Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Pitolisant (new therapeutic indication: narcolepsy, with or without cataplexy, (children and adolescents, 6 - 17 years))

of 21 September 2023

At its session on 21 September 2023, the Federal Joint Committee (G-BA) resolved to amend the 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Pitolisant in accordance with the resolution of 19 January 2017:

Pitolisant

Resolution of: 21 September 2023
Entry into force on: 21 September 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 February 2023):

Wakix is indicated in adults, adolescents and children from the age of 6 years for the treatment of narcolepsy with or without cataplexy.

Therapeutic indication of the resolution (resolution of 21 September 2023):

Wakix is indicated in children and adolescents (6 – 17 years) for the treatment of narcolepsy with or without cataplexy.

1. Extent of the additional benefit and significance of the evidence

The medicinal product Wakix with the active ingredient pitolisant is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Children and adolescents (6 – 17 years) with narcolepsy with or without cataplexy</u>

Extent of the additional benefit and significance of the evidence of pitolisant:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Children and adolescents (6 – 17 years) with narcolepsy with or without cataplexy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths have occurred.
Morbidity	↑	Advantage in the endpoint of excessive daytime sleepiness using CGI-C EDS.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant differences for the benefit assessment; in detail, advantages in some specific AEs (SOC infections and infestations).

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

P11-06 study:

RCT over eight weeks (plus one week washout period), pitolisant vs placebo

Mortality

Endpoint	Pitolisant N = 72		Placebo N = 38		Intervention vs control
	N[a]	*Patients with event until week 9 n (%)*	N[a]	*Patients with event until week 9 n (%)*	Effect estimator[b] p value[b]
Overall mortality					
Deaths[c]	73	0 (0.0)	37	0 (0.0)	-

[1] Data from the dossier assessment of the G-BA (published on 3. Juli 2023), and from the amendment to the dossier assessment from 25 August 2023, unless otherwise indicated.

Morbidity

Endpoint	**Pitolisant N = 72**			**Placebo N = 38**			Intervention vs control
Cataplexy symptomatology using CGI-C[d, e]							
	N	*Patients with event until week 8 n (%)[f]*		N	*Patients with event until week 8 n (%)[f]*		RR [95% CI][g] p value[h]
Improvement[i] ≤ 3 points	56[j]	28 (38.9)		28[j]	9 (23.7)		1.64 [0.87; 3.11] 0.12
Excessive daytime sleepiness using CGI-C EDS[d]							
	N	*Patients with event until week 8 n (%)[k]*		N	*Patients with event until week 8 n (%)[k]*		RR [95% CI][g] p value[h]
Improvement[i] ≤ 3 points	69[j]	43 (59.7)		37[j]	14 (36.8)		1.62 [1.03; 2.55] 0.016
Depressive symptomatology using CDI-2 SF[d, l]							
	N[a]	*Baseline MV (SD)*	*End of week 7 MV (SD)*	N[a]	*Baseline MV (SD)*	*End of week 7 MV (SD)*	Effect estimator[b] p value[b]
Total score (0-24 points)	71[m]	4.4 (3.5)	3.6 (3.2)	36[m]	3.8 (3.0)	3.5 (2.8)	n.d.
Suicidality using C-SSRS[l]							
	N[a]	*Patients with event n (%)*		N[a]	*Patients with event n (%)*		Effect estimator[b] p value[b]
Suicide risk[n]	73[m]	1 (1.4)		37[m]	2 (5.3)		n.d.
Narcolepsy symptoms using UNS[d] *(presented additionally)*							
	N	*Baseline MV (SD)*	*End of week 8 MV (SD)*	N	*Baseline MV (SD)*	*End of week 8 MV (SD)*	SMD[o] [95% CI] p value
Total score (0-44 points)	72	24.63 (7.80)	18.23 (8.14)	38	23.7 (9.1)	21.77 (9.25)	-0.53 [-0.93; -0.13] n.d.

Side effects

Endpoint	Pitolisant N = 72		Placebo N = 38		Intervention vs control
Summary of the AEs[p]					
	N[a]	*Patients with event, n (%)*	N[a]	*Patients with event, n (%)*	RR [95% CI][r] p value[s]
AE (presented additionally)	73	22 (30.1)	37	13 (35.1)	-
Severe AEs[q]	73	2 (2.7)	37	0 (0.0)	2.57 [0.13; 52.14] n.d.
SAE[q]	73	0 (0.0)	37	0 (0.0)	-
AEs which led to the discontinuation of the study medication	73	0 (0.0)	37	0 (0.0)	-
Specific adverse events with incidence ≥ 10% (MedDRA system organ class, PT)					
Nervous system disorders (SOC)	73	14 (19.2)	37	4 (10.8)	1.77 [0.63; 5.01] n.d.
Psychiatric disorders (SOC)	73	11 (15.1)	37	4 (10.8)	1.39 [0.48; 4.08] n.d.
Infections and infestations (SOC)	73	3 (4.1)	37	7 (18.9)	0.22 [0.06; 0.79] n.d.
Headache (PT)	73	14 (19.2)	37	3 (8.1)	2.37 [0.72; 7.72] n.d.

a. SAS population: The safety population differs slightly from the FAS population (intervention: N = 72; control: N = 38).
b. Only descriptive analyses were planned.
c. Fatalities were recorded using safety.
d. Higher values indicate higher disease activity.
e. The endpoint was only evaluated in subjects with cataplexy symptomatology, such as type 1 narcolepsy. At baseline, type 1 narcolepsy was diagnosed in 61 (84.7%) subjects in the intervention arm and 29 (76.3%) subjects in the control arm.
f. The percentage of subjects refers to the sub-population with cataplexy symptomatology (type 1 narcolepsy).
g. Relative risk [95% CI] post-hoc non-stratified, calculated from available data.
h. The p value was calculated using Chi^2 test based on the available data. Imputations were not planned according to SAP. According to SAP, no stratified/adjusted analyses were planned.
i. Response was defined as a CGI-C score of 1 (significantly improved), 2 (very improved) or 3 (slightly improved).
j. The number corresponds to those subjects who were used to calculate the respective statistics. The number of available data differs from the number of available data at visit V7 (day 56) after 8 weeks of treatment.
k. The percentage was calculated in relation to the FAS population.
l. The endpoint was recorded as a safety endpoint in the study P11-06, but is assigned to the morbidity category in the present benefit assessment.
m. The number corresponds to those subjects who were used to calculate the respective statistics. The number of available data at baseline (intervention: n = 73; control: n = 37) differs slightly at visit V6 (day 49) after 7 weeks of treatment.
n. The suicide risk (yes/no) was collected by the investigators by means of a semi-structured interview.

o. The calculation was done post-hoc for module 4.
p. The results for the safety endpoints are presented: (start of taking the study medication - end of taking the study medication) + 7 days (phase-out period). The data collection period corresponds to the blinded 9-week study phase.
q. A study-specific severity classification was made at the discretion of the medical investigators.
r. The relative risk was calculated post-hoc. No information on statistical analysis procedure could be identified.
s. According to SAP, a descriptive evaluation was planned. No p values were calculated for the dossier or as part of the written statement by the company.

Abbreviations used:

CDI-2 SF: Childhood Depression Inventory - 2 Short Form; C-SSRS: Columbia-Suicide Severity Rating Scale; CGI-C: Clinical Global Impression of Change; EDS: Excessive Daytime Sleepiness; FAS: Full Analysis Sample; n.d.: no data; CI: confidence interval; MedDRA:: Medical Dictionary for Regulatory Activities; MV: mean value; n.c.: not calculable; RR: relative risk; PT: preferred term; SAP: statistical analysis plan; SAS: safety analysis set; SD: standard deviation; SMD: standardised mean difference; SOC: system organ class; (S)AE: (serious) adverse event; UNS: Ullanlinna Narcolepsy Scale

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

Children and adolescents (6 – 17 years) with narcolepsy with or without cataplexy

approx. 120 – 650 patients

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 Wakix (active ingredient: pitolisant) at the following publicly accessible link (last access: 1 September 2023):

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

Treatment with pitolisant should only be initiated and monitored by doctors experienced in treating sleep disorders.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pitolisant	€ 2,891.85[2] - € 5,935.14[3]

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2023

Costs for additionally required SHI services: not applicable

5. Designation of 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 the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Children and adolescents (6 – 17 years) with narcolepsy with or without cataplexy

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

[2] The lowest annual treatment costs result from the daily dose of 18 mg.
[3] The highest annual treatment costs are reached at a daily dose of 9 mg per day.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 21 September 2023.

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

Berlin, 21 September 2023

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

Prof. Hecken