Gemeinsamer Bundesausschuss

Idebenone (reassessment after the deadline: Leber's Hereditary Optic Neuropathy)

Resolution of: 15 September 2022 Valid until: unlimited
Entry into force on: 15 September 2022
Federal Gazette, BAnz AT 26 10 2022 B1

Therapeutic indication (according to the marketing authorisation of 8 September 2015):

Raxone is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON).

Therapeutic indication of the resolution (resolution of 15 September 2022):

See therapeutic indication according to marketing authorisation.

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

Idebenone 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).

Adolescents and adults with visual impairment due to Leber's Hereditary Optic Neuropathy (LHON)

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

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

Study results according to endpoints:[1]

Adolescents and adults with visual impairment due to Leber's Hereditary Optic Neuropathy (LHON)

[1] Data from the dossier assessment of the G-BA (published on 1. July 2022), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred in the RHODOS study. No events relevant to the benefit assessment resulted from the single-arm studies.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	No relevant differences for the benefit assessment.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

RHODOS study: Idebenone vs placebo; randomised, double-blind phase II study, 24-week data

Mortality

RHODOS study endpoint	Idebenone		Placebo		Idebenone vs placebo
	N[a]	Deaths n (%)	N[a]	Deaths n (%)	Effect estimator
Overall mortality	55	0 (0.0)	30	0 (0.0)	-[b]

Morbidity

RHODOS study endpoint	Idebenone			Placebo			Idebenone vs placebo
	N[c]	Baseline MV (SD)	Estimated change[n] Week 24 to baseline [95% CI]	N[c]	Baseline MV (SD)	Estimated change[n] Week 24 to baseline [95% CI]	Estimated difference[n] [95% CI]; p value[d]
Visual acuity (logMAR) – continuous							
Best improvement in visual acuity[e]	55	n.d.[f]	-0.15 [-0.23; -0.07]	30	n.d.[f]	-0.09 [-0.19; 0.02]	-0.06 [-0.18; 0.06]; 0.34

RHODOS study endpoint	Idebenone			Placebo			Idebenone vs placebo
	N[c]	Baseline MV (SD)	Estimated change[n] Week 24 to baseline [95% CI]	N[c]	Baseline MV (SD)	Estimated change[n] Week 24 to baseline [95% CI]	Estimated difference[n] [95% CI]; p value[d]
Change in best visual acuity	55	n.d.[f]	-0.04 [-0.13; 0.05]	30	n.d.[f]	0.06 [-0.06; 0.17]	-0.10 [-0.23; 0.03]; 0.14
Change in visual acuity in the best eye	55	n.d.[f]	-0.04 [-0.13; 0.06]	30	n.d.[f]	0.07 [-0.05; 0.19]	-0.11 [-0.24; 0.03]; 0.12
	N	Patients with event n (%)		N	Patients with event n (%)		RR [95% CI]; p value
Visual acuity (logMAR) – Responder analyses							
CRR 0.2[g, h]	53[i]	16 (30.2)		28[i]	2 (7.1)		4.23 [1.05; 17.08]; 0.023[j]
"off-chart" to "on-chart"[h]	53[i]	7 (28.0)		28[i]	0 (0.0)		8.08 [0.50; 131.24]; 0.07[j]
≥ 0.2 logMAR in "best improvement in visual acuity" (corresponds to ≥ 10 ETDRS letters)	53[k]	20 (37.7)		29[k]	7 (24.1)		1.56 [0.75; 3.25]; 0.23[l]
≥ 0.2 logMAR in "best visual acuity" (corresponds to ≥ 10 ETDRS letters)	53[k]	14 (26.4)		29[k]	5 (17.2)		1.53 [0.61; 3.83]; 0.42[l]
CRW[m]	53[i]	2 (3.8)		28[i]	2 (7.1)		n.d.
Colour contrast sensitivity							
There are no usable data.							

Health-related quality of life

RHODOS study Endpoint	
Visual Function Index (VF-14)	*There are no usable data.*

Side effects

RHODOS study endpoint	Idebenone		Placebo		Idebenone vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value[h]
Adverse events (presented additionally)					
	55	49 (89.1)	30	26 (86.7)	1.26 [0.33; 4.85]; 0.737[j]
Serious adverse events (SAE)					
	55	1 (1.8)	30	1 (3.3)	0.55 [0.04, 8.41]; 1.00[j]
Severe adverse events					
	55	2 (3.6)	30	0 (0.0)	2.77 [0.14, 55.84]; 0.54[j]
Adverse events with therapy discontinuation					
	55	1 (1.8)	30	0 (0.0)	1.66 [0.07, 39.55]; 1.00[j]

[a] The safety population includes all randomised patients.
[b] No assessment possible due to missing events.
[c] Analysis based on all randomised subjects. At week 24, values in the idebenone arm were n = 52 and in the placebo arm n = 27.
[d] MMRM with baseline values as covariates and treatment group, disease history, mutation type, visit and the interaction of visit and treatment group as fixed factors.
[e] Primary endpoint.
[f] Data only available for ITT population with exclusion of three patients with incorrect or missing values.
[g] Improvement in visual acuity from off-chart to on-chart (at least 1.6 logMAR) or with improvement of at least 0.2 logMAR (within on-chart). It is unclear whether the components used were improvement of at least 0.2 log-MAR in "best improvement in visual acuity" or in "best visual acuity".
[H] Calculated post hoc.
[i] Evaluation only available for mITT population, which excludes one more subject from the placebo arm with spontaneous healing compared to the ITT population.
[j] Fisher's exact test.
[k] Evaluation based on the ITT population (exclusion of three subjects due to insufficient visual acuity data at baseline or week 24).
[l] Fisher's exact test. A stratified Cochran-Mantel-Haenszel test was planned a priori.
[m] Deterioration by ≥ 10 letters or to off-chart.
[n] Analysis according to MMRM (observed cases: at week 24, data were imputed for 6 patients in the respective population).

Abbreviations used:
CRR: clinically relevant recovery; CRW: clinically relevant worsening; n.d.: no data available; CI: confidence interval; logMAR: logarithm of the minimum angle of resolution; (m)ITT: (modified) intention to treat; MMRM: mixed model repeated measures; MV: mean value; RR: Relative Risk; SD: standard deviation; (S)AE: (Serious) Adverse Event.

LEROS study: Idebenone; prospective, uncontrolled, intervention study

Mortality

LEROS study Endpoint	**Idebenone**	
	N	Deaths n (%)
Overall mortality	196	1 (0.5)

Morbidity

LEROS study Endpoint	**Idebenone**				
	Baseline	Month 6	Month 12	Month 18	Month 24
	n (%) MV (SD) *Median (min; max)*				
Change in best visual acuity[a] (safety population, N = 198[c])					
Visual acuity in the best eye (log-MAR)	196 (98.9) 1.15 (0.60) *1.32 (-0.14; 1.80)*	171 (86.4) 1.17 (0.62) *1.38 (-0.20; 1.80)*	151 (76.2) 1.11 (0.61) *1.28 (-0.20; 1.80)*	141 (71.2) 1.05 (0.62) *1.22 (-0.16; 1.80)*	125 (63.1) -[b] -[b]
Change from baseline (log-MAR)	/	71 (86.4) 0.00 (0.42) *0.00 (-1.20; 1.70)*	151 (76.2) -0.06 (0.52) *-0.06 (-1.74; 1.90)*	141 (71.2) -0.12 (0.51) *-0.08 (-1.78; 1.84)*	-[b]
Change within the best eye at baseline[a] (mITT population, N = 181[d])					
Visual acuity in the best eye (log-MAR)	No data available	166 (91.7) 1.26 (0.54) 1.41 (-0.12; 1.80)	147 (81.2) 1.27 (0.52) 1.42 (-0.12; 1.80)	n.d.	122 (67.4) -[b] -[b]
	Baseline	Month 6	Month 12	Month 18	Month 24
	n (%) MV (SD) *Median (min; max)*	n (%) LS mean [95% CI][e] (change in letters) p value[e]	n (%) LS mean [95% CI][e] (change in letters) p value[e]	n (%) MV (SD) *Median (min; max)*	n (%) MV (SD) *Median (min; max)*
Change from baseline (log-MAR)	/	166 (91.7) -0.07 [-0.13; -0.01] (+3 letters) 0.0287	147 (81.2) -0.17 [-0.25; -0.09] (+8 letters) < 0.0001	n.d.	-[b]

LEROS study Endpoint	Idebenone	
	N	Patients with event n (%)
Visual acuity (logMAR) – Responder analyses[f]		
Month 6		
CRR 0.2[g]	166[i]	41 (20.9)
CRR 0.3[g]	166[i]	29 (14.8)
Improvement by ≥ 0.2 logMAR (corresponds to ≥ 10 ETDRS letters)	166[i]	37 (18.9)
Off-chart to on-chart	166[i]	14 (7.1)
CRW[h]	128[j]	33 (16.8)
Month 12		
CRR 0.2[g]	147[i]	58 (29.6)
CRR 0.3[g]	147[i]	45 (23.0)
Off-chart to on-chart	147[i]	18 (9.2)
CRW[h]	118[j]	26 (13.3)
Month 18		
Off-chart to on-chart	141[i]	20 (10.2)

Health-related quality of life

LEROS study Endpoint
Health-related quality of life was not collected.

Side effects

LEROS study Endpoint	Idebenone	
	N[c]	Patients with event n (%)
Adverse events (presented additionally)	198	154 (77.8)
Serious adverse events (SAEs)[k]	198	27 (13.6)
Severe adverse events	198	13 (6.6)
Adverse events with therapy discontinuation	198	10 (5.1)
Adverse events with incidence ≥ 10% according to MedDRA system organ class Preferred term		
Infections and infestations	198	72 (36.4)

LEROS study Endpoint	Idebenone	
	N[c]	Patients with event n (%)
Nasopharyngitis	198	33 (16.7)
Gastrointestinal disorders	198	65 (32.8)
Nervous system disorders	198	53 (26.8)
Headache	198	37 (18.7)
Investigations	198	53 (26.8)
Respiratory, thoracic and mediastinal disorders	198	32 (16.2)
General disorders and administration site conditions	198	29 (14.6)
Psychiatric disorders	198	29 (14.6)
Musculoskeletal and connective tissue disorders	198	25 (12.6)
Injury, poisoning and procedural complications	198	20 (10.1)

[A] Evaluated post hoc.
[b] Percentage of existing values too low compared to ITT.
[c] All enrolled study participants who received at least one dose of the study medication.
[d] All enrolled study participants with mutation type (G11778A, G3460A and T14484C) who received at least one dose of the study medication and with at least one measurement of visual acuity at baseline.
[e] MMRM details (with treatment group, sex, visual acuity at the start of the study and mutation as factors) from Module 4. There, the mean difference was estimated in comparison to the historical control.
[f] Only existing information is shown.
[g] Improvement in visual acuity from off-chart to on-chart (at least 1.6 logMAR) or with improvement of at least 0.2 logMAR or 0.3 logMAR (within on-chart).
[h] Deterioration by ≥ 10 letters or to off-chart.
[i] Evaluation in the mITT population (N = 181).
[j] The higher percentage of missing values compared to CRR could be due to the exclusion of subjects who were already off-chart at baseline and thus had no chance to deteriorate. However, information on this could not be identified.
[k] This information from the study report does not include deaths. This does not correspond to the operationalisation determined a priori. One death occurred in the course of the LEROS study. In Module 4, the data for severe AEs and SAEs are reversed compared to the data presented here (from the study report): there, severe AEs are reported for n = 27 and SAEs for n = 13.

Abbreviations used:
CRR: clinically relevant recovery; CRW: clinically relevant worsening; (m)ITT: (modified) intention to treat; n.d.; no data available; CI: confidence interval; logMAR: logarithm of the minimum angle of resolution; LS: least squares; MMRM: mixed model repeated measures; MV: mean value; SD: standard deviation

PAROS study: Idebenone; prospective, uncontrolled, register-based safety study (PASS study)

Mortality

PAROS study Endpoint	**Idebenone**	
	N	Deaths n (%)
Overall mortality	224	1 (0.4)

Morbidity

PAROS study Endpoint	**Idebenone**
Visual acuity	*There are no usable data.*
Visual field determination	*There are no usable data.*
Colour contrast sensitivity	*There are no usable data.*

Health-related quality of life

PAROS study Endpoint
Health-related quality of life was not collected.

Side effects

PAROS study Endpoint	**Idebenone**	
	N[a]	Patients with event n (%)
Adverse events (presented additionally)	224	130 (58.0)
Serious adverse events (SAEs)[b]	224	26 (11.6)
Severe adverse events[b]	224	12 (5.4)
Adverse events with therapy discontinuation	224	34 (15.2)
Adverse events with incidence ≥ 10% according to MedDRA system organ class Preferred term		
General disorders and administration site conditions	224	34 (15.2)
Medicinal product ineffective	224	27 (12.1)
Metabolism and nutrition disorders	224	36 (16.1)
Investigations	224	29 (12.9)
Gastrointestinal disorders	224	24 (10.7)
[a] All enrolled study participants who received at least one dose of the study medication.		

PAROS study Endpoint	Idebenone	
	N[a]	Patients with event n (%)
[b] Data from Module 4. The data in the study report do not include any deaths. This does not correspond to the operationalisation determined a priori (see chapter 2.3.4 Sicherheit). In the course of the PAROS study, one death occurred (see chapter 2.3.1 Mortalität), so that the data from Module 4 include one more subject than the data from the study report. Abbreviations used: MedDRA: Medical Dictionary for Regulatory Activities		

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

Adolescents and adults with visual impairment due to Leber's Hereditary Optic Neuropathy (LHON)

approx. 1,400 – 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: 15 August 2022):

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

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

This medicinal product was approved under “special conditions”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product.

The European Medicines Agency will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

4. Treatment costs

Annual treatment costs:

Adolescents and adults with visual impairment due to Leber's Hereditary Optic Neuropathy (LHON)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Idebenone	€ 55,261.85

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2022

Costs for additionally required SHI services: not applicable