Justification

Gemeinsamer Bundesausschuss

to the Resolution 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

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 a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 10, 1st half sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 10, 2nd half sentence SGB V). Section 35a, paragraph 1, sentence 10 1st half sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with the Chapter 5, Sections 5 et seq. of the Rules of Procedure of the G-BA (VerfO) has not been carried out. Only the extent of the additional benefit has to be demonstrated.

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 retail prices including VAT exceeds € 50 million in the last twelve calendar months. According to Section 35a, paragraph 1, sentence 11 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, paragraphs 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 10 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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 provided by the G-BA is evaluated exclusively on the basis of the approval studies.

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 11 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment of 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient idebenone in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO is 1 October 2015. 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, number 1 VerfO on 30 September 2015.

Idebenone for the treatment of vision disorders in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON) is authorised as a medicinal product for the treatment of a rare disease 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 10, 1st half sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit is assessed on the basis of the approval 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 4 January 2016 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 G15-11) 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 evaluated the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1 numbers 1 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of idebenone.

In light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

Approved therapeutic indication of idebenone (Raxone®) in accordance with the product information:

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

Extent of the additional benefit:

[1] General Methods, Version 4.1 dated 28 November 2013. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

The pharmaceutical company presented the pivotal RHODOS study to answer the question on the extent of the additional benefit of idebenone. Furthermore, the pharmaceutical company presented the supportive investigations RHODOS Observational Follow-Up (RHODOS-OFU) and Expanded Access Program (EAP) as well as a historical Case Record Survey (CRS). The assessment of the extent of the additional benefit is based on the RHODOS study. RHODOS-OFU, EAP, and the CRS cannot be considered because they do not permit any statements beyond the RHODOS study.

The RHODOS study is a multi-centre, double-blind, randomised, placebo-controlled, parallel Phase II study involving 85 patients aged 14 to 65 with Leber's Hereditary Optic Neuropathy (LHON) at a ratio of 2:1. The study investigated the efficacy, safety, and tolerability of idebenone compared with placebo. The patients in the intervention arm received a daily dose of three times 300 mg idebenone according to the product information. The study duration was 24 weeks.

Endpoints identified in the RHODOS study included the best improvement in visual acuity in one eye after 24 weeks (primary endpoint), the change in best visual acuity after 24 weeks of treatment, the change in visual acuity of the best eye at start of study after 24 weeks, and colour contrast sensitivity. Adverse events and quality of life were also identified as endpoints.
Data analysis of visual acuity endpoints was performed at the end of study at 24 weeks and was based on an ITT population of 82 patients.
In summary, the extent of the additional benefit of idebenone is assessed as follows:
There is a non-quantifiable additional benefit.

Justification:

The G-BA classifies the extent of the additional benefit of idebenone as non-quantifiable based on the criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. An additional benefit exists but is non-quantifiable because the scientific data basis does not permit this.
For the decision in the present indication, it is relevant that an advantage with regard to patient-relevant endpoints of idebenone could not be shown compared to placebo. A quantification of the additional benefit is therefore not possible.

The exclusion of three patients with erroneous measured values[2] from the analysis before unblinding represents a deviation from the ITT principle and is assessed critically.

Furthermore, the *post hoc* exclusion of another patient from the ITT analysis because an improvement in visual acuity before treatment (described as modified ITT, mITT) contradicts the ITT principle and is questionable from a methodological point of view. By analogy with the view of the EMA, these analyses were judged to be methodologically inadequate and were therefore not taken into account.

In addition, the response criteria chosen by the pharmaceutical company for the low visual acuity range are not considered appropriate because of the lack of validation studies and unclear clinical relevance and are therefore not considered.

Mortality

No deaths were observed in the RHODOS study.

All in all, no statement on the extent of the additional benefit can be derived with regard to mortality on the basis of the results available.

[2] According to the pharmaceutical company in the written statement procedure

Morbidity

Best improvement in visual acuity after 24 weeks

The “Best improvement in visual acuity after 24 weeks”, primary endpoint of the RHODOS study was defined as the best improvement in visual acuity in one eye of each patient as measured by the change in logMAR between start of study and week 24.
With respect to the endpoint “Best improvement in visual acuity after 24 weeks”, no statistically significant difference was found 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 with the visual acuity of the best eye at the start of study. With respect to the endpoint “Change in best visual acuity after 24 weeks”, no statistically significant difference was found between the study arms.

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

The “Change in visual acuity of the best eye after 24 weeks” was defined as the change in the eye with the best visual acuity at start of study measured at week 24. With respect to the endpoint “Change in visual acuity of the best eye after 24 weeks”, no statistically significant difference was found between the study arms.

Overall, it is questionable to what extent the assessment of visual acuity in the therapeutic indication comprehensively reflects the symptomatology of the disease with respect to the visual acuity endpoints.

Change in colour contrast sensitivity after 24 weeks
At this endpoint, the colour contrast sensitivity for the colours red-green (protan) and yellow-blue (tritan) was measured but only in one study centre. Results are therefore available for only one sub-group. In addition, the analysis is based on the number of eyes. The proportion of patients with an improvement in colour contrast sensitivity remains unclear.

There was no statistically significant difference between the study arms regarding the perception of red-green. With regard to the perception of the colours yellow-blue, the study centre showed a statistically significant advantageous effect of idebenone compared with placebo.
The estimated difference between the groups was −13.63 ± 5.05 (95% CI): [−23.61; −3.66]; p = 0.008); this was due to a decrease in colour confusion in the idebenone group and an opposite change after 24 weeks in the placebo group.

Taken together, no statement on the extent of the additional benefit can be derived with regard to morbidity on the basis of the results available.

Quality of life

No usable data on quality of life were available.

Side effects

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

All in all, no statement on the extent of the additional benefit can be derived with regard to side effects on the basis of the results available.

Summary

In the overall view of the present results, the G-BA comes to the following assessment of the extent of the additional benefit: an additional benefit does exist, but this is non-quantifiable; at present, with the limited scientific data basis, it is impossible to quantify the extent of the additional benefit for patient-relevant endpoints.

Limitation:

The limitation of the period of validity of the resolution on the benefit assessment of idebenone has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V. These result from the conditions attached to the marketing authorisation of idebenone.

Compliance with the conditions attached to the marketing authorisation:

The medicinal product Raxone® with the active ingredient idebenone has been approved by the European Medicines Agency (EMA), under “exceptional circumstances” in accordance with Article 14, paragraph 8 of Regulation (EC) No. 726/2004 in conjunction with Article 22 of Directive 2001/83/EC.

Accordingly, in exceptional cases and following consultation with the applicant, the marketing authorisation may be granted under certain conditions concerning, in particular, the safety of the medicinal product, the information to the relevant authorities on any incident relating to its use, and the measures to be taken. The marketing authorisation may be granted only if the applicant can demonstrate that, for objective and verifiable reasons, complete data on the efficacy and safety of the medicinal product when used as intended cannot be provided and must be based on one of the grounds listed in Annex I to Directive 2001/83/EC. The maintenance of the marketing authorisation shall be subject to the annual reassessment of these conditions.

The EMA has therefore linked the marketing authorisation of idebenone to the condition that the pharmaceutical company submit further comprehensive clinical data on the efficacy and safety of the medicinal product idebenone to the approval authority for testing. For this purpose, a register (see EPAR on Raxone®, page 80) must be set up in order to record data on long-term safety.

At the end of the limitation period, the G-BA is to be provided with the data and further evidence requested by the EMA. These will enable a more reliable assessment of the extent of the additional benefit with regard to patient-relevant endpoints in long-term therapy with idebenone and are suitable to remedy the uncertainties with regard to the assessment of the extent of the additional benefit in the remarks described above.

An overall period of 2 years is considered appropriate for this purpose.

The pharmaceutical company can request advice on specific requirements on the part of the G-BA for the data to be submitted by the deadline in accordance with Chapter 5, Section 7 VerfO of the G-BA.

In accordance with Section 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of idebenone shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier on the medicinal product idebenone to the G-BA at the latest on the day of expiry of the deadline (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO).

The possibility that a benefit assessment of idebenone can be carried out at an earlier point in time for other reasons remains unaffected by this.

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).

The G-BA bases its resolution on the patient numbers stated in the assessment of the IQWiG. This corresponds to approx. 1,500–3,000 patients, whereby the upper value of the range is subject to a certain degree of uncertainty.

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: 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.

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: 1 February 2016).

Costs of the medicinal product:

With regard to consumption, the average annual consumption of film-coated tablets was determined.

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

Treatment duration:

The product information states that there is no data from controlled clinical trials on continuous treatment with idebenone for more than six months. However, no maximum treatment duration is specified. If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

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

Usage and consumption:

Designation of the therapy	Potency (mg)	Consumption by potency/ treatment day (mg)	Quantity per package (film-coated tablets)	Average annual consumption (film-coated tablets)
Medicinal product to be assessed				
Idebenone	150	6 × 150	180	2190

Costs:

Costs of the medicinal product:

Designation of the therapy	Costs (pharmacy sales price)	Costs after deduction of statutory rebates
Medicinal product to be assessed		
Idebenone	€ 8637.22	€ 8142.75 [€ 1.77[1]; € 492.70[2]]
Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2016 [1] Rebate according to Section 130 SGB V [2] Rebate according to Section 130a SGB V		

Costs for additionally required SHI services:

No costs for additionally required SHI services must be considered.

3. Bureaucratic costs

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

The pharmaceutical company submitted a dossier on 10 September 2015. A formal preliminary examination of the completeness of the dossier was carried out by the Secretariat of the G-BA in accordance with Chapter 5, Section 11, paragraph 2 of the VerfO. The final dossier was submitted on 30 September 2015. The relevant date for the first placing on the market of the active ingredient idebenone in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO is 1 October 2015.

The benefit assessment of the G-BA was published on 4 January 2016 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 25 January 2016.

The oral hearing was held on 9 February 2016.

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 8 March 2016, and the proposed resolution was approved.

At its session on 17 March 2016, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 August 2015	Consultation on the benefit assessment procedure
Subcommittee Medicinal products	24 November 2015	Information on the results of the completeness check of the dossier
Subcommittee Medicinal products	22 December 2015	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	2 February 2016	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 February 2016	Conduct of the oral hearing
Working group Section 35a	16 February 2016 1 March 2016	Consultation on the dossier evaluation 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	8 March 2016	Advice and consensus on the draft resolution
Plenum	17 March 2016	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 March 2016

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

Prof Hecken