IQWiG Reports – Commission No. A19-04

Melatonin (Insomnia in children and adolescents with autism spectrum disorder and/or Smith-Magenis syndrome) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Melatonin (Schlafstörungen bei Kindern und Jugendlichen mit Autismus-Spektrum-Störung und/oder Smith-Magenis-Syndrom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 April 2019). 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:
Melatonin (Insomnia in children and adolescents with autism spectrum disorder and/or Smith-Magenis syndrome) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
11 January 2019

Internal Commission No.:
A19-04

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:

- No medical and scientific advisor was available for the present assessment.

IQWiG employees involved in the dossier assessment:

- Christina Braun
- Katharina Hirsch
- Simone Johner
- Christopher Kunigkeit
- Sabine Ostlender
- Inga Overesch
- Volker Vervölgyi
- Carolin Weigel

Keywords: melatonin, sleep initiation and maintenance disorders, autism spectrum disorder, Smith-Magenis syndrome, child, adolescent, benefit assessment

Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **3**
2.3 Information retrieval and study pool **4**
2.4 Results on added benefit **7**
2.5 Probability and extent of added benefit **7**
2.6 List of included studies **7**
References for English extract **8**

List of tables[2]

Page

Table 2: Research question of the benefit assessment of melatonin 1
Table 3: Melatonin – probability and extent of added benefit 3
Table 4: Research question of the benefit assessment of melatonin 4
Table 5: Melatonin – probability and extent of added benefit 7

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASD	autism spectrum disorder
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SMS	Smith-Magenis syndrome

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 melatonin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 11 January 2019.

Research question

The aim of this report was to assess the added benefit of melatonin in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient.

This resulted in 1 research question for the present assessment, for which the G-BA specified the ACT presented in Table 2.

Table 2: Research question of the benefit assessment of melatonin

Subindication	**ACT**[a]
Insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient	Best supportive care[b, c]
a: Presentation of the ACT specified by the G-BA. b: Best supportive care 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. c: The specified ACT was the regular approach in the treatment situation to be consulted in this context, and should be applied both in the intervention arm and the comparator arm of a planned study. Accompanying/continuing psychotherapeutic measures in accordance with the psychotherapy guideline can be applied as part of best supportive care (BSC) in case of a corresponding therapeutic indication, within the framework of a study in both treatment arms. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the specification of the G-BA and also cited BSC as ACT. However, in the further explanations, it considers BSC to be sufficiently implemented by placebo control. This limitation was inadequate.

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 3 months were used for the derivation of the added benefit.

Results

Study used by the company (NEU_CH_7911)

The company used the study NEU_CH_7911 for the assessment of the added benefit of melatonin. Study NEU_CH_7911 is a double-blind RCT that compares melatonin versus placebo. Included were 125 children and adolescents aged 2 to 17.5 years with insomnia and autism spectrum disorder and/or certain neurogenetic diseases (e.g. Smith-Magenis syndrome) who had responded inadequately to sleep hygiene measures. Children and adolescents who had not yet received documented behavioural therapy (sleep hygiene measures) underwent 4-week basic therapy with sleep hygiene training and behavioural therapy. Then, all children and adolescents were randomly assigned to the two treatment arms and received daily melatonin doses of 2 mg or placebo for 13 weeks (double-blinded). If necessary, the dose could be escalated to 5 mg after 2 weeks. The double-blind phase was followed by a 91-week open-label extension phase in which all children and adolescents received melatonin. This phase permitted escalation of the dose to 10 mg; dose reduction was also possible.

The NEU_CH_7911 study was unsuitable for the derivation of an added benefit of melatonin in comparison with the ACT.

The comparator therapy “placebo” used in the NEU_CH_7911 study without further measures for symptom alleviation and improvement of the quality of life is no adequate implementation of the ACT “BSC”. In case of need, measures such as sleep hygiene trainings or psycho-therapeutic measures such as behavioural therapies should be offered during the entire study duration also for children and adolescents who had responded inadequately to sleep hygiene measures in the past. This was the only way to ensure that all study participants had the possibility to receive the best possible individually optimized treatment at any time. These non-drug interventions should not only involve children and adolescents participating in the study, but also their parents and/or caregivers. Overall, the NEU_CH_7911 study is thus unsuitable for the derivation of an added benefit of melatonin versus the ACT in the present research question and is therefore not used for the present benefit assessment.

Summary

In its dossier, the company presented no suitable data to assess the added benefit of melatonin in comparison with the ACT for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient. This resulted in no hint of an added benefit of melatonin 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]

On the basis of the results presented, probability and extent of the added benefit of the drug melatonin compared with the ACT are assessed as follows:

Table 3 presents a summary of probability and extent of the added benefit of melatonin.

Table 3: Melatonin – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient	Best supportive care[b, c]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care 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.
c: The specified ACT was the regular approach in the treatment situation to be consulted in this context, and should be applied both in the intervention arm and the comparator arm of a planned study. Accompanying/continuing psychotherapeutic measures in accordance with the psychotherapy guideline can be applied as part of best supportive care (BSC) in case of a corresponding therapeutic indication, within the framework of a study in both treatment arms.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of melatonin in comparison with BSC as ACT for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient.

This resulted in 1 research question for the present assessment, for which the G-BA specified the ACT presented in Table 4.

[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 4: Research question of the benefit assessment of melatonin

Subindication	**ACT**[a]
Insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient	Best supportive care[b, c]
a: Presentation of the ACT specified by the G-BA. b: Best supportive care 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. c: The specified ACT was the regular approach in the treatment situation to be consulted in this context, and should be applied both in the intervention arm and the comparator arm of a planned study. Accompanying/continuing psychotherapeutic measures in accordance with the psychotherapy guideline can be applied as part of best supportive care (BSC) in case of a corresponding therapeutic indication, within the framework of a study in both treatment arms. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the specification of the G-BA and also cited BSC as ACT. However, in the further explanations, it considers BSC to be sufficiently implemented by placebo control. This limitation was inadequate (see Section 2.7.1 of the full dossier assessment).

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 3 months 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 melatonin (status: 27 November 2018)
- bibliographical literature search on melatonin (last search on 19 November 2018)
- search in trial registries for studies on melatonin (last search on 19 November 2018)

To check the completeness of the study pool:

- search in trial registries for studies on melatonin (last search on 25 January 2019)

No relevant study was identified from the check.

Study used by the company (NEU_CH_7911)

The company used the study NEU_CH_7911 for the assessment of the added benefit of melatonin.

Study NEU_CH_7911 is a double-blind RCT that compares melatonin versus placebo. Included were 125 children and adolescents aged 2 to 17.5 years with insomnia and autism spectrum

disorder and/or certain neurogenetic diseases (e.g. Smith-Magenis syndrome) who had responded inadequately to sleep hygiene measures. Children and adolescents who had not yet received documented behavioural therapy (sleep hygiene measures) underwent 4-week basic therapy with sleep hygiene training and behavioural therapy. This phase also served as wash-out phase for any hypnotic drug. All children and adolescents who still had insomnia subsequently received placebo for 2 weeks (run-in phase, single-blind). Children and adolescents who had already received sleep hygiene measures in the past were directly included in the run-in phase and only underwent a prior 2-week wash-out phase in case of need. Then, all children and adolescents were randomly assigned to the two treatment arms and received daily melatonin doses of 2 mg or placebo for 13 weeks (double-blinded). In case of need, the dose could be escalated from 2 mg to 5 mg after 2 weeks. The double-blind phase was followed by a 91-week open-label extension phase in which all children and adolescents received melatonin. In this phase, the dose could be escalated from 2 mg to 5 mg or from 5 mg to 10 mg, if necessary; dose reduction was also possible, e.g. due to adverse events (AEs). Finally, there was a 2-week run-out phase in which all included children and adolescents received placebo.

The NEU_CH_7911 study was unsuitable for the derivation of an added benefit of melatonin in comparison with the ACT. This is justified below.

ACT not implemented in the NEU_CH_7911 study

The G-BA specified BSC as ACT. 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. The G-BA provided no precise information on how the ACT "BSC" had to be implemented. However, it clarified that, within a planned study, the specified ACT was to be used both in the intervention arm and the comparator arm. Accompanying/continuing psychotherapeutic measures in accordance with the psychotherapy guideline can be applied as part of BSC in case of a corresponding therapeutic indication, within the framework of a study in both treatment arms.

Several non-drug treatment options are available for the treatment of insomnia. Besides sleep hygiene measures, psychotherapeutic treatment including behavioural therapies (e.g. extinction of undesired behaviour, bedtime restriction or planned reveille of the child before an expected night terror attack [pavor nocturnus]) present further examples for the treatment of insomnia [3-6]. Sleep hygiene measures can present an essential basis for good sleep also in cases where they alone were insufficient to remedy insomnia [5]. Therefore, these measures should also be continued when insomnia is treated with drug therapies [6,7].

There are thus several possibilities for the adequate implementation of BSC. There is no information on whether the children and adolescents participating in the NEU_CH_7911 study (as well as their parents and/or caregivers) received corresponding treatment for symptom alleviation and improvement of the quality of life in addition to melatonin or placebo in the double-blind phase. On the contrary, an amendment to the study protocol explicitly emphasised that sleep hygiene measures did not have to be continued during the study.

The comparator therapy "placebo" used in the NEU_CH_7911 study without further measures is thus no adequate implementation of the ACT "BSC". In case of need, measures such as sleep hygiene trainings or psychotherapeutic measures such as behavioural therapies should be offered during the entire study duration also for children and adolescents who had responded inadequately to sleep hygiene measures in the past. This was the only way to ensure that all study participants had the possibility to receive the best possible individually optimized treatment at any time. These non-drug interventions should not only involve children and adolescents participating in the study, but also their parents and/or caregivers [3,6]. Overall, the NEU_CH_7911 study is thus unsuitable for the derivation of an added benefit of melatonin versus the ACT in the present research question. Deviating from the company's assessment, it is thus not used for the present benefit assessment.

Further limitations of the NEU_CH_7911 study

Sleep hygiene measures

The approval only allows the use of melatonin when sleep hygiene measures were insufficient. Sufficient information on whether the population included in study NEU_CH_7911 met this criterion is not available.

In the NEU_CH_7911 study, recording of the sleep hygiene measures implemented in the past was covered by the single question of whether the child and/or the adolescent had already undergone a sleep hygiene training before. Among other things, there is no information on how long ago the sleep hygiene training had taken place and what exactly was trained. Those who had not undergone sleep hygiene training in the past received 4-week sleep hygiene training and behavioural therapy in the NEU_CH_7911 study. This applied to 9 (15.0%) of the children and adolescents in the melatonin arm and to 12 (18.5%) children and adolescents in the placebo arm. Further information on this sleep hygiene training is not provided in the study documentation.

In addition, it was questionable whether 4-week basic therapy with sleep hygiene training and behavioural therapy was sufficient to draw a conclusion for an inadequate response to sleep hygiene measures. The cognitive-behavioural treatment programmes recommended by the S1 guideline "Non-organic sleep disorders" [3], for instance, comprise 6 sessions for the parents or their children. The company presented no justification for the choice of a 4-week duration of the basic therapy.

Study duration

Duration of the double-blind phase of direct comparison of the NEU_CH_7911 study was 13 weeks. A minimum study duration of 3 months is considered sufficient for the assessment of the added benefit. However, a longer study duration is desirable in order to draw informative conclusions on long-term clinical improvements, particularly as melatonin is planned to be applied as long-term medication.

Moreover, escalation of the melatonin dose to up to 10 mg planned in accordance with the approval was impossible during the treatment phase of only 13 weeks in the NEU_CH_7911 study.

2.4 Results on added benefit

In its dossier, the company presented no suitable data to assess the added benefit of melatonin in comparison with the ACT for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient. This resulted in no hint of an added benefit of melatonin in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of melatonin. An added benefit of melatonin for is therefore not proven for the present therapeutic indication.

The result of the assessment of the added benefit of melatonin in comparison with the ACT is summarized in Table 5.

Table 5: Melatonin – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, when sleep hygiene measures were insufficient	Best supportive care[b, c]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care 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.
c: The specified ACT was the regular approach in the treatment situation to be consulted in this context, and should be applied both in the intervention arm and the comparator arm of a planned study. Accompanying/continuing psychotherapeutic measures in accordance with the psychotherapy guideline can be applied as part of best supportive care (BSC) in case of a corresponding therapeutic indication, within the framework of a study in both treatment arms.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of major added benefit of melatonin in comparison with BSC based on the study used by it.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie. Nichtorganische Schlafstörungen (F51) [online]. 07.2018 [Accessed: 17.01.2019]. URL: https://www.awmf.org/uploads/tx_szleitlinien/028-012l_S1_Nichtorganische_Schlafstoerungen_2018-07.pdf.

4. Nunes ML, Bruni O. Insomnia in childhood and adolescence: clinical aspects, diagnosis, and therapeutic approach. J Pediatr 2015; 91(1): 26-35.

5. Vriend JL, Corkum PV, Moon EC, Smith IM. Behavioral interventions for sleep problems in children with autism spectrum disorders: current findings and future directions. J Pediatr Psychol 2011; 36(9): 1017-1029.

6. Scottish Intercollegiate Guidelines Network. Assessment, diagnosis and interventions for autism spectrum disorders: a national clinical guideline. Edinburgh: SIGN; 2016. (SIGN Publications; Volume 145). URL: https://www.sign.ac.uk/assets/sign145.pdf.

7. G. V, Holdt Henningsen K, Eyssen M, Benahmed N, Christiaens W, Bouchez MH et al. Management of autism in children and young people: a good clinical practice guideline (GCP) [online]. 04.11.2014 [Accessed: 22.03.2019]. (KCE Reports; Volume 233). URL: https://kce.fgov.be/sites/default/files/atoms/files/KCE_233_Autism_Report_0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-04-melatonin-sleep-disorders-benefit-assessment-according-to-35a-social-code-book-v.11473.html.