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 According to Section 35a SGB V – Idebenone

of 17 March 2016

At its session on 17 March 2016, 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 18 February 2016 (Federal Gazette, BAnz AT 22/04/2016 B3), as follows:

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

Idebenone

Resolution of: 17 March 2016
Entry into force on: 17 March 2016
Federal Gazette, BAnz AT DD MM YYYY Bx

Approved therapeutic indication (according to the marketing authorisation of 8 September 2015):
Idebenone (Raxone®) is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON).

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

Idebenone 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. In accordance with Section 35a, paragraph 1, sentence 10, 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).

Extent of the additional benefit:

Non-quantifiable

Study results of the RHODOS study according to endpoints:[1]

Mortality				
No events were observed.				
Morbidity				
Endpoint	**Estimated change[a] [95% CI] (change in letters)**		**Estimated difference[a] Mean ± standard error [95% CI] (change in letters)**	**p value**
	Idebenone	**Placebo**	**Idebenone vs placebo**	
Best improvement in visual acuity after 24 weeks[b, c, d]				
N[e]	53	29		
Week 24	−0.135 [−0.216; −0.054] (+6 letters)	−0.071 [−0.176; 0.034] (+3 letters)	−0.064 ± 0.061 [−0.184; 0.055] (3 letters)	0.291
Change in best visual acuity after 24 weeks[b, d]				
N[f]	53	29		
Week 24	−0.035 [−0.126; 0.055] (+1 letter)	0.085 [−0.032; 0.203] (−4 letters)	−0.120 ± 0.068 [−0.255; 0.014] (6 letters)	0.078
Change in visual acuity of the best eye (from start of study) after 24 weeks [b, d]				
N[e]	53	29		
Week 24	−0.030 [−0.120; 0.060] (+1 letter)	0.098 [−0.020; 0.215] (−4 letters)	−0.128 ± 0.068 [−0.262; 0.006] (6 letters)	0.061
Endpoint	**Estimated change[a] [95% CI]**		**Estimated difference[a] Mean ± standard error [95% CI]**	**p value**
	Idebenone	**Placebo**	**Idebenone vs placebo**	
Change in protan and tritan colour perception (colour contrast sensitivity) since start of study[b, d, g]				
N[g]	54	22		
Protan (% colour confusion)				
Week 24	1.37 [−4.67; 7.41]	5.25 [−2.47; 12.97]	−3.88 ± 3.28 [−10.37; 2.60]	0.239
Tritan (% colour confusion)				
Week 24	−7.27 [−16.63; 2.09]	6.36 [−5.58; 18.30]	−13.63 ± 5.05 [−23.61; −3.66]	0.008
Quality of life				
No usable data are available.				

[1] Data from the RHODOS study from the G-BA benefit assessment of 4 January 2016.

Side effects	Idebenone (N = 55) *n (%)*	Placebo (N = 30) *n (%)*	RR [95% CI][h] ARR [95% CI][h]	p value[i]
Patients with at least one AE	49 (89.1)	26 (86.7)	1.26 [0.33; 4.85] 0.02 [−0.12; 0.17]	0.737
Of which patients with at least one treatment-related AE	4 (7.3)	1 (3.3)	2.27 [0.24; 21.33] 0.04 [−0.05; 0.13]	0.652
Patients with at least one severe AE	2 (3.6)	0	2.85 [0.13; 61.33] 0.04 [−0.03; 0.11]	0.538
Of which patients with at least one severe treatment related AE	1 (1.8)	0	1.68 [0.07; 42.49] 0.02 [−0.04; 0.08]	1.000
Patients with at least one SAE[j]	1 (1.8)	1 (3.3)	0.54 [0.03; 8.90] −0.02 [−0.09; 0.06]	1.000
Death	0	0	cannot be estimated	
Patients with AE leading to therapy discontinuation[k]	1 (1.8)	0	1.68 [0.07; 42.49] 0.02 [−0.04; 0.08]	1.000
Patients with SAE leading to therapy discontinuation [k]	0	0	cannot be estimated	

a Analysis in accordance with MMRM (Observed cases: at week 24 data were imputed to the respective population for 6 patients).
b ANCOVA model
c Primary endpoint of the Rhodos study
d Exclusion of three patients from analysis because insufficient visual acuity data at baseline or week 24
e N = number of patients in the analysis
f N = number of eyes/patients in the analysis
g Monocentric survey; N = number of eyes in analysis
h Additionally specified in the dossier by the pharmaceutical company. This information cannot be found in the study report.
i Exact Fisher test
j SOC and PT
k Therapy discontinuations because of AE after 24 weeks

Abbreviations used:

ARR: absolute risk reduction; CI: confidence interval; N: number of patients or eyes in the analysis; n: patients with event; PT: preferred term; RR: relative risk; SOC: system organ class; AE: adverse event; SAE: serious adverse event

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

approx. 1,500 - 3,000 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 Raxone® (active ingredient: idebenone) at the following publicly accessible link (last access: 18 January 2016): http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/003834/WC500193836.pdf

Treatment should be initiated and monitored by a physician experienced in the treatment of Leber's Hereditary Optic Neuropathy (LHON).

There is no data from controlled clinical trials on continuous treatment with idebenone for more than six months.

This medicinal product was authorised under "exceptional circumstances". This means that because of the rarity of the disease, it was not possible to obtain complete information about the medicinal product. The EMA will examine any new information made available and update the summary of product characteristics as appropriate.

4. Treatment costs

Annual treatment costs[2]:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Idebenone	€ 99,070.13

[2]Medicinal product costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2016

II. Entry into force

1. **The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 17 March 2016.**
2. **The period of validity of the resolution is limited to 1 April 2018.**

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

Berlin, 17 March 2016

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

Prof Hecken