Resolution

Gemeinsamer Bundesausschuss

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

At its session on 4 July 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient melatonin as follows:

Melatonin

Resolution of: 4 July 2019
Entry into force on: 4 July 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 20 September 2018):

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.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

Appropriate comparator therapy:

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.

Extent and probability of the additional benefit of melatonin compared with best supportive care:

Hint for a minor additional benefit.

Study results according to endpoints:

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

Results of the NEU_CH_7911 study [1]:

Endpoint category Endpoint	Melatonin		Placebo		Melatonin vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Mortality					
Overall mortality	60	0 (0)	65	0 (0)	-

[1] Data from the dossier evaluation of the IQWiG (A19-04) and from the addendum (A19-47) to the dossier evaluation.

Endpoint category Endpoint	Melatonin			Placebo			Melatonin vs placebo
	N[a]	Values at the start of study MV[b] (SD)	Change at week 15 MV[c] (SE)	N[a]	Values at the start of study MV[b] (SD)	Change at week 15 MV[c] (SE)	MD [95% CI] p value[c]
Morbidity							
Total sleep duration (minutes)	no data available	457.21 (101.28)	51.03 (10.46)	no data available	459.85 (109.22)	18.71 (10.82)	32.32 [2.38; 62.26] 0.035
Sleep latency (minutes)	no data available	95.16 (59.25)	−37.77 (6.82)	no data available	98.76 (73.90)	−12.57 (7.01)	−25.20 [−44.61; −5.80] 0.011
Emotional function and behaviour function (CGAS)[d]	no data available	45.5 (19.42)	1.96 (1.33)	no data available	47.5 (18.43)	1.84 (1.36)	0.13 [−3.64; 3.89] 0.948
Behavioural strengths and abnormalities (SDQ)							
SDQ Overall problem value[e]	no data available	20.2 (5.28)	−0.84 (0.39)	no data available	21.1 (5.86)	0.17 (0.41)	−1.01 [−2.12; 0.11] 0.077
Behavioural problems	no data available	3.0 (2.00)	−0.24 (0.14)	no data available	3.5 (1.98)	0.05 (0.14)	−0.29 [−0.69; 0.11]
Emotional problems	no data available	4.3 (2.69)	−0.11 (0.23)	no data available	4.3 (2.98)	−0.02 (0.24)	−0.10 [−0.75; 0.55]
Hyperactivity/ attention problems	no data available	8.0 (2.00)	−0.47 (0.20)	no data available	8.0 (2.27)	0.07 (0.21)	−0.54 [−1.12; 0.03]
Problems in dealing with peers	no data available	4.9 (2.15)	−0.02 (0.15)	no data available	5.4 (2.11)	0.03 (0.16)	−0.05 [−0.49; 0.39]
SDQ pro-social behaviour[f]	No data available	4.9 (2.94)	0.21 (0.24)	No data available	4.4 (2.89)	0.34 (0.25)	−0.13 [−0.81; 0.55] 0.702
SDQ impact score[e]	No data available	5.3 (2.84)	−0.57 (0.28)	No data available	5.3 (2.69)	0.16 (0.30)	−0.74 [−1.55; 0.08] 0.076
Quality of life							
No data available.							

a: Number of patients included in the evaluation unclear; however, based on the responses it is certain that it is sufficiently high
b: Corresponds to the time of randomisation: week 2 of the study
c: Mean and SE (change at week 15 per treatment group) as well as MD, 95% CI, and p value (group comparison): MMRM
d: Higher values mean better function; a positive group difference corresponds to an advantage for melatonin

e: Higher values mean better more problems or a greater impairment; a negative group difference corresponds to an advantage for melatonin
f: Higher values mean better pro-social behaviour; a positive group difference corresponds to an advantage for melatonin
CGAS: Children's Global Assessment Scale; CI: confidence interval; MD: Mean Value Difference; MMRM: mixed model with repeated measurements; MV: Mean Value; N: Number of patients evaluated; RCT: randomised controlled study; SE: standard error; SD: standard deviation; SDQ: Strength and Difficulties Questionnaire; vs: versus

Endpoint category Endpoint	Melatonin		Placebo		Melatonin vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Side effects					
AE (additionally shown)[b]	60	51 (85.0)	65	50 (76.9)	-
SAEs	60	0 (0)	65	1 (1.5)	0.36 [0.01; 8.69] 0.515
Withdrawal because of AE[b]	60	1 (1.7)	65	1 (1.5)	1.08 [0.07; 16.94] > 0.999
Somnolence (PT, AE)[b]	60	17 (28.3)	65	8 (12.3)	2.30 [1.07; 4.94] 0.027

a: IQWiG calculation of RR, 95% CI (asymptotic) and p value (unconditional exact test, CSZ method). In the case of 0 events in one study arm, the correction factor 0.5 was used to calculate RR and CI in both study arms.
b: Discrepancy between information in Modules 4 A and 5 of the dossier. The data shown are from Module 5.
CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event; vs: versus

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 8,000–86,000 patients

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

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Melatonin	€928.07–3,744.66
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2019)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 4 July 2019.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 4 July 2019

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

Prof Hecken