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)
Daridorexant (insomnia)

of 12 May 2023

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

Due to the prescription restriction according to the Pharmaceuticals Directive (AM-RL); Annex III; No. 32 for hypnotics/hypnogenic agents or sedatives (sleep-inducing, sleep-initiating, sleep-promoting or tranquilisers) for the treatment of insomnia, except for short-term therapy up to 4 weeks, the benefit assessment according to Section 35a SGB V for the active ingredient daridorexant is limited to the reimbursable part of the indication at the time the resolution was adopted for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning, for the therapy duration of up to 4 weeks.

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient daridorexant on 15 November 2022 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 November 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 February 2023 on the G-BA website (www.g-ba.de), 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 daridorexant compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well the addendum drawn up by the G-BA on the benefit assessment. 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 daridorexant.

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 Daridorexant (Quviviq) in accordance with the product information

Quviviq is indicated for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning.

Therapeutic indication of the resolution (resolution of 12 May 2023):

Quviviq is indicated for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning; application for up to 4 weeks.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning

Appropriate comparator therapy for daridorexant:

Short-term drug therapy with short-acting benzodiazepines or non-benzodiazepine receptor agonists, followed by best-supportive-care.

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

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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. For the treatment of insomnias, besides daridorexant, active ingredients from the different product classes of benzodiazepines (lormetazepam, flurazepam, triazolam, nitrazepam, temazepam, brotizolam, flunitrazepam, midazolam, lorazepam, oxazepam), antihistamines (diphenhydramine, doxylamine, hydroxizine), sedative neuroleptics (melperone, pipamperone, promethazine), non-benzodiazepine receptor agonists (zopiclone, zolpidem, eszopiclone) as well as clomethiazole, L-tryptophan, chloral hydrate or melatonin are approved. These agents are usually limited to short-term use and sometimes to insomnias associated with a concomitant disease.

on 2. Non-organic insomnias constitute an indication for the use of psychotherapy according to Section 27 of the Psychotherapy Guideline.

on 3. There are no resolutions that have established the patient-relevant benefit of medicinal products in the present therapeutic indication. There are prescription restrictions due to the Pharmaceuticals Directive (AM-RL):

- Prescription restrictions according to AM-RL; Annex III; No. 32: Hypnotics/hypnogenic agents or sedatives (sleep-inducing, sleep-initiating, sleep-promoting or tranquilisers): for the treatment of insomnia,
  - except for short-term therapy up to 4 weeks
  - except for treatment lasting longer than 4 weeks in medically justified individual cases.
  - except for the treatment of disturbed sleep-wake rhythm (non-24-hour sleep-wake syndrome) in totally blind subjects.
  - except for the treatment of sleep disorders (insomnia) in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome when sleep hygiene measures have been inadequate

  Long-term use of hypnotics/hypnogenic agents or sedatives must be particularly justified.

- Prescription restrictions according to AM-RL; Annex III; No. 45: Tranquillisers.

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 therapeutic indication.

In summary, the assessment of the evidence and the approval of the available therapies were decisive in determining the appropriate comparator therapy for daridorexant in the present therapeutic indication.

In the overall view of the available literature, the best evidence regarding a patient-relevant benefit is available for cognitive behavioural therapy (CBT) and represents the generally preferable therapy in the therapeutic indication. Both the S3 guideline of the German Society for Sleep Research and Sleep Medicine (DGSM, currently under revision)[2] and the European Guideline[3] mention cognitive behavioural therapy for insomnia (CBT-I) as the first treatment option. According to the S3 guideline, medicinal therapy can be offered if CBT-I has not been sufficiently effective or is not feasible. For this reason, it is assumed that for patients with sleep disorders, CBT-I is to be regarded as the treatment standard, and depending on its effectiveness and feasibility, medicinal therapy will be offered. From the written and oral statements it emerged that only about 11 % of the affected patients in Germany are treated with a CBT-I.

From the evidence presented, it is clear that among medicinal therapies, benzodiazepines and non-benzodiazepine receptor agonists are among the best studied product classes for this therapeutic indication. However, the statements on the described effects mainly refer to a short-term application. Short-term therapy is understood to be a treatment period of up to 4 weeks, whereby the respective approved duration of use of the medicinal products must be observed.

The evidence base on non-benzodiazepine receptor agonists and benzodiazepines in the evidence synopsis is comparable.

There are also studies in the therapeutic indication on sedating antidepressants that examine patients with insomnia without a connection to a depressive illness. These medicinal products are not approved for the sole treatment of insomnia and are therefore not intended as appropriate comparator therapy in the present therapeutic indication.

Against the background of the side effect profile of long-acting benzodiazepines, the determination of the appropriate comparator therapy for benzodiazepines is mainly limited to short-acting benzodiazepines. Overall, the G-BA concludes that a short-term medicinal therapy with short-acting benzodiazepines or non-benzodiazepine receptor agonists, followed by BSC, should be established as the appropriate comparator therapy for daridorexant for the treatment of adults with insomnia who have not responded to cognitive behavioural therapy or for whom this is not suitable or feasible. With regard to the duration of action of benzodiazepines, the G-BA follows the assessment of the EMCDDA.[4] According to this, short-acting benzodiazepines approved for the treatment of insomnia are brotizolam, flunitrazepam, lorazepam, lormetazepam, midazolam, oxazepam, temazepam and triazolam.

[2] German Society for Sleep Research and Sleep Medicine (DGSM) 2017. Non-restorative sleep/insomnia: Insomnia in adults; S3 guideline, long version; version 2.0.
[3] Riemann, D. et al., 2017. European guideline for the diagnosis and treatment of insomnia.
[4] European Monitoring Centre for Drugs and Drug Addiction: Benzodiazepines (retrieved 27.04.2023): https://www.emcdda.europa.eu/publications/drug-profiles/benzodiazepines_de

"Best supportive care" (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

For adults with sleep disorders (insomnia) whose symptoms have persisted for at least 3 months and have a significant impact on daytime activity, the additional benefit is not proven.

Justification:

The pharmaceutical company submits the results of the 201 study. This is a double-blind, randomised study with the treatment arms daridorexant (dosage relevant for the benefit assessment: 50 mg/d; n= 61), zolpidem (10 mg/d; n= 60) and placebo (not relevant), which was conducted in 38 study sites in Germany, Israel, Spain, Sweden, Hungary and the USA. Adult patients between 18 and 64 years of age with chronic insomnia disorder, defined according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and poor sleep quality (Insomnia Severity Index score ≥ 15) and insufficient sleep quantity were included. Patients were excluded from the study if they had psychiatric diseases or neurological disorders that may affect sleep, motor performance or perception, including Parkinson's disease, pre-dementia, dementia, other neurodegenerative diseases and stroke. Patients had to meet the following criteria in their self-reported history on at least 3 nights per week and for at least 3 months before study entry: Latency to fall asleep ≥ 30 minutes, total duration of waking phases after sleep onset ≥ 30 minutes and total sleep duration ≤ 6.5 hours. Prior to study inclusion, sleep quantity criteria had to be confirmed by polysomnography on 2 nights. Patients who received CBT within 1 month before start of the study were excluded from the study. Also during the study, CBT and other psychological therapies, except for general advice on sleep hygiene, were not allowed. The double-blind treatment period in the study was 30 days (screening phase of 14-28 days beforehand), with a subsequent follow-up of 30 days as well.

In addition, the pharmaceutical company presents an evidence transfer for adults aged ≥ 65 years based on study 201 and study 301, in which daridorexant was compared with placebo.

As described above, it is assumed that for patients with sleep disorders, CBT-I is to be regarded as the treatment standard, and depending on its effectiveness and feasibility, medicinal therapy will be offered. In study 201, however, there is no information available on whether the patients included had received pre-treatment with a CBT-I or whether a CBT-I was not feasible. In addition, patients who received CBT-I within one month before the start of the

study were excluded from the study. For this reason, uncertainties must be assumed for the assessment of the additional benefit, as it is unclear what effects CBT-I would have on the results for medicinal therapy. The study can nevertheless be used for the assessment, as the focus of the benefit assessment is on the level of medicinal therapy and the uncertainty for the feasibility of CBT-I exists for both study arms. In the written and oral statement procedure, it was also stated that the availability of a CBT-I is very limited overall, so that the exclusion of those patients who received a CBT-I within one month before the start of the study does not lead to a relevantly distorted representation with regard to the medical treatment situation.

The evidence transfer presented on the basis of a placebo-controlled study is not taken into account for the assessment of the additional benefit, as it is assumed that although there are uncertainties regarding the exclusion of patients over 65 years of age, the study 201 sufficiently represents the target population of the therapeutic indication overall.

Extent and probability of the additional benefit

Mortality

There were no deaths in the studies.

Morbidity

Severity grade of insomnia
The severity grade of insomnia was assessed using the Insomnia Severity Index (ISI), which is considered a sufficiently valid instrument. The questionnaire includes 7 items (difficulty falling asleep, difficulty staying asleep, problem waking up too early in the morning, satisfaction with current sleep behaviour, influence of sleep problems on daily functioning, perception of sleep problem by others, and concern/pressure about current sleep problems), which are rated on a Likert scale. Higher values reflect more severe insomnia. The ISI was completed by the study participants at the beginning of the screening phase and at the end of the treatment phase. The change in total value between these two time points was not statistically significant between treatment arms.

Self-reported sleep parameters recorded via sleep diaries
The study participants received a sleep diary (SDQ), which they filled out during the screening phase and treatment phase (one questionnaire each for the morning and evening). Included were assessments of insomnia using various visual analogue scales (sleep quality, depth of sleep, morning sleepiness, daytime wakefulness and daytime activity). Direct patient relevance results from the patient-reported assessment.

In addition, parameters on sleep quantity (wake phases after sleep onset, latency to fall asleep and total sleep duration) were recorded in the sleep diary via a morning and an evening questionnaire. Since it is unclear to what extent these sleep parameters allow conclusions to be drawn about sleep quality, these endpoints are only used as a supplement for the evaluation.

There was no statistically significant difference between the treatment arms in the endpoints mentioned - with the exception of the patient-reported total sleep time, which was only used as a supplement. As the effect in total sleep time is not reflected in the endpoints on sleep quality, the patient relevance is unclear.

Polysomnography
In order to characterise the quantitative sleep parameters, a measurement was also taken using polysomnography. The same sleep quantity endpoints were collected as in the sleep diary. Since it is unclear to what extent these sleep parameters allow conclusions to be drawn about sleep quality, these endpoints are also only used as a supplement for the evaluation. Here, there was a statistically significant difference between the treatment groups in the total duration of waking phases after sleep onset, but again with unclear patient relevance.

Quality of life

Health-related quality of life was not collected in the study.

Side effects

For the endpoints severe adverse events and discontinuation due to adverse events, there was no statistically significant difference between the treatment groups.

Overall assessment

From study 201, results are available on endpoints in the categories of mortality, morbidity and side effects comparing daridorexant with zolpidem. Regarding mortality and side effects no statistically significant difference was detected between the treatment groups. This also applies to the directly patient-relevant endpoints of morbidity, which were recorded by means of a sleep diary. Statistically significant differences to the advantage of daridorexant in patient-reported and polysomnographically collected sleep quantity parameters cannot be considered due to unclear patient relevance and because they are not reflected in sleep quality parameters.
Overall, there are therefore no differences between daridorexant and the appropriate comparator therapy that are relevant for the benefit assessment. The additional benefit of daridorexant is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Quviviq" with the active ingredient daridorexant. Daridorexant is used to treat adults with insomnia whose symptoms have persisted for at least 3 months and have a significant effect on daytime activity. The subject of this evaluation is exclusively the use of daridorexant over a period of up to 4 weeks.

The G-BA determined short-term medicinal therapy with short-acting benzodiazepines or non-benzodiazepine receptor agonists, followed by best supportive care, to be the appropriate comparator therapy.

The pharmaceutical company presents the results of the randomised, double-blind study 201, in which daridorexant was compared with zolpidem over a treatment period of 4 weeks in patients with sleep disorders. Patients with psychiatric diseases or neurological disorders and patients who received cognitive behavioural therapy (CBT) within one month before the start of the study were excluded from the study. CBT was also not permitted during the study.

Since insomnia-specific CBT (CBT-I) is considered the treatment standard for patients with insomnia and medicinal therapy is offered depending on its effectiveness and feasibility,

uncertainties must be assumed for the assessment of the additional benefit, since it is unclear what effects CBT-I would have on the results of medicinal therapy.

There were no deaths in the studies.

In the morbidity category, the severity grade of insomnia was assessed using the Insomnia Severity Index (ISI) as well as self-reported sleep parameters (sleep quality, depth of sleep, morning sleepiness, daytime wakefulness and daytime activity) via sleep diaries. In addition, parameters on sleep quantity are considered by means of a sleep diary and polysomnography. Overall, there is no difference between the treatment arms that is relevant for the evaluation.

Health-related quality of life was not collected in the study. For the endpoints severe adverse events and discontinuation due to adverse events, there was no statistically significant difference between the treatment groups.

Overall, there are therefore no differences between daridorexant and the appropriate comparator therapy that are relevant for the benefit assessment. The additional benefit of daridorexant 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. 1,900 – 79,000) is based on the target population in statutory health insurance (SHI). The resolution is based on the information from the dossier assessment of the IQWiG (A22-123).

Uncertainties arise from the pharmaceutical company's choice of definitional criteria for insomnia based on ICD-10 coding (F51.0). On the one hand, this definition is not limited to the insomnia that has been present for three months, as required by the approval for the use of daridorexant. On the other hand, taking into account further diagnosis codes may result in more patients.

Furthermore, the evaluation of the pharmaceutical company refers to accounting data of working persons, which leads to uncertainty when transferred to the general population, as well as to underestimation for the lower limit of the information on patient numbers by limiting it to patients with a certificate of incapacity for work.

Furthermore, the upper limit is uncertain due to the choice of medicinal therapy used to identify the patients.

Overall, the lower limit of patient numbers can be assumed to be an underestimate, while the upper limit is uncertain.

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 Quviviq (active ingredient: daridorexant) at the following publicly accessible link (last access: 30 March 2023):

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

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 April 2023).

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.

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.

Treatment period:

The use of hypnotics/hypnogenic agents or sedatives is limited to 4 weeks.

According to the product information for the active ingredients lormetazepam, temazepam, flunitrazepam, lorazepam and the non-benzodiazepine receptor agonists, the maximum treatment duration of 4 weeks includes a discontinuation phase that is to be adjusted gradually. The same applies to the 2-week treatment period for brotizolam and triazolam. Therefore, it can be assumed that the consumption for these active ingredients is usually lower in this phase, but not quantifiable.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Daridorexant	1 x day for 28 weeks	28	1	28
Appropriate comparator therapy				
Benzodiazepines				
Lormetazepam	1 x day for 28 weeks	28	1	28
Triazolam	1 x day for 14 weeks	14	1	14
Temazepam	1 x day for 28 weeks	28	1	28

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Brotizolam	1 x day for 14 weeks	14	1	14
Flunitrazepam	1 x day for 28 weeks	28	1	28
Midazolam	1 x day for 28 weeks	28	1	28
Lorazepam	1 x day for 28 weeks	28	1	28
Oxazepam	1 x day for 28 weeks	28	1	28
Non-benzodiazepine receptor agonists				
Zolpidem	1 x day for 28 weeks	28	1	28
Zopiclone	1 x day for 28 weeks	28	1	28
Eszopiclone	1 x day for 28 weeks	28	1	28
Best supportive care	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					
Daridorexant	50 mg	50 mg	1 x 50 mg	28	28 x 50 mg
Appropriate comparator therapy					
Benzodiazepines					
Lormetazepam	1 mg	1 mg	1 x 1 mg	28	28 x 1 mg
Triazolam	0.125 mg – 0.25 mg	0.125 mg – 0.25 mg	0.5 x 0.25 mg - 1 x 0.25 mg	14	7 x 0.25 mg - 14 x 0.25 mg
Temazepam	10 - 20 mg	10 - 20 mg	1 x 10 mg – 1 x 20 mg	28	28 x 10 mg – 28 x 20 mg
Brotizolam	0.125 mg – 0.25 mg	0.125 mg – 0.25 mg	0.5 x 0.25 mg - 1 x 0.25 mg	14	7 x 0.25 mg - 14 x 0.25 mg
Flunitrazepam	0.5 mg – 1 mg	0.5 mg – 1 mg	0.5 x 1 mg – 1 x 1 mg	28	14 x 1 mg – 28 x 1 mg
Midazolam OS (2 mg/ml)	7.5 mg – 15 mg =	7.5 mg – 15 mg =	1 x 7.5 mg – 1 x 15 mg =	28	28 x 7.5 mg – 28 x 15 mg =

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	3.75 ml - 7.5 ml	3.75 ml - 7.5 ml	3.75 ml -7.5 ml		105 ml – 210 ml
Lorazepam	0.5 mg – 2.5 mg	0.5 mg – 2.5 mg	0.5 x 1 mg – 1 x 2.5 mg	28	14 x 1 mg – 28 x 2.5 mg
Oxazepam	10 mg – 30 mg	10 mg – 30 mg	1 x 10 mg – 2 x 15 mg	28	28 x 10 mg – 56 x 15 mg
Non-benzodiazepine receptor agonists					
Zolpidem	10 mg	10 mg	1 x 10 mg	28	28 x 10 mg
Zopiclone	7.5 mg	7.5 mg	1 x 7.5 mg	28	28 x 7.5 mg
Eszopiclone	1 mg – 3 mg	1 mg – 3 mg	1 x 1 mg – 1 x 3 mg	28	28 x 1 mg – 28 x 3 mg
Best supportive care	Different from patient to patient				

Costs:

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					
Daridorexant 50 mg	20 FCT	€ 159.21	€ 2.00	€ 14.04	€ 143.17
Appropriate comparator therapy					
Brotizolam 0.25 mg[5]	20 TAB	€ 14.48	€ 2.00	€ 0.25	€ 12.23
Eszopiclone 1 mg[5]	30 FCT	€ 15.35	€ 2.00	€ 0.32	€ 13.03
Eszopiclone 3 mg[5]	30 FCT	€ 18.78	€ 2.00	€ 0.59	€ 16.19
Flunitrazepam 1 mg[5]	20 FCT	€ 14.48	€ 2.00	€ 0.25	€ 12.23
Lorazepam 1 mg[5]	20 TAB	€ 12.85	€ 2.00	€ 0.12	€ 10.73
Lorazepam 2.5 mg[5]	20 TAB	€ 14.09	€ 2.00	€ 0.22	€ 11.87
Lormetazepam 1 mg[5]	20 TAB	€ 14.48	€ 2.00	€ 0.25	€ 12.23
Midazolam 2 mg/ml	30 OS	€ 18.79	€ 2.00	€ 0.36	€ 16.43
Midazolam 2 mg/ml	100 OS	€ 23.80	€ 2.00	€ 0.59	€ 21.21
Oxazepam 10 mg[5]	10 TAB	€ 11.97	€ 2.00	€ 0.05	€ 9.92
Oxazepam 10 mg[5]	20 TAB	€ 12.38	€ 2.00	€ 0.09	€ 10.29

[5] Fixed reimbursement rate

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
Oxazepam 15 mg[5]	10 TAB	€ 12.16	€ 2.00	€ 0.07	€ 10.09
Oxazepam 15 mg[5]	50 TAB	€ 13.91	€ 2.00	€ 0.21	€ 11.70
Temazepam 10 mg[5]	10 SC	€ 12.58	€ 2.00	€ 0.10	€ 10.48
Temazepam 10 mg[5]	20 SC	€ 13.60	€ 2.00	€ 0.18	€ 11.42
Temazepam 20 mg[5]	10 SC	€ 13.11	€ 2.00	€ 0.14	€ 10.97
Temazepam 20 mg[5]	20 SC	€ 14.48	€ 2.00	€ 0.25	€ 12.23
Triazolam 0.25 mg[5]	20 TAB	€ 14.48	€ 2.00	€ 0.25	€ 12.23
Triazolam 0.25 mg[5]	10 TAB	€ 13.11	€ 2.00	€ 0.14	€ 10.97
Zolpidem 10 mg[5]	10 FCT	€ 13.53	€ 2.00	€ 0.18	€ 11.35
Zolpidem 10 mg[5]	20 FCT	€ 15.40	€ 2.00	€ 0.33	€ 13.07
Zopiclone 7.5 mg[5]	14 FCT	€ 14.27	€ 2.00	€ 0.24	€ 12.03
Abbreviations: FTA = Film-coated tablet; OS = Oral solution; TAB = Tablet; SC = Soft capsules					

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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.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Daridorexant

According to Section 35a, paragraph 3, sentence 4, SGB V, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing

authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the requirements of Section 35a paragraph 3, sentence 4, SGB V. The G-BA does not carry out a review of the content on the basis of the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 26 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 15 November 2022, the pharmaceutical company submitted a dossier for the benefit assessment of daridorexant to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 16 November 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 daridorexant.

The dossier assessment by the IQWiG was submitted to the G-BA on 08 February 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2023. The deadline for submitting statements was 9 March 2023.

The oral hearing was held on 27 March 2023.

By letter dated 28 March 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 21 April 2023.

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 3 May 2023.

At its session on 12 May 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 October 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	24 January 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	22 March 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 March 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment
Working group Section 35a	5 April 2023 26 April 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	3 May 2023	Concluding discussion of the draft resolution
Plenum	12 May 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 12 May 2023

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

Prof. Hecken