to receive optimal care. Standard therapy includes, in particular, CPAP. Standard therapy is assumed to be continued. Weight-reducing measures may represent add-on treatment strategies.
c. For patients who refuse or do not tolerate CPAP therapy, the reasons for refusal or intolerance to CPAP should be documented.
d. Where optimization options are exhausted, the G-BA deems continuation of the existing OSA therapy to be acceptable.

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

The company identifies optimized standard therapy of the underlying OSA as the ACT and thereby follows the G-BA's specification.

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 concurs with the company's inclusion criteria.

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 list on pitolisant (status: 1 September 2021)
- bibliographical literature search on pitolisant (last search on 1 September 2021)
- search in trial registries/trial results databases for studies on pitolisant (last search on 1 September 2021)
- search on the G-BA website for pitolisant (last search on 1 September 2021)

To check the completeness of the study pool:

- search in trial registries for studies on pitolisant (last search on 15 November 2021); for search strategies, see Appendix A of the full dossier assessment

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of pitolisant in comparison with the ACT.

Due to the lack of relevant directly comparative studies, the company expanded the information retrieval in Module 4 A to RCTs suitable for an indirect comparison via a common comparator and subsequently to non-randomized comparative trials or all study types (other investigations).

The company explains that no suitable studies are available for assessing the added benefit of pitolisant in comparison with the ACT. As supplementary information, the company's Module 4 A presents the HAROSA I [3] and HAROSA II studies [4] with treatment durations of 12 weeks each.

The data presented by the company as supplementary information are unsuitable for drawing conclusions on the added benefit of pitolisant in comparison with the ACT. This is justified below.

Evidence provided by the company

HAROSA I study

The HAROSA I study is a randomized, double-blind, placebo-controlled study with pitolisant. It included adult patients with diagnosed OSA. The OSA diagnosis was established using the criteria of the International Classification of Sleep Disorders, second edition (ICSD-2) [3,5]. Patients had to have an apnoea-hypopnoea index (AHI) of ≤ 10 events/h during sleep, as measured within the past 12 months or 2 weeks before randomization by means of

polysomnography with nCPAP. Before study start, patients had to have received nCPAP therapy for ≥ 3 months and still suffer from EDS despite prior efforts to establish efficient nCPAP therapy. At the time of study inclusion, nCPAP therapy was to be used for ≥ 4 h/day, and daytime sleepiness as measured by the ESS had to be ≥ 12.

The HAROSA I study comprises a 12-week double-blind study phase and a subsequent optional open-label extension phase. The double-blind study phase included 244 patients, randomized in a 3:1 ratio either to treatment with pitolisant (N = 183) or to placebo (N = 61).

The double-blind treatment period started with a phase of pitolisant dose escalation or modification. From Week 4, the existing pitolisant dose was kept stable for the remaining 9-week period. This departs from the Summary of Product Characteristics (SPC) of pitolisant [6], which states that the dose can be decreased or increased at any time according to the physician assessment and the patient's response.

In the 2 weeks before randomization (wash-out phase), patients were asked to discontinue disallowed co-medications (e.g. all drugs indicated for treating somnolescence, tricyclic antidepressants, psychostimulants). During the course of the study, the use of such drugs or surgical therapies (including uvulopalatopharyngoplasty [UPPP]) or mandibular advancement splints for the treatment of the underlying OSA was also disallowed. After the 12-week double-blind study phase, patients in the intervention or comparator arm were eligible for optionally continuing or initiating pitolisant treatment in the open-label, 40-week extension phase.

The primary outcome of the HAROSA I study was a change in ESS score between baseline and treatment end. Secondary outcomes included outcomes from the morbidity and side effects categories.

HAROSA II study

The HAROSA II study is a randomized, double-blind, placebo-controlled study with pitolisant. It included adult patients with diagnosed OSA who have refused nCPAP therapy and whose daytime sleepiness score as measured by ESS was ≥ 12. The OSA diagnosis was established according to ICSD-2 criteria [4,5]. Patients had to have an AHI ≥ 15 events/h during sleep as measured by means of polysomnography within the past 12 months or 2 weeks before randomization.

Like the HAROSA I study, HAROSA II comprises a double-blind study phase and an extension phase. The double-blind study phase included a total of 268 patients, randomized in a 3:1 ratio either to treatment with pitolisant (N = 201) or to placebo (N = 67).

The pitolisant dosing regimen as well as disallowed concomitant medications and therapies for the underlying OSA during the study also correspond to the requirements described in the HAROSA I study (see information on HAROSA I).

Over the course of the study and taking into account their cardiovascular profile, patients were asked whether they wanted to reconsider their refusal of nCPAP therapy. Patients who then consented to nCPAP therapy had the option of discontinuing their study participation.

The primary outcome in the HAROSA II study was a change in ESS score between baseline and treatment end. Secondary outcomes included outcomes from the morbidity and side effects categories.

Unsuitability of the data presented by the company from the HAROSA I and HAROSA II studies for the benefit assessment

Insufficient durations of the HAROSA I and HAROSA II studies

Both RCTs are unsuitable for the benefit assessment in the therapeutic indication of OSA because of their short treatment duration of 12 weeks. OSA is a chronic disease requiring life-long treatment [7,8]. The IQWiG General Methods likewise state 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. Since not only short-term effects, but particularly long-term effects are of interest, long-term studies are necessary to draw any conclusions on added benefit. This not only applies to statements on benefit outcomes, but also to harm outcomes since adverse events (AEs) might not manifest until after prolonged use of the drug.

The company likewise concludes that no suitable studies are available for assessing any added benefit of pitolisant. Nevertheless, the company presents, as supplementary information, the results of the two 12-week studies HAROSA I [3] and HAROSA II [4] and argues that while they do not allow assessing long-term effects, they suggest a long-term added benefit of pitolisant. On this basis, the company claims a hint of non-quantifiable added benefit for pitolisant.

The company's rationale was not accepted. For the benefit assessment of pitolisant versus the ACT in the therapeutic indication, studies at least 24 weeks in duration are required for a benefit-harm comparison.

ACT not implemented in the HAROSA I and HAROSA II studies

The G-BA has specified optimized standard therapy of the underlying OSA as the ACT in the present therapeutic indication. As explained below, this ACT was not implemented in the HAROSA I and HAROSA II studies.

HAROSA I study

The HAROSA I study included patients who had received nCPAP therapy (≥ 4 h/day) for treating OSA for at least 3 months before enrolment. The study documents do not explicitly show whether patients in both study arms continued nCPAP therapy during the study. The study protocol originally specified that compliance with nCPAP therapy was to be checked at each study visit, but after a protocol change, these data were documented only at Visit 1 (2 weeks

before randomization). The company's Module 4 A states that, while nCPAP compliance was not systematically surveyed in the HAROSA I study, this was part of routine follow-up, and investigators did not observe any unexpected decrease in nCPAP compliance.

While technically, patients can be assumed to have continued nCPAP therapy of the underlying OSA during study treatment, no information is available on whether optimizations of nCPAP therapy were planned or carried out during study treatment. According to the G-BA, unmodified continuation of the existing OSA therapy is an acceptable ACT where optimization options have been exhausted (see Table 4). While the inclusion criteria required that efforts be made regarding the efficiency of nCPAP therapy before study inclusion, it is unclear which criteria were used to assess the efficiency of nCPAP therapy and whether patients received optimized nCPAP therapy before study start.

In addition, the HAROSA I study did not use any other primary OSA therapies (except CPAP therapy). National and international guidelines list CPAP therapy as a reference method. But various other OSA treatment options or optimizations are recommended in this therapeutic indication [7-10]. They include, for instance, modification of the duration of PAP use as well as a switch of masks, pressure changes, or the use of humidifiers. In addition, changing the PAP therapy mode may be considered. Options include automatic positive airway pressure (APAP) and bi-level techniques. Alternatively, treatment might be switched to a different method, such as a mandibular advancement splint. Another option is combination therapy consisting of PAP therapy and a mandibular advancement splint or possibly surgery. Furthermore, in patients with positional OSA, positional therapy can be considered, and in overweight patients, concomitant measures for weight loss are recommended [7-9].

The HAROSA I study disallowed, both before and during study treatment, any alternative treatment methods, such as mandibular advancement splints and surgery (including UPPP) for the treatment of the underlying OSA [3]. However, these treatment methods represent further optimization options of the primary OSA therapy. All things considered, therefore, the HAROSA I study cannot be assumed to have implemented the ACT of optimized standard therapy of the underlying OSA.

Study HAROSA II

The HAROSA II study included patients who refused nCPAP therapy. In Module 4 A, the company states that in the visits during the study, patients were asked whether they want to reconsider their position on CPAP therapy. However, the study documents provide discrepant information as to whether patients were asked this question throughout the course of the study or only after the end of the double-blind study phase. Patients who agreed to CPAP therapy had the option of discontinuing the study. Consequently, patients who received standard therapy of the underlying OSA in accordance with the ACT were not further followed up. According to information provided in the European Public Assessment Report (EPAR) [5], a total of 6 patients discontinued the HAROSA II study to use nCPAP therapy.

Further alternative treatment methods for the underlying OSA, such as mandibular advancement splints and surgery (including UPPP) were disallowed, both before enrolment and during study treatment. HAROSA II thereby disallowed treatment methods deemed relevant by national and international guidelines (see information on HAROSA I). Therefore, it is safe to assume that the study population's underlying OSA was not treated. The EPAR likewise points out that patients in the HAROSA II study did not receive primary therapy of the underlying OSA [5].

Overall, the HAROSA II study did not implement the ACT.

Questionable implementation of the approval population for pitolisant in the HAROSA II study

As per its approval, pitolisant is indicated for adult patients with OSA whose EDS has not been satisfactorily treated by, or who have not tolerated, primary OSA therapy, such as CPAP. The therapeutic indication therefore requires patients to have received prior treatment with at least 1 primary OSA therapy.

The HAROSA II study included patients who refused nCPAP therapy. The inclusion criteria of the HAROSA II study do not provide any further information on the prior treatment of the study population. According to the information provided in the company's Module 4 A, there was also no record of the reasons for which patients refused nCPAP therapy. Overall, it is unclear whether patients had been treated with CPAP or another OSA therapy at any time prior to enrolment. In Module 4 A, the company merely states that the OSA diagnosis was established an average of 11.9 months prior and that it is safe to assume that (1) attempts were made since this time to optimize CPAP compliance and (2) alternative treatment options have been weighed before patients were offered enrolment in the HAROSA II study.

Overall, it is therefore questionable to what extent prior treatment with primary OSA therapy, as required by the SPC, applies to the HAROSA II study population.

Summary

All things considered, no data suitable for answering the research question of this benefit assessment are available. In general, due to their short treatment duration, the HAROSA I and HAROSA II studies are unsuitable for assessing the added benefit of pitolisant versus the ACT. In addition, the ACT was inadequately implemented in both studies, and the HAROSA II study population may not correspond to the approval population of pitolisant.

2.4 Results on added benefit

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

2.5 Probability and extent of added benefit

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

Table 5: Pitolisant – probability and extent of added benefit

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

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, patients in both study arms are assumed to receive optimal care. Standard therapy includes, in particular, CPAP. Standard therapy is assumed to be continued. Weight-reducing measures may represent add-on treatment strategies.
c. For patients who refuse or do not tolerate CPAP therapy, the reasons for refusal or intolerance to CPAP should be documented.
d. Where optimization options are exhausted, the G-BA deems continuation of the existing OSA therapy to be acceptable.

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

The above-described assessment deviates from that made by the company, which claims a hint of a non-quantifiable added benefit on the basis of data from the HAROSA I and HAROSA II studies presented as supplementary information.

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 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.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. Pepin JL, Georgiev O, Tiholov R et al. Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP: A Randomized Trial. Chest 2021; 159(4): 1598-1609. https://dx.doi.org/10.1016/j.chest.2020.09.281.

4. Dauvilliers Y, Verbraecken J, Partinen M et al. Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment. A Randomized Trial. Am J Respir Crit Care Med 2020; 201(9): 1135-1145. https://dx.doi.org/10.1164/rccm.201907-1284OC.

5. European Medicines Agency. Ozawade; Assessment report [online]. 2021 [Accessed: 21.12.2021]. URL: https://www.ema.europa.eu/documents/assessment-report/ozawade-epar-public-assessment-report_en.pdf.

6. Bioprojet Pharma. Ozawade 4,5 mg/18 mg Filmtabletten [online]. 2021 [Accessed: 14.12.2021]. URL: https://www.fachinfo.de.

7. Deutsche Gesellschaft für Schlafforschung und Schlafmedizin. S3-Leitlinie Nicht erholsamer Schlaf/Schlafstörungen – Kapitel „Schlafbezogene Atmungsstörungen“ [online]. 2017 [Accessed: 14.12.2021]. URL: https://www.awmf.org/uploads/tx_szleitlinien/063-001l_S3_SBAS_2017-08_2_verlaengert_und_Hinweis_Teil-Aktualisierung_2020-07.pdf.

8. Epstein LJ, Kristo D, Strollo PJ Jr et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009; 5(3): 263-276.

9. Stuck BA, Arzt M, Fietze I et al. Teil-Aktualisierung S3-Leitlinie Schlafbezogene Atmungsstörungen bei Erwachsenen. Somnologie 2020; 24(3): 176-208. https://dx.doi.org/10.1007/s11818-020-00257-6.

10. Fietze I, Blum HC, Grüger H et al. Diagnostik und Therapie der residualen Tagesschläfrigkeit bei Patienten mit therapierter obstruktiver Schlafapnoe. Somnologie 2021; 25(2): 99-109. https://dx.doi.org/10.1007/s11818-021-00305-9.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-140.html.