Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM -RL): Annex XII – Resolution on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V Glycerol phenylbutyrate (New Therapeutic Indication: Urea Cycle Disorders in Infants Aged 0 to < 2 Months)

of 4 July 2019

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, the additional medicinal 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 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 evaluation 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. Only the extent of the additional benefit is 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 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.

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

On 1 March 2018, the active ingredient glycerol phenylbutyrate was listed for the first time in "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 18 December 2018, glycerol phenylbutyrate received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 No. 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (*OJ L* 334, 12 December 2008, p. 7).

On 15 January 2019 the pharmaceutical company has submitted a dossier in accordance with Section 4 paragraph 3 No. 2 AM-NutzenV in conjunction with Chapter 5 Section 8 paragraph 1 number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient glycerol phenylbutyrate with the new therapeutic indication (urea cycle disorders in infants aged 0 to < 2 months) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

Glycerol phenylbutyrate for the treatment of urea cycle disorders 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 11, 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 15 April 2019 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 G12-01) 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 the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1–4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of glycerol phenylbutyrate.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of glycerol phenylbutyrate (Ravicti®) in accordance with the product information

RAVICTI is indicated for use as adjunctive therapy in patients with urea cycle disorders (UCDs), including deficiencies in carbamoyl phosphate synthetase I (CPS), ornithine

1 General Methods, version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG), and ornithine translocase (hyperammonaemia-hyperornithinaemia-homocitrullinuria syndrome, HHH), who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, protein-free calorie supplements).

2.1.2 Extent of the additional benefit

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

Non-quantifiable additional benefit for glycerol phenylbutyrate has been established for infants aged 0 to < 2 months with urea cycle disorders that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

Justification:

The pharmaceutical company submitted the open single-arm studies HPN-100-009, HPN-100-012SO, HPN-100-012SE, HPN-100-014 and S-525-2010 for assessment of the extent of the additional benefit of glycerol phenylbutyrate in infants aged 0 to < 2 months with urea cycle disorders.

The assessment of the extent of additional benefit in the therapeutic indication under consideration only draws on findings from the study HPN-100-009.

The HPN-100-012SO and HPN-100-012SE studies are not included in the present benefit assessment as the children in these studies were at least two months old when included in the study. The HPN-100-014 and S-525-2010 studies are not included in the present benefit assessment as no results are yet available for these studies.

The HPN-100-009 study is an open, phase IV, control arm-less, multicentre study evaluating the safety, efficacy and pharmacokinetics of glycerol phenylbutyrate in children up to two years of age. A total of 27 patients were included in the study: 17 patients aged < 2 months and 10 patients aged ≥ 2 months. In 1 of the 17 patients aged < 2 months who were included in the study, consent to participate in the study was withdrawn before the first dose of the study medication was administered.

The study consists of a screening phase (within the 30 days preceding day 1 of the study), a transition phase (on days 1 to 7) and a subsequent safety extension phase (up to 2 years). During the transition phase, treatment (from sodium phenylbutyrate) was switched to glycerol phenylbutyrate. During the safety extension phase, the safety of glycerol phenylbutyrate was investigated for a minimum of six months and a maximum of two years. Endpoints included successful transition to glycerol phenylbutyrate with controlled levels of ammonia (i.e. no clinical symptoms and ammonia levels < 100 µmol/l) and the rate of hyperammonaemic crises during the first six months of treatment with glycerol phenylbutyrate. The study was conducted between 2014 and 2017 in the USA and Canada.

As there is no control arm in the HPN-100-009 study, it is assumed that it has a high risk of bias at study and endpoint level. Comparative conclusions cannot be drawn due to the study's one-armed design and the lack of indirect comparisons.

With regard to the study data, it should be noted that six patients of the remaining 16 patients aged < 2 months left the study prematurely and that it can be assumed that the health status

of these children was not subsequently monitored. Four of the six children dropped out of the study due to a liver transplant.

Mortality

No deaths occurred.

Morbidity

Successful transition to glycerol phenylbutyrate while maintaining ammonia levels

Successful transition to glycerol phenylbutyrate while maintaining ammonia levels was determined by the subjects answering an appropriate question from trial personnel. For children aged from 0 to < 2 months after a minimum of 72 hours of continuous monitoring of ammonia levels, answering the question in the affirmative required the following criteria to be fulfilled: no signs and symptoms of hyperammonaemia, ammonia levels <100 µmol/l, and agreement by the trial personnel that the patient was fit to be discharged from hospital.

As most of the children included in the study (n=10; 62.5% of the safety population) were already stable before the transition to glycerol phenyl butyrate, a successful transition is not considered to be directly relevant to the patient.

Moreover, there are grounds to doubt the validity of the answer given to the question, for instance the possibility of validly assessing several of the signs and symptoms of hyperammonaemia in children aged <2 months (e.g. nausea, headache, irritability). The ammonia level measured is also influenced by many factors (e.g. time to the last consumption of food and measurement of the ammonia level or heavy strain on the respiratory muscles); it remains unclear, however, whether the measurement was standardised.

Due to the lack of clear patient relevance and the limited validity, the results of this endpoint will not be considered in assessing the extent of the additional benefit. As this was one of the study's primary efficacy endpoints, the results are presented as supplementary information.

Hyperammonaemic crises

Hyperammonaemic crises are considered to be patient relevant. However, as mentioned regarding the endpoint "Successful transition to glycerol phenylbutyrate while maintaining ammonia levels", uncertainties remain both in the ability to establish the signs and symptoms of hyperammonaemia and in the measurement of ammonia levels.

During the study, a total of five children suffered at least one hyperammonaemic crisis. All these hyperammonaemic crises occurred during the safety extension. The rate of hyperammonaemic crises was 0.003 per child per day.

Quality of life

No health-related quality of life data was collected

Side effects

All the children in the trial suffered at least one adverse event (AE), with six children (37.5%) suffering at least one grade 3 AE and eleven children (68.8%) suffering at least one serious adverse event (SAE).

The most frequent grade 3 AEs were in the system organ classes "Infections and infestations" and "Metabolism and nutrition disorders". The only AE that occurred in more than one child was "hyperammonaemia" at a severity of grade 3. No grade 4 or 5 adverse

events occurred. In one child, elevated liver enzyme values, assessed as a grade 1 AE, led to discontinuation of the study medication and withdrawal from the trial.

The most frequent grade 3 SAEs were also in the system organ classes "Infections and infestations" and "Metabolism and nutrition disorders". The most common preferred term SAE was "hyperammonaemia". No other SAE occurred in more than one child.

EPAR considers the safety profile of glycerol phenylbutyrate in children <2 months of age to be similar to that of glycerol phenylbutyrate in older patients.

On the basis of the available data, however, it is unclear which AEs occurred and how many children suffered these before an age of two months.

Overall assessment

In summary, the current assessment of the extent of the additional benefit of glycerol phenylbutyrate for infants aged 0 to <2 months is made on the basis of mortality, morbidity and side effects from the open phase IV study HPN-100-009, with no control arm and a high risk of bias. During the study, at least one hyperammonaemic crisis occurred in 5 out of 16 children treated with glycerol phenylbutyrate. Due to a lack of comparative data, assessing the extent of the additional benefit with regard to mortality and morbidity is, likewise, impossible. Quality of life data have not been submitted. Due to a lack of comparative data, assessing the extent of the additional benefit with regard to side effects is, likewise, impossible.

Due to the methodological limitations of the study and the overall limited evidence base, the G-BA, taking into account the severity of the disease, the written statements and the oral hearing, classifies, on the basis of the criteria in Article 5 paragraph 7 AM-NutzenV, the extent of the additional benefit of glycerol phenylbutyrate as non-quantifiable. Thus, on the basis of the submitted data, it is not possible to quantitatively assess the extent of the effect or the additional benefit into one of the three categories 'low', 'considerable' or 'substantial'.
An additional benefit does exist, but this is non-quantifiable; at present, with the limited scientific data available, it is impossible to quantify the extent of the additional benefit for patient-relevant endpoints.

2.1.3 Summary of the assessment

The pharmaceutical company submitted the open single-arm studies HPN-100-009, HPN-100-012SO, HPN-100-012SE, HPN-100-014 and S-525-2010 for assessment of the extent of the additional benefit of glycerol phenylbutyrate in infants aged 0 to <2 months with urea cycle disorders. For this therapeutic indication the assessment of the additional benefit of the drug only draws on findings from the HPN-100-009 study, as other studies either included patients of more than two years of age or are yet to publish results. With regards to mortality, morbidity and side effects, the benefit assessment drew on the results of the open phase IV study HPN-100-009, which lacked a control arm and had a high risk of bias. The morbidity endpoint "Successful transition to glycerol phenylbutyrate while maintaining ammonia levels" was not taken into account in the assessment due to its lack of explicit relevance to patients and limited validity. During the study, at least one hyperammonaemic crisis occurred in 5 out of 16 children treated with glycerol phenylbutyrate. Due to a lack of comparative data, assessing the extent of the additional benefit with regard to mortality and morbidity is, likewise, impossible. Quality of life data have not been submitted. Due to a lack of comparative data, assessing the extent of the additional benefit with regard to safety is, likewise, impossible.

Due to the methodological limitations of the study and the overall limited evidence base, the G-BA, taking into account the severity of the disease, the written statements and the oral

hearing, classifies, on the basis of the criteria in Article 5 paragraph 7 AM-NutzenV, the extent of the additional benefit of glycerol phenylbutyrate as non-quantifiable. Thus, on the basis of the submitted data, it is not possible to quantitatively assess the extent of the effect or the additional benefit into one of the three categories 'low', 'considerable' or 'substantial'.
An additional benefit does exist, but this is non-quantifiable; at present, with the limited scientific data available, it is impossible to quantify the extent of the additional benefit for patient-relevant endpoints.

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 the statutory health insurance (SHI). These are based on the data from the pharmaceutical company's dossier. The figures, however, are subject to uncertainties; they were not calculated, for instance, on the basis of current data on the number of live births. It is also unclear to what extent the determined incidence rates could be extrapolated onto the German healthcare system, having been collected both in other regions (e.g. Canada, USA) and over varying periods of time. Furthermore, it is unclear to what extent mortality rates were considered in determining incidence rates.

2.3 Requirements for a quality-assured application

The requirements of 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 Ravicti® (active ingredient: glycerol phenylbutyrate) at the following publicly accessible link (last access: 4 April 2019):

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

Treatment with glycerol phenylbutyrate may only be initiated and monitored by specialists who are experienced in the diagnosis and treatment of patients with urea cycle disorders.

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 June 2019).

The product information specifies a glycerol phenylbutyrate dosage of between 4.5ml/m^2/day to 11.2ml/m^2/day. Dosages dependent on body weight (BW) or body surface area (BSA) were calculated on figures of average bodily dimensions of infants at one month of age (average body length: boys 55.99 cm, girls 54.94 cm, average body weight: boys 4.49 kg, girls 4.2 kg)[2]. Thus, the average body surface area for boys and girls aged one month is 0.25m^2 (calculated as per Du Bois 1916).

The lower limit of the range is therefore the smallest possible dosage (4.5ml/m^2 BSA/day), whereas the upper limit is the largest (11.2ml/m^2 BSA/day). Each individual dose should be rounded up to the nearest 0.1ml. According to the product information the total daily dosage should be divided into equal doses and taken at each meal or feeding (i.e. three to six times daily).

2 Contributions to Federal Health Reporting, Robert Koch Institute, Berlin, 2013: Reference percentiles for anthropometric measures and blood pressure from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)

It was decided to employ treatment costs for a period of two months, calculated on the basis of the mean BSA of one-month-old babies, even if the duration of individual treatment and/or the BSA vary over time. Treatment was administered continuously, but the costs for children over two months of age and the costs for adults were already presented in the resolutions of 16 August 2018 and 29 September 2018.

The shelf life of the medicinal product is limited to 14 days after the bottle has been opened for the first time, so discards after 14 days need to be taken into account. The calculated lower average dosage of 1.2ml/day, therefore results in one bottle being consumed every 14 days.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ Year
Medicinal product to be assessed				
Glycerol phenylbutyrate	continuously, 3–6 x daily	60.8	1	60.8

Usage and consumption:

Designation of the therapy	Dosage	Dose/patient/day of treatment	Consumption based on medication potency/treatment day	No. treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Glycerol phenylbutyrate	4.5ml/m^2/day	1.2ml	1.2ml	60.8	73.0ml
	11.2ml/m^2/day	3ml	3ml		182.4ml

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail 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 product:

Designation of the therapy	Package 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					
Glycerol phenylbutyrate	1.1 g/ml 25ml	€289.13	€1.77	€0.00	€287.36

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 June 2019

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 in calculating costs.

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

On 15 January 2019, the pharmaceutical company submitted a dossier for the benefit assessment of glycerol phenylbutyrate to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

The benefit assessment of the G-BA was published on 15 April 2019 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 6 May 2019.

The oral hearing was held on 27 May 2019.

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 statements received and the oral hearing were discussed at the session of the subcommittee on 24 June 2019, and the proposed resolution was approved.

At its session on 4 July 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 April 2019	Information of the benefit assessment of the G-BA
Working group Section 35a	22 May 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 May 2019	Conduct of the oral hearing
Working group Section 35a	5 June 2019 19 June 2019	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 statement procedure
Subcommittee Medicinal products	25 June 2019	Concluding discussion of the proposed resolution
Plenum	4 July 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 July 2019

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

Prof Hecken