

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**

**Idebenone (reassessment after the deadline: Leber's Heredi-
tary Optic Neuropathy)**

of 15 September 2022

At its session on 15 September 2022, 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. Annex XII is amended as follows:

- 1. The information on idebenone in the version of the resolution of 13 March 2016 (Federal Gazette, BAnz AT 04.05.2016 B3), last modified on 18 January 2018 and on 22 November 2019, is repealed.**
- 2. Annex XII shall be amended in alphabetical order to include the active ingredient idebenone as follows:**

Idebenone

Resolution of: 15 September 2022
Entry into force on: 15 September 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

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 | Base-line MV (SD) | Estimated change ⁿ Week 24 to baseline [95% CI] | N ^c | Base-line 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 | Base-line MV (SD) | Estimated change ⁿ Week 24 to baseline [95% CI] | N ^c | Base-line 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 | | | | | | | |
| <i>There are no usable data.</i> | | | | | | | |

Health-related quality of life

| RHODOS study Endpoint | |
|-------------------------------|----------------------------------|
| Visual Function Index (VF-14) | <i>There are no usable data.</i> |

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 |
| <p>^a The safety population i includes all randomised patients.</p> <p>^b No assessment possible due to missing events.</p> <p>^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.</p> <p>^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.</p> <p>^e Primary endpoint.</p> <p>^f Data only available for ITT population with exclusion of three patients with incorrect or missing values.</p> <p>^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 logMAR in "best improvement in visual acuity" or in "best visual acuity".</p> <p>^h Calculated post hoc.</p> <p>ⁱ Evaluation only available for mITT population, which excludes one more subject from the placebo arm with spontaneous healing compared to the ITT population.</p> <p>^j Fisher's exact test.</p> <p>^k Evaluation based on the ITT population (exclusion of three subjects due to insufficient visual acuity data at baseline or week 24).</p> <p>^l Fisher's exact test. A stratified Cochran-Mantel-Haenszel test was planned a priori.</p> <p>^m Deterioration by ≥ 10 letters or to off-chart.</p> <p>ⁿ Analysis according to MMRM (observed cases: at week 24, data were imputed for 6 patients in the respective population).</p> <p>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.</p> | | | | | |

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 |
|--|
| <i>Health-related quality of life was not collected.</i> |

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 $\geq 10\%$ 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 | <i>There are no usable data.</i> |
| Visual field determination | <i>There are no usable data.</i> |
| Colour contrast sensitivity | <i>There are no usable data.</i> |

Health-related quality of life

| PAROS study Endpoint |
|--|
| <i>Health-related quality of life was not collected.</i> |

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.

^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.

| PAROS study Endpoint | Idebenone | |
|---|----------------|------------------------------|
| | N ^a | Patients with event n (%) |
| 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

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 15 September 2022.

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

Berlin, 15 September 2022

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

Prof. Hecken