Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolution on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V Melatonin

of 4 July 2019

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 statutory health insurance funds,
6. Requirement 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient melatonin is regarded as a new active ingredient within the meaning of Section 35a, paragraph 1 SGB V in conjunction with Chapter 5, Section 2, Sentence 3, number 2 VerfO insofar as it has been granted a marketing authorisation for paediatric use according to Articles 5 to 15 of Regulation (EC) No. 726/2004 in accordance with Article 38, paragraph 1 of Regulation (EC) No. 1901/2006 – Regulation on paediatric medicinal products. The relevant date for the first placing on the (German) market of the active ingredient melatonin in the present therapeutic indication in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 January 2019. 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, number 1 VerfO on 11 January 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 April 2019, 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 melatonin 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 melatonin.

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 melatonin (Slenyto®) in accordance with the product information

Slenyto is indicated for the treatment of sleep disorders (insomnia) in children and adolescents aged 2–18 years with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome where sleep hygiene measures have been insufficient.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents aged 2–18 years with sleep disorders associated with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome (SMS) where sleep hygiene measures have been insufficient:

Best supportive care.

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

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 according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

On 1. There are no medicinal products explicitly approved for sleep disorders in children and adolescents with the aforementioned pre-existing conditions.

On 2. Psychotherapy in accordance with Section 26 of the Psychotherapy Guideline.

On 3. There are no resolutions of the G-BA on the benefit assessment in the therapeutic indication.

On 4. The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in the present indication. In this respect, it can be stated that the data basis for medicinal therapies and treatment cascades is very limited overall in the present therapeutic indication. Sleep hygiene measures and psychotherapy are recommended in the guidelines. However, a preference for certain forms or concepts of therapy cannot be derived from the evidence available. The G-BA therefore considers best supportive care (BSC) to be an appropriate comparator therapy, which should be part of both the intervention arm and the comparator arm (possibly replacing melatonin with placebo to ensure blinding) within a planned study. Accompanying/continued psychotherapeutic measures according to the psychotherapeutic guideline can be used as a component of BSC within the framework of a study in both treatment arms if indicated accordingly.

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

2.1.3 Extent and probability of the additional benefit

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

Hint for a minor additional benefit.

Justification:

To demonstrate the additional benefit, the pharmaceutical company presents the results of the randomised, double-blind, and multi-centre clinical study, NEU-CH-7911. The study was conducted at ten study centres in Europe and 14 study centres in the US. It included 125 children and adolescents (2 to 17.5 years) with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome (SMS) and sleep disorders who did not respond adequately to sleep hygiene measures. However, the proportion of SMS patients was low (4/125). Patients without prior sleep hygiene measures received a four-week basic therapy with sleep hygiene training before the start of the study. After a two-week run-in phase with placebo, patients were randomised to two study arms with melatonin therapy (2–5 mg/d; n = 60) and placebo (n = 65), respectively. Double-blind treatment was performed for 13 weeks followed by a 91-week open extension phase with up to 10 mg/d melatonin.

Even if the concrete measures of the accompanying therapy were not documented in detail, it can be assumed that, against the background of the sleep hygiene training carried out before the start of study, adequate care and support of the patients (in the sense of BSC) took place during the study; the study is used for the benefit assessment.

Because of the one-armed approach without comparison in the extension phase, this part of the study is not suitable for deriving the additional benefit. The following considerations of the results therefore refer exclusively to the double-blind phase.

Mortality

No patient died in the study.

Morbidity

In the study, the sleep-related endpoints of total sleep duration and sleep latency were collected by means of a sleep diary. Both a statistically significant increase in sleep duration (32.32 min) and a statistically significant reduction in sleep latency (25.20 min) were observed. In principle, an increase in the duration of sleep is important and desirable in this therapeutic indication. Even if the prolongation of the total sleep duration should in principle be accompanied by an improvement in the quality of sleep, in the present therapeutic indication, it is nevertheless considered appropriate to use the aforementioned improvements to derive an additional benefit.

However, the clinical relevance of the changes observed remains unclear. The extent of improvement of these sleep-related endpoints is estimated to be minor.

The responder analyses on total sleep duration and sleep latency presented are not used because the responder thresholds selected by the pharmaceutical company are not validated.

In addition, the Composite Sleep Disturbance Index (CSDI) was surveyed. According to the pharmaceutical company, this measures sleep quality. However, because of the insufficiently demonstrated validity of the instrument in the therapeutic indication, it cannot be considered when deriving an additional benefit. Overall, there are no relevant data on sleep quality.
The emotional function and behaviour function were determined using the Children's Global Assessment Scale CGAS). With CGAS, the general functionality of the affected child is usually assessed on a scale from 0 to 100 by the investigator with the support of the parents/caregivers. In the present indication, the CGAS is considered validated, although it should be noted that the pharmaceutical company uses a modified and non-validated version in which the emotional function and behavioural function were queried instead of the general functionality. In addition, the query was made for the period 3 months (not 1 month). However, this does not affect the assessment because no statistically significant differences between the treatment groups are found. The responder analysis carried out by the pharmaceutical company (patients with at least 71 points) was not pre-specified in the study and is also not validated for the questionnaire version used. It is therefore not taken into account for the assessment of the additional benefit.

Behavioural strengths and anomalies were measured using the Strength and Difficulties Questionnaire (SDQ). The questionnaire consists of 25 items, which are divided into five factors (emotional problems, behavioural problems, hyperactivity and attention problems, problems with peers, pro-social behaviour). A score from 0 to 10 per factor can result. For the first four factors, an overall problem value (0 to 40 points) is also calculated. The SDQ Impact Score (0 to 10 points) measures additional difficulties at home, at school, with friends, and during leisure activities as well as how much the child suffers from the difficulties. These evaluations are regarded as valid in this therapeutic indication and are used for the assessment of the additional benefit. The "Externalising Score" (summary of the factors behavioural problems and hyperactivity and attention problems) additionally considered by the pharmaceutical company is not used because the data are represented by the other evaluations. There is no statistically significant difference between the treatment arms either for the SDQ factors or for the impact score.

Quality of life

In the NEU-CH-7911 study, no data were collected for the endpoint health-related quality of life.

Side effects

For the endpoints SAE and withdrawal because of AE, there is no statistically significant difference between the treatment arms. A statistically significant difference to the detriment of melatonin compared with BSC/placebo is found in the AE somnolence (28.3% vs 12.3%, p = 0.027).

Reliability of data

The reliability of data is to be regarded as limited because of several aspects. First, because of the short duration of the study (randomised phase), the study design only permits a statement for a period of 13 weeks, which is regarded as short in the present indication of a chronic disease. In addition, in the study, the accompanying measures (e.g. continuation of sleep hygiene) in the sense of BSC did not have to be documented.

The clinical relevance of the statistically significant improvement in total sleep duration and sleep latency observed cannot be conclusively assessed. The decreasing return rate of the morbidity questionnaires during the course of the study with clear differences between the treatment arms increases the risk of bias of the morbidity endpoints.

For the endpoints of overall mortality and adverse events, the risk of bias is low.

Because of the uncertainties, the reliability of data is to be classified as a hint.

Overall assessment

For the endpoint mortality, no difference between treatment groups was found because no deaths occurred. For the endpoints total sleep duration and sleep latency, there were statistically significant differences in favour of melatonin compared with BSC. The clinical relevance of these cannot be conclusively assessed, and the extent is estimated to be minor. The health-related quality of life was not investigated in the studies.

In the category side effects, no statistically significant difference between treatment groups can be observed in the overall rates (AE, SAE, and therapy discontinuations because of AE). In the PT somnolence, a statistically significant difference to the detriment of melatonin can be observed. In the overall view, this result does not lead to a downgrading of the additional benefit.

Based on the results of the study, in the morbidity category, an advantage can be derived for melatonin over BSC in paediatric patients aged 2–18 years with sleep disorders associated with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome if sleep hygiene measures were inadequate.

Overall, there is a hint for a minor additional benefit.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment for the active ingredient melatonin in the therapeutic indication sleep disorders (insomnia) in paediatric patients aged 2–18 years with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome if sleep hygiene measures were inadequate.

The NEU-CH-7911 study was considered for the assessment of the additional benefit of melatonin compared with the appropriate comparator therapy best supportive care (BSC). 125 patients aged 2 to 17.5 years were included.

With regard to the endpoint category mortality, there were no statistically significant differences.

In the category morbidity, there are statistically significant advantages of melatonin with respect to total sleep duration and sleep latency; the extent of these is estimated to be minor. There were no statistically significant differences for other evaluation-relevant endpoints (emotional function and behavioural function as well as behavioural strengths and abnormalities).

No data are available in the health-related quality of life category.

In the side effects category, there was an increase in somnolence under melatonin.

The reliability of data is limited because of the short duration of the study, the accompanying measures that were not precisely documented, the decreasing return rates of the morbidity questionnaires, and the clinical relevance of the observed results that cannot be conclusively assessed.

Overall, there is a hint for a minor additional benefit.

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

The number of patients (approx. 8,000–86,000) is based on the calculations of the pharmaceutical company and IQWiG evaluations. The numbers of patients with the underlying diseases autism spectrum disorder and Smith-Magenis syndrome were initially recorded separately. Here there are uncertainties concerning the diagnosis delimitation and prevalence data of the sources used. In addition, the proportion of patients with sleep disorders and patients who responded inadequately to sleep hygiene measures is also based on uncertain sources. The non-uniform use of the terms autism spectrum disorder, sleep disturbances, and sleep hygiene measures in the publications considered also complicates an exact determination. The total number of patients indicated is therefore to be regarded as uncertain.

2.3 Requirements for a quality-assured application

The requirements of 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 Slenyto® (active ingredient: melatonin) at the following publicly accessible link (last access: 15 May 2019):

https://www.ema.europa.eu/documents/product-information/slenyto-epar-product-information_de.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 June 2019).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Melatonin	continuously, 1 x daily	365	1	365
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care	different for each individual patient			

Usage and consumption:

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Melatonin	2 mg –	2 mg –	2 × 1 mg -	365	730 × 1 mg –
	10 mg	10 mg	2 × 5 mg	365	730 × 5 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 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 product were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Melatonin 1 mg	30 SRT	€41.61	€1.77	€1.70	€38.14
Melatonin 5 mg	30 SRT	€164.14	€1.77	€8.48	€153.89
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Abbreviations: SRT = sustained-release tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 June 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

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

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 22 May 2018.

On 11 January 2019, the pharmaceutical company submitted a dossier for the benefit assessment of melatonin to the G-BA in due time in accordance with Chapter 5, Section 8 number 1, sentence 2 VerfO.

By letter dated 11 January 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient melatonin.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 April 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 April 2019. The deadline for submitting written statements was 23 April 2019.

The oral hearing was held on 27 May 2019.

By letter dated 27 May 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 14 June 2019.

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 statements received and the oral hearing were discussed at the session of the subcommittee on 25 June 2019, and the proposed resolution was approved.

At its session on 4 July 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	22 May 2018	Determination of the appropriate comparator therapy
Working group Section 35a	15 May 2019	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	27 May 2019	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	5 June 2019 19 June 2019	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	25 June 2019	Concluding discussion of the proposed resolution
Plenum	4 July 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 July 2019

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

Prof Hecken