Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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 Hereditary Optic Neuropathy)

of 15 September 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient idebenone (Raxone) to be assessed for the first time on 30 September 2015. For the resolution of 17 March 2016 made by the G-BA in this procedure, a limitation up to 01 April 2018 was pronounced. At the pharmaceutical company's request, this limitation was extended until 1 September 2020 by the resolution of the G-BA of 18 January 2018.

At the pharmaceutical company's request, this limitation was again extended until 1 April 2022 by the resolution of the G-BA of 20 November 2019.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Raxone recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 March 2022.

Idebenone indicated for the treatment of Leber's Hereditary Optic Neuropathy 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.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 July 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G22-08) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of idebenone.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Idebenone (Raxone) in accordance with the product information

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 the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of idebenone is assessed as follows:

For adolescents and adults with visual impairment due to Leber's Hereditary Optic Neuropathy (LHON), there is a hint for a non-quantifiable additional benefit for idebenone since the scientific data does not allow quantification.

Justification:

The pharmaceutical company uses the RHODOS and RHODOS-OFU (single follow-up of the RHODOS study) studies, data from an early access programme (SNT-EAP-001), the PAROS (SNT-IV-003) and LEROS (SNT-IV-005) studies as well as a phase I/II study (Ishikawa et al., 2021) in the dossier for assessment of the benefit assessment of idebenone. For the LEROS study, the pharmaceutical company also presents a prospective indirect comparison in which a combined data set from the retrospective case series SNT-CRS-002 and SNT-IR-006 was used as a historical control.

The present benefit assessment is based on the phase II RHODOS study, assessed as early as 2016, supplemented by the data from the single-arm LEROS and PAROS studies, which have now been submitted for the first time. The single-arm studies were part of the limitation requirements for reassessment after the deadline.

The RHODOS-OFU, SNT-EAP-001, Ishikawa 2021 studies could not be used for methodological reasons. The prospective indirect comparison without a bridge comparator (LEROS vs SNT-CRS-002 and SNT-IR-006) could also not be additionally considered overall in the assessment of the extent of additional benefit due to methodological limitations.

RHODOS study

The RHODOS study is a multicentre, double-blind, randomised placebo-controlled parallel phase II study that enrolled a total of 85 patients with one of the three primary mutations G11778A, G3460A or T14484C aged 14 to 65 years with Leber's Hereditary Optic Neuropathy (LHON) in a 2:1 ratio. The study investigated the efficacy, safety and tolerability of idebenone versus placebo. The patients in the intervention arm received a daily dosage of three times 300 mg idebenone according to the product information. The duration of the study was 24 weeks.

Endpoints collected in the RHODOS study included best visual acuity improvement in one eye at a time after 24 weeks (primary endpoint), change in best visual acuity after 24 weeks of treatment, change in best visual acuity at the start of the study after 24 weeks, and colour contrast sensitivity. Furthermore, adverse events and quality of life were recorded as endpoints.

The data analysis of the visual acuity endpoints was performed by the pharmaceutical company at the end of the study after 24 weeks and is based on an ITT population of 82 patients. Deviating from this, the benefit assessment may be based on an evaluation of the ITT population on the basis of all 85 randomised patients.

LEROS study

The LEROS study is a prospective, non-controlled intervention study that was also conducted as a marketing authorisation requirement by the EMA with the aim of assessing the long-term safety and efficacy of idebenone in subjects with LHON.

By its initial resolution on idebenone, the G-BA required the submission of the LEROS study for the new benefit assessment after the expiry of the deadline. The data from the LEROS study are presented in the resolution. Due to the single-arm design of the LEROS study, no additional information could be provided overall for the assessment of the extent of the additional benefit beyond the comparator data of the RHODOS study.

PAROS study

The PAROS study is a prospective, registry-based, non-controlled safety study conducted as a marketing authorisation requirement of the EMA. Data should be collected on the long-term safety and efficacy of idebenone in subjects with LHON. Here, idebenone was administered at the discretion of clinical staff in terms of dose and duration as part of routine care. Patients presenting for their LHON disease were enrolled continuously and prospectively by the physicians involved. The data were collected as part of routine medical care.

By its initial resolution on idebenone, the G-BA required the submission of the PAROS study for the new benefit assessment after the expiry of the deadline. The data on mortality and safety of the PAROS study are presented in the resolution, while the results on morbidity are not shown due to methodological limitations. Due to the single-arm design of the PAROS study, no additional information could be provided overall for the assessment of the extent of the additional benefit beyond the comparator data of the RHODOS study.

Results of the RHODOS study

Mortality

No deaths were observed in the RHODOS study.

Morbidity

The pharmaceutical company submits different operationalisations for the morbidity endpoint of visual acuity. From these, the following operationalisations for visual acuity can be considered for the present benefit assessment:

Best visual acuity improvement after 24 weeks

The "best visual acuity improvement after 24 weeks", primary endpoint of the RHODOS study, was defined as the best improvement in visual acuity in one eye at a time of each patient, measured by the change in logMAR between the start of the study and week 24.

Neither the continuous evaluations presented nor the responder analyses on the threshold of ≥ 10 ETDRS letters (improvement by at least 0.2 logMAR) showed a statistically significant difference between the study arms.

Change in best visual acuity after 24 weeks

The "change in best visual acuity after 24 weeks" was defined as the visual acuity of the best eye at week 24 compared to the visual acuity of the best eye at the start of the study.

Neither the continuous evaluations presented, nor the responder analyses on the threshold of ≥ 10 ETDRS letters (improvement by at least 0.2 logMAR) showed a statistically significant difference between the study arms

Change in visual acuity in the best eye (at the start of the study) after 24 weeks

The change in visual acuity of the best eye after 24 weeks was defined as the change in the eye that had the best visual acuity at the start of the study, measured at week 24. Regarding the endpoint change in visual acuity of the best eye after 24 weeks, no statistically significant difference was found between the study arms.

In addition, responder analyses are available for the combined evaluation as CRR 0.2, operationalised as visual acuity improvement from off-chart to on-chart (at least 1.6 logMAR) or with improvement by at least 0.2 logMAR (within on-chart). Although these show a statistically significant difference between the treatment groups, it remains unclear whether the components used were improvement by at least 0.2 logMAR in "best visual acuity improvement" or in "best visual acuity".

Overall, with regard to the visual acuity endpoints, it is questionable to what extent the sole recording of visual acuity (in one eye) in the therapeutic indication comprehensively depicts the symptoms of the disease.

Colour contrast sensitivity

This endpoint measured the colour contrast sensitivity for the colours red-green (Protan) and yellow-blue (Tritan). However, the monocentric assessment leads to limitations in validity: As the study site did not form a stratification factor of randomisation, it is unclear to what extent the study arms were fully comparable. The accompanying deviation from the ITT population leads to additional limitations.

In addition, the evaluation of the eyes, in contrast to an evaluation of patients, complicates the interpretation of results and only allows limited statements on patient-relevant effects. The percentage of patients with an improvement in colour contrast sensitivity remains unclear.

Overall, no usable data on colour contrast sensitivity were available for the new benefit assessment.

<u>Quality of life</u>

No usable data regarding quality of life were available.

<u>Side effects</u>

No statistically significant differences were found between the idebenone and placebo-treated patient groups with regard to side effects.

Overall assessment

For the benefit assessment of idebenone for the treatment of visual impairment in adolescents and adults with LHON, results on mortality, morbidity and side effects are available on the basis of the RHODOS RCT.

No deaths occurred in the RHODOS study.

In the morbidity category, no statistically significant differences were observed between the treatment arms for the endpoints "best visual acuity improvement after 24 weeks", "change in best visual acuity after 24 weeks" and "change in visual acuity in best eye (at the start of the study) after 24 weeks".

No usable data regarding quality of life were available.

In the side effects category, no statistically significant differences were observed between the treatment and control arms.

The additional data from the single-arm PAROS and LEROS studies submitted in the context of the new benefit assessment after the deadline for the assessment of long-term effects do not provide any additional information for the assessment of the extent of the additional benefit beyond the comparator data from the RHODOS study. No statements on the extent of additional benefit can be derived from the overall analysis of the available results. A quantitative assessment of the extent of the effect and a quantification of the additional benefit according to the categories "minor", "considerable" or "major" on the basis of the data presented is not possible. Taking into account the severity of the disease, the written statements and the oral hearing, the G-BA classifies the extent of additional benefit for idebenone for the treatment of visual impairments in adolescents and adults with LHON as non-quantifiable on the basis of the criteria in Section 5 paragraph 7 of the AM-NutzenV since the scientific data does not allow quantification.

Significance of the evidence

For the RHODOS RCT used for the benefit assessment, the risk of bias at study level is assessed as low.

However, due to methodological limitations and restrictions of the RHODOS study, which were already the subject of the initial assessment, the risk of bias of the visual acuity endpoint is unclear: Thus, the exclusion of three patients with erroneous readings before unblinding from the analysis represents a deviation from the ITT principle and is assessed as critical. Furthermore, the post-hoc exclusion of another patient from the ITT analysis due to a visual acuity improvement before the start of treatment (presentation as modified ITT, mITT) contradicts the ITT principle and is to be assessed as questionable from a methodological point of view. In analogy to the view of the EMA, these analyses were assessed as methodologically inadequate and consequently did not receive any attention.

Furthermore, the risk of bias of the PAROS and LEROS studies is estimated to be high due to the uncontrolled study design.

In the overall assessment, this results in a hint for a non-quantifiable additional benefit with regard to the significance of the evidence, since the scientific data does not allow quantification.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the medicinal product Raxone with the active ingredient idebenone due to the expiry of the limitation of the resolution of 17 March 2016. Idebenone is approved for the treatment of visual disorders in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON). Idebenone was approved under "exceptional circumstances" as an orphan drug.

For the benefit assessment, the RHODOS study and the data from the single-arm LEROS and PAROS studies were considered for adolescents and adults with visual impairments due to LHON. The data from the single-arm PAROS and LEROS studies do not provide any additional information for the assessment of the extent of additional benefit beyond the comparator data from the RHODOS study. The indirect comparison presented could not be used due to methodological limitations.

No deaths were observed in the RHODOS study. In the morbidity category, for the endpoint of visual acuity, no statistically significant differences were observed between the treatment arms. No usable data regarding quality of life were available. In the side effects category, no statistically significant differences were observed between the treatment and control arms.

The overall assessment of adolescents and adults with visual impairments due to LHON identified a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

For the lower limit of the range shown, the G-BA bases the resolution on the patient numbers derived by the pharmaceutical company. The prevalence chosen by the pharmaceutical company for the upper limit of the range (3.22 cases per 100,000 people) does not take into account the upper limit of the 95% confidence interval (4.1 cases per 100,000 people) and is thus underestimated. Therefore, the resolution for the upper limit of the range is based on the patient numbers from the resolution of 17 March 2016.

2.3 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 "exceptional circumstances". 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2022).

The dosage of 150 mg film-coated tablets six times a day (total 900 mg daily) recommended in the idebenone product information was used as the basis for calculation.

Treatment period:

The idebenone product information states that there are no data from controlled clinical studies on continuous treatment with idebenone for longer than six months. However, no maximum treatment duration is given. If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Idebenone	3 x daily	365	1	365

Consumption:

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g., because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Idebenone	150 mg	900 mg	6 x 150 mg	365	2,190 x 150 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Idebenone 150 mg	180 FCT	€ 4,543.84	€ 1.77	€ 0.00	€ 4,542.07
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 15 August 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 30 March 2022, the pharmaceutical company submitted a dossier for the benefit assessment of idebenone to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 1 July 2022 together with the IQWiG

assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 July 2022.

The oral hearing was held on 8 August 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 September 2022, and the draft resolution was approved.

At its session on 15 September 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 June 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	3 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2022	Conduct of the oral hearing
Working group Section 35a	17 August 2022 31 August 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	6 September 2022	Concluding discussion of the draft resolution
Plenum	15 September 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 September 2022

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

Prof. Hecken