Daridorexant (insomnia)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A22-123 Version: 1.0 Status: 8 February 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Daridorexant (Insomnie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Daridorexant (insomnia) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

16 November 2022

Internal Project No.

A22-123

Address of publisher

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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

No feedback was received in the framework of the present dossier assessment.

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Keywords

Daridorexant, Sleep Initiation and Maintenance Disorders, Benefit Assessment

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CBT	cognitive behavioural therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
eCRF	electronic case report form
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISI	Insomnia Severity Index
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 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 daridorexant. 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 16 November 2022.

Research question

The aim of this report is to assess the added benefit of daridorexant in comparison with the appropriate comparator therapy (ACT) in adult patients with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning, and who have not responded to cognitive behavioural therapy (CBT) or for whom this type of therapy is not suitable or not feasible.

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

Table 2: Research question of the benefit assessment of daridorexant

Therapeutic indication	**ACT**[a]
Adults with insomnia, characterized by symptoms present for at least 3 months, who have not responded to CBT or for whom this type of therapy is not suitable or not feasible[b, c, d]	Short-term drug treatment[e] with short-acting benzodiazepines or **non-benzodiazepine receptor agonists**, followed by BSC[f]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. According to the SPC for daridorexant, these are adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning.
c. The G-BA points out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead of prescribing drugs. According to the G-BA, it is assumed in the present therapeutic indication that CBT was carried out before the start of drug treatment and that the patient did not respond sufficiently or that CBT could not be carried out. It must be documented whether CBT was carried out or could not be carried out. Patients already receiving CBT at study enrolment may continue CBT.
d. According to the G-BA, it is assumed that the therapeutic indication includes both patients with and patients without accompanying diseases. It is assumed that the underlying/accompanying diseases (e.g. depression) are optimally treated.
e. Short-term treatment is understood to mean a treatment duration of up to 4 weeks, taking into account the respective approved duration of use of the drug.
f. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; CBT: cognitive behavioural therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Deviating from the specification of the G-BA, the company investigated 2 research questions (A1 and A2). Its research question A1 corresponds to that of the G-BA. According to the company, the additional research question A2 refers to adult patients with insomnia who are generally not prescribed any drugs. The benefit assessment is conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of added benefit.

Results

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

The company, in contrast, identified study 201, in which daridorexant, zolpidem and placebo were administered, and used it in its assessment. In addition, it presented an evidence transfer for adults aged ≥ 65 years based on study 301, which compared daridorexant with placebo. The company identified this study for its research question A2.

Evidence provided by the company

Study 201

Study 201 is a multicentre, double-blind, randomized study with daridorexant, zolpidem and placebo. The study included adult patients between 18 and 64 years of age with chronic insomnia disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria, poor sleep quality (Insomnia Severity Index [ISI] score ≥ 15) and insufficient sleep quantity. Patients who had received CBT within 1 month prior to study start were excluded from the study. CBT was also not allowed during the study.

In study 201, a total of 360 patients were randomly allocated in a 1:1:1:1:1:1 ratio to treatment with different dosages of daridorexant (5 mg [N = 60], 10 mg [N = 59], 25 mg [N = 60], 50 mg [N = 61]), 10 mg zolpidem (N = 60), or placebo (N = 60). Primary outcome of the study was the total time spent awake after sleep onset.

Evidence transfer

As study 201 included only adults with chronic insomnia disorder who were aged 18 to 64 years, the company presented an evidence transfer for adults aged ≥ 65 years based on study 301. Study 301 is a multicentre, double-blind, randomized study, in which 2 dosages of daridorexant were compared with placebo. Adult patients with chronic insomnia disorder according to DSM-5 criteria, an ISI score of ≥ 15, and identical criteria for sleep quantity as in study 201 were included.

Study 201 and evidence transfer are not suitable for the benefit assessment

Study 201

Study 201 presented by the company is unsuitable for the benefit assessment. This is due in particular to the fact that no information is available on pretreatment with CBT or on unsuitability for CBT. The G-BA pointed out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead of prescribing drugs. According to the G-BA, it is therefore assumed in the present therapeutic indication that CBT was carried out before the start of drug treatment and that the patient did not respond sufficiently or that CBT could not be carried out. Various clinical practice guidelines for the treatment of insomnia also list CBT as the first treatment option. In addition, documentation is required by the G-BA as to whether CBT was carried out or could not be carried out.

Furthermore, there is no information available on the extent to which pretreatment with CBT has an influence on the effects of subsequent drug therapy. Overall, it is unclear whether the data presented are applicable to the research question of the present benefit assessment. The study is therefore not used for the benefit assessment.

In addition, study 201 with an 8-week study duration is too short in the therapeutic indication of insomnia, in which daridorexant can be used as a possible long-term treatment. Besides, there are deviations from the recommendations of the respective Summaries of Product Characteristics (SPCs) in study 201. The possible effects of the fixed treatment duration of 4 weeks in the study and the lack of a tapering phase for the drug zolpidem (e.g. rebound effect) for the patients are unclear.

Evidence transfer

As study 201 is not suitable for the benefit assessment, the evidence transfer carried out by the company for the age group ≥ 65 years is also not relevant for the benefit assessment and is therefore not commented on further.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of daridorexant 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]

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

Table 3: Daridorexant – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with insomnia, characterized by symptoms present for at least 3 months, who have not responded to CBT or for whom this type of therapy is not suitable or not feasible[b, c, d]	Short-term drug treatment[e] with short-acting benzodiazepines or **non-benzodiazepine receptor agonists**, followed by BSC[f]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. According to the SPC for daridorexant, these are adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning.
c. The G-BA points out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead of prescribing drugs. According to the G-BA, it is assumed in the present therapeutic indication that CBT was carried out before the start of drug treatment and that the patient did not respond sufficiently or that CBT could not be carried out. It must be documented whether CBT was carried out or could not be carried out. Patients already receiving CBT at study enrolment may continue CBT.
d. According to the G-BA, it is assumed that the therapeutic indication includes both patients with and patients without accompanying diseases. It is assumed that the underlying/accompanying diseases (e.g. depression) are optimally treated.
e. Short-term treatment is understood to mean a treatment duration of up to 4 weeks, taking into account the respective approved duration of use of the drug.
f. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; CBT: cognitive behavioural therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of daridorexant in comparison with the ACT in adult patients with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning, and who have not responded to CBT or for whom this type of therapy is not suitable or not feasible.

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

Table 4: Research question of the benefit assessment of daridorexant

Therapeutic indication	**ACT**[a]
Adults with insomnia, characterized by symptoms present for at least 3 months, who have not responded to CBT or for whom this type of therapy is not suitable or not feasible[b, c, d]	Short-term drug treatment[e] with short-acting benzodiazepines or **non-benzodiazepine receptor agonists**, followed by BSC[f]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. According to the SPC for daridorexant [3], these are adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning.
c. The G-BA points out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead of prescribing drugs. According to the G-BA, it is assumed in the present therapeutic indication that CBT was carried out before the start of drug treatment and that the patient did not respond sufficiently or that CBT could not be carried out. It must be documented whether CBT was carried out or could not be carried out. Patients already receiving CBT at study enrolment may continue CBT.
d. According to the G-BA, it is assumed that the therapeutic indication includes both patients with and patients without accompanying diseases. It is assumed that the underlying/accompanying diseases (e.g. depression) are optimally treated.
e. Short-term treatment is understood to mean a treatment duration of up to 4 weeks, taking into account the respective approved duration of use of the drug.
f. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; CBT: cognitive behavioural therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Deviating from the specification of the G-BA, the company investigated 2 research questions (A1 and A2). Its research question A1 corresponds to that of the G-BA. For this research question, it followed the ACT of the G-BA and selected the drug zolpidem from the drug class of non-benzodiazepine receptor agonists as comparator therapy.

According to the company, the additional research question A2 refers to adult patients with insomnia who are generally not prescribed any drugs. For this research question, it designated optimized non-drug care at the physician's discretion and according to availability (operationalized as placebo) as comparator therapy. The company also included sleep hygiene and/or CBT measures. The patient population cited by the company for its research question

A2 and the chosen comparator therapy do not correspond to the specification of the G-BA. The benefit assessment is conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 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 daridorexant (status: 16 September 2022)
- bibliographical literature search on daridorexant (last search on 16 September 2022)
- search in trial registries/trial results databases for studies on daridorexant (last search on 16 September 2022)
- search on the G-BA website for daridorexant (last search on 16 September 2022)

To check the completeness of the study pool:

- search in trial registries for studies on daridorexant (last search on 6 December 2022); for search strategies, see I Appendix A of the full dossier assessment

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

The company, in contrast, identified study 201 [4,5], in which daridorexant, zolpidem and placebo were administered, and used it in its assessment. In addition, it presented an evidence transfer for adults aged ≥ 65 years based on study 301 [6], which compared daridorexant with placebo. The company identified this study for its research question A2.

Evidence provided by the company

Study 201

Study 201 is a multicentre, double-blind, randomized study with daridorexant, zolpidem and placebo. The study included adult patients between 18 and 64 years of age with chronic insomnia disorder according to DSM-5 criteria and poor sleep quality (ISI score ≥ 15). In addition, patients had to have insufficient sleep quantity. In their self-reported history, patients had to fulfil the following criteria on at least 3 nights per week and for at least 3 months prior to study start: ≥ 30 minutes to fall asleep, total time spent awake after sleep onset ≥ 30 minutes, and total sleep time ≤ 6.5 h. Prior to study inclusion, sleep quantity criteria had to be confirmed by polysomnography on 2 nights. Patients who had received CBT within 1 month prior to study start were excluded from the study. CBT and other psychological therapies, excluding common advice related to sleep hygiene, were also not allowed during the study.

The study consisted of a screening phase of 2 to a maximum of 4 weeks, a double-blind treatment phase of 4 weeks, and a follow-up phase of 4 weeks.

In study 201, a total of 360 patients were randomly allocated in a 1:1:1:1:1:1 ratio to treatment with different dosages of daridorexant (5 mg [N = 60], 10 mg [N = 59], 25 mg [N = 60], 50 mg [N = 61]), 10 mg zolpidem (N = 60), or placebo (N = 60). Randomization was stratified by sex.

Treatment with daridorexant and zolpidem partly deviated from the recommendations of the corresponding SPC [3,7] (see discussion of the suitability of study 201 below). Dose adjustments were not allowed for either drug.

Primary outcome of the study was the total time spent awake after sleep onset. Secondary outcomes were outcomes from the morbidity and side effects categories.

Evidence transfer

As study 201 included only adults with chronic insomnia disorder who were aged 18 to 64 years, the company presented an evidence transfer for adults aged ≥ 65 years based on study 301. Study 301 is a multicentre, double-blind, randomized study, in which 2 dosages of daridorexant were compared with placebo. Adult patients with chronic insomnia disorder according to DSM-5 criteria, an ISI score of ≥ 15, and identical criteria for sleep quantity as in study 201 were included.

Study 201 and evidence transfer are not suitable for the benefit assessment

Study 201

Study 201 presented by the company is unsuitable for the benefit assessment. This is due in particular to the fact that no information is available on pretreatment with CBT or on unsuitability for CBT. The G-BA pointed out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead of prescribing drugs. According to the G-BA, it is therefore assumed in the present therapeutic indication that CBT was carried out before the start of drug treatment and that the patient did not respond sufficiently or that CBT could not be carried out. Various clinical practice guidelines for the treatment of insomnia [8-10] also list CBT as the first treatment option. In addition, documentation is required by the G-BA as to whether CBT was carried out or could not be carried out.

In the submitted dossier, the company did not provide any information on whether or not patients had been pretreated with CBT and thus did not address the requirement of the G-BA. Rather, according to the study protocol, patients who had received CBT within 1 month prior to study start were excluded from enrolment. The electronic case report form (eCRF) also shows that there was no specific question regarding any pretreatment with CBT. Thus, it cannot be assumed that pretreatment with CBT was documented in the study.

Furthermore, there is no information available on the extent to which pretreatment with CBT has an influence on the effects of subsequent drug therapy. Overall, it is unclear whether the data presented are applicable to the research question of the present benefit assessment. The study is therefore not used for the benefit assessment.

In addition, study 201 with an 8-week study duration is too short in the therapeutic indication of insomnia, in which daridorexant can be used as a possible long-term treatment.

Besides, there are deviations from the recommendations of the corresponding SPC in study 201 [3,7]. According to the SPC [3], the treatment duration with daridorexant should be as short as possible and the appropriateness of continued treatment should be assessed within 3 months and periodically thereafter. However, the study protocol specified a fixed period of 4 weeks for treatment with daridorexant. Since the appropriateness should be assessed within the first 3 months and treatment only covered 1 month in total, it is ultimately unclear whether, and if so, how many patients were treated for a shorter or longer period than necessary. According to the SPC [7], the duration of treatment with zolpidem should also be as short as possible, but in contrast to daridorexant, it should not exceed 4 weeks including a period of tapering off. However, analogous to daridorexant, the study protocol specified a fixed period of 4 weeks of treatment. In addition, neither Module 4 A nor the study documents provide any information on the implementation of a tapering phase. The possible effects of the fixed treatment duration in the study and the lack of a tapering phase (e.g. rebound effect) for the patients are unclear.

Evidence transfer

As study 201 is not suitable for the benefit assessment, the evidence transfer carried out by the company for the age group ≥ 65 years is also not relevant for the benefit assessment and is therefore not commented on further.

I 4 Results on added benefit

No suitable data are available for the benefit assessment of daridorexant in comparison with the ACT in adult patients with insomnia, characterized by symptoms present for at least 3 months, who have not responded to CBT or for whom this type of therapy is not suitable or not feasible. There is no hint of an added benefit of daridorexant in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Daridorexant – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with insomnia, characterized by symptoms present for at least 3 months, who have not responded to CBT or for whom this type of therapy is not suitable or not feasible[b, c, d]	Short-term drug treatment[e] with short-acting benzodiazepines or **non-benzodiazepine receptor agonists**, followed by BSC[f]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. According to the SPC for daridorexant [3], these are adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning.
c. The G-BA points out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead of prescribing drugs. According to the G-BA, it is assumed in the present therapeutic indication that CBT was carried out before the start of drug treatment and that the patient did not respond sufficiently or that CBT could not be carried out. It must be documented whether CBT was carried out or could not be carried out. Patients already receiving CBT at study enrolment may continue CBT.
d. According to the G-BA, it is assumed that the therapeutic indication includes both patients with and patients without accompanying diseases. It is assumed that the underlying/accompanying diseases (e.g. depression) are optimally treated.
e. Short-term treatment is understood to mean a treatment duration of up to 4 weeks, taking into account the respective approved duration of use of the drug.
f. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; CBT: cognitive behavioural therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The assessment described above differs from that of the company, which derived an indication of considerable added benefit for all patients in the therapeutic indication, irrespective of age, on the basis of study 201 and taking into account its transfer of evidence, for its research question A1.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-123.html.