Resolution

Gemeinsamer Bundesausschuss

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

of 1 August 2019

At its session on 1 August 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), last changed on DD Month YYY (BAnz AT DD MM YYY BX), to be amended as follows:

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

Mexiletine

Resolution of: 1 August 2019
Entry into force on: 1 August 2019
BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18/12/2018):

Namuscla® is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

1. Extent of the additional benefit of the medicinal product

Mexiletine is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (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). 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).

Adult patients with non-dystrophic myotonic disorders:

Extent of the additional benefit:

Non-quantifiable

Study results according to endpoints:[1]

Adult patients with non-dystrophic myotonic disorders:

MYOMEX study: Randomised, double-blind and placebo-controlled 2-stage cross-over Phase III study. Included were patients with myotonia congenita and patients with paramyotonia congenita aged 18 to 65 years.

Mortality

Endpoint	Mexiletine	Placebo	Mexiletine vs Placebo
Overall mortality	No deaths occurred.		

[1]Data from the dossier evaluation by the G-BA (published on 2 May 2019) as well as the amendment of the G-BA unless indicated otherwise.

Morbidity

VAS severity of muscle stiffness *(mITT population)*	**Mexiletine**		**Placebo**		**Mexiletine vs placebo**
	Start of treatment (mm)[a]	**Absolute change at the beginning of the treatment period (mm)**[b]	**Start of treatment (mm)**[a]	**Absolute change at the beginning of the treatment period (mm)**[b]	**p value**[c] **MD**[d] **[95% CI]; p value** **Hedges' g [95% CI]; p value**
Treatment period 1					
Mean (SD)	n = 12 68.1 (14.8)	n = 12 −47.8 (21.2)	n = 13 70.1 (17.0)	n = 13 −12.3 (37.5)	0.003 −35.5 [−60.7; −10.3]; 0.008 −1.11 [−1.98; −0.25]; 0.01
Treatment period 2					
Mean (SD)	n = 13 64.0 (28.1)	n = 13 −36.0 (32.4)	n = 12 80.7 (18.4)	n = 12 −5.4 (20.4)	No data available −30.6 [−53.0; −8.2]; 0.01 −1.08 [−1.94; −0.22]; 0.02
Combined analysis (n = 25)					
Mean (SD)	66.0 (22.3)	−41.7 (27.7)	75.2 (18.1)	−9.0 (30.1)	< 0.001 no data available[e]

INQoL: Symptom present[f]	**Total** (n = 25) **n (%)**	**Mexiletine** (n = 25) **n (%)**	**Placebo** (n = 25) **n (%)**
	Start of study	**End of treatment**	
Presence of symptoms at the end of each treatment period - mITT population			
Muscle weakness	24 (96)	20 (80)	23 (92)
Muscle block	24 (96)	24 (96)	23 (92)
Pain	17 (68)	8 (32)	18 (72)
Fatigue	20 (80)	13 (52)	20 (80)

Health-related quality of life

INQoL domain or sub-domain *(mITT population)*	Mexiletine MV (SD)			Placebo MV (SD)			Mexiletine vs placebo
	Baseline[g]	End of treatment	Absolute change from baseline	Baseline[g]	End of treatment	Absolute change from baseline	p value[h] MD[d] [95% CI]; p value Hedges' g [95% CI]; p value
Treatment period 1	n = 12			n = 13[i]			
Symptoms domain							
Muscle weakness[j]	61.8 (29.2)	27.2 (15.8)	−34.6 (30.3)	64.8 (26.1)	56.3 (31.5)	−8.5 (23.5)	No data available −26.1 [−48.8; −3.4]; 0.026 −0.94 [−1.78; −0.09]; 0.032
Muscle block[j]	70.6 (17.7)	23.3 (9.9)	−47.4 (21.9)	67.6 (27.4)	64.8 (29.6)	−2.8 (35.3)	No data available −44.6 [−68.9; −20.3]; 0.001 −1.45 [−2.36; −0.55]; 0.003
Pain[j]	38.2 (26.0)	8.3 (14.8)	−29.8 (26.7)	38.9 (37.0)	46.1 (34.2)	7.3 (16.5)	No data available −37.1 [−55.9; −18.3]; < 0.001 −1.63 [−2.56; −0.70]; < 0.001
Fatigue[j]	61.8 (17.4)	11.9 (13.3)	−50.0 (19.8)	47.0 (40.9)	43.7 (41.1)	−3.2 (22.0)	No data available −46.8 [−64.1; −29.5]; < 0.001 −2.16 [−3.18; −1.14]; < 0.001
Quality of life domain							
Activity	59.7 (22.3)	17.1 (9.3)	−42.6 (26.7)	62.2 (17.1)	55.8 (26.4)	−6.4 (16.1)	No data available −36.2 [−54.9; −17.5] < 0.001 −2.63 [−3.75; −1.52] < 0.001
Independence	32.2 (25.6)	5.8 (7.3)	−26.4 (21.9)	34.3 (23.5)	35.9 (24.2)	1.4 (17.4)	No data available −27.8 [−44.3; −11.3] 0.002 −1.37 [−2.26; −0.47] 0.004

INQoL domain or sub-domain *(mITT population)*	Mexiletine MV (SD)			Placebo MV (SD)			Mexiletine vs placebo
	Baseline[g]	End of treatment	Absolute change from baseline	Baseline[g]	End of treatment	Absolute change from baseline	p value[h] MD[d] [95% CI]; p value Hedges' g [95% CI]; p value
Social relations	34.9 (23.5)	8.5 (8.2)	−26.5 (22.3)	27.4 (25.3)	30.2 (28.5)	2.8 (14.4)	No data available −29.3 [−45.2; −13.4] 0.001 −1.52 [−2.44; −0.61] 0.002
Emotions	56.0 (26.4)	16.7 (12.4)	−39.3 (30.6)	47.2 (26.0)	42.5 (29.9)	−4.7 (16.0)	No data available −34.6 [−55.5; −13.7] 0.003 −1.39 [−2.29; −0.49] 0.004
Body perception	49.3 (30.4)	21.8 (24.9)	−27.5 (31.0)	53.6 (21.7)	49.1 (27.5)	−4.5 (32.5)	No data available −23.0 [−49.3; 3.3] 0.083 −0.70 [−1.53; 0.13] 0.093
Combined analysis	n = 12	n = 25		n = 13[k]	n = 25[k]		
Symptoms domain							
Muscle weakness[j]	61.8 (29.2)	30.5 (24.3)	−32.8 (29.5)	64.8 (26.1)	61.7 (28.8)	−1.7 (23.2)	< 0.001 no data available[e]
Muscle block[j]	70.6 (17.7)	30.5 (20.3)	−38.5 (29.2)	67.6 (27.4)	66.1 (30.8)	−3.0 (30.8)	< 0.001 no data available[e]
Pain[j]	38.2 (26.0)	12.9 (22.8)	−25.7 (34.3)	38.9 (37.0)	46.3 (34.3)	7.8 (19.4)	< 0.001 no data available[e]
Fatigue[j]	61.8 (17.4)	23.8 (30.2)	−30.3 (31.5)	47.0 (40.9)	55.8 (36.1)	1.7 (20.6)	< 0.001 no data available[e]
Quality of life domain							
Activity	59.7 (22.3)	28.1 (23.9)	−32.9 (26.0)	62.3 (17.1)	60.7 (24.7)	−0.3 (18.4)	< 0.001 no data available[e]
Independence	32.2 (25.6)	16.2 (21.0)	−16.8 (28.0)	34.3 (23.5)	34.4 (22.9)	1.1 (16.3)	< 0.001 no data available[e]
Social relations	34.9 (23.5)	17.2 (17.9)	−13.9 (24.5)	27.4 (25.3)	35.6 (27.5)	4.6 (15.6)	< 0.001 no data available[e]
Emotions	56.0	22.6	−28.9	47.2	50.0	−1.5	< 0.001

INQoL domain or sub-domain *(mITT population)*	Mexiletine MV (SD)			Placebo MV (SD)			Mexiletine vs placebo
	Baseline[g]	End of treatment	Absolute change from baseline	Baseline[g]	End of treatment	Absolute change from baseline	p value[h] MD[d] [95% CI]; p value Hedges' g [95% CI]; p value
	(26.4)	(19.1)	(28.1)	(26.0)	(28.0)	(23.4)	no data available[e]
Body perception	49.3 (30.4)	27.4 (22.7)	−24.1 (32.4)	53.6 (21.7)	50.2 (26.3)	−1.3 (31.0)	< 0.001 no data available[e]
Overall quality of life[l]	48.5 (21.1)	27.1 (21.6)	−20.7 (24.6)	47.0 (20.5)	49.9 (22.7)	2.6 (15.0)	< 0.001 no data available[e]

Side effects

Patients with at least one…	Mexiletine n (%)	Placebo n (%)
Treatment period 1	n = 12	n = 13
AE	4 (33.3)	6 (46.2)
SAE	0	0
AE that led to discontinuation of the trial drug	0	0
Treatment period 2	n = 13	n = 12
AE	11 (84.6)	3 (25.0)
SAE	0	0
AE that led to discontinuation of the trial drug	1 (7.7)	0
Combined analysis	n = 25	n = 25
AE	15 (60.0)	9 (36.0)
SAE	0	0
AE that led to discontinuation of the trial drug	1 (4.0)	0
MedDRA System Organ Class[m] Preferred Term	**Mexiletine Patients with event n (%)**	**Placebo Patients with event n (%)**
Combined analysis	n = 25	n = 25
Gastrointestinal disorders	6 (24.0)	2 (8.0)
Infections and infestations	5 (20.0)	3 (12.0)
Psychiatric disorders	4 (16.0)	0
Sleep disorders	3 (12.0)	0
Nervous system disorders	3 (12.0)	3 (12.0)
Musculoskeletal and connective tissue disorders	3 (12.0)	0

a) VAS value at the beginning of the treatment period measured on Day 1 (beginning of treatment period 1) or Day 22 (beginning of treatment period 2).
b) The absolute change at the beginning of the treatment period is measured as the difference between the value on Day 18 and Day 1 for treatment period 1 or Day 39 and Day 22 for treatment period 2.
c) Based on a linear mixed model using the ranks of VAS as dependent variables and fixed effects for diagnosis, treatment, period, baseline value, and interaction diagnosis-treatment as well as random effects for the individual. The p value indicated corresponds to the p value for the treatment effect.
d) Mean difference of the absolute change in the mexiletine treatment period minus the change in the placebo treatment period.
e) There are no effect estimators that take into account the intra-individual dependence of the data according to the cross-over design of the study.
f) Measured by means of INQoL: The results presented under morbidity describe the presence of disease symptoms regardless of their severity.
g) INQoL baseline values were collected only at baseline and not at the beginning of treatment period 2.
h) Based on a linear mixed model using the INQoL ranks as dependent variables and fixed effects for diagnosis, treatment, period, baseline value, and interaction diagnosis-treatment as well as random effects for the individual. The p value indicated corresponds to the p value for the treatment effect.
i) Baseline placebo and absolute change from baseline N = 12 for the sub-domain independence and overall quality of life.
j) The INQoL score for each symptomatic sub-domain is composed of 1. the extent of the symptom, 2. the extent of difficulty because of the symptom, and 3. the significance of the difficulty for the participant because of the symptom.
k) Baseline placebo N = 12 and absolute change from baseline for placebo N = 24 for the sub-domain independence and overall quality of life.
l) Quality of life score of the INQoL based on the sub-domains activity, independence, social relationship, emotions, and body awareness.
m) AE with an incidence ≥ 10% in the *MYOMEX* study.

Abbreviations: INQoL: Individualised Neuromuscular Quality of Life Questionnaire; CI: Confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; mITT: modified intention to treat; MV: Mean; MD: Mean difference, n: number; pC: pharmaceutical company; RR: Relative Risk; SD: standard deviation; (S)AE: (serious) adverse event(s); VAS: visual analogue scale.

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

Adult patients with non-dystrophic myotonic disorders:

approx. 530–650 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 Namuscla® (active ingredient: mexiletine) at the following publicly accessible link (last access: 29 April 2019):

https://www.ema.europa.eu/en/documents/product-information/namuscla-epar-product-information_de.pdf

Treatment with mexiletine should only be initiated and monitored by specialists who are experienced in the treatment of patients with myotonia.

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide a training manual for doctors or a patient passport for all medical personnel and all patients.

4. Treatment costs

Annual treatment costs:

Adult patients with non-dystrophic myotonic disorders:

Designation of the therapy	Annual treatment costs/patient
Mexiletine	€ 13,659.18–40,977.53

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 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 1 August 2019.

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

Berlin, 1 August 2019

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

Prof Hecken