Resolution

Gemeinsamer Bundesausschuss

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

At its session on 4 July 2019 the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD Month YYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of glycerol phenylbutyrate in accordance with the resolution of 16 August 2018:

Courtesy translation – only the German version is legally binding.

Glycerol phenylbutyrate

Resolution of: 4 July 2019
Entry into force on: 4 July 2019
Federal Gazette, BAnz. AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 27 November 2015):

RAVICTI is indicated for use as adjunctive therapy in adult and paediatric patients aged ≥ 2 months with urea cycle disorders (UCDs), including deficiencies in carbamoyl phosphate synthetase I (CPS), ornithine 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).

New therapeutic indication (according to the marketing authorisation of 18 December 2018):

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

1. Extent of the additional benefit of the medicinal product

Glycerol phenylbutyrate is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. Pursuant to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (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). 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).

Infants aged 0 to < 2 months with urea cycle disorders that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

Extent of the additional benefit:

Non-quantifiable

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Study results according to endpoints:[1]

HPN-100-009 Study: Non-controlled, open phase IV study[2]

Endpoint	**Glycerol phenylbutyrate (GPB)**	
	N	*Patients with event n (%)*
Mortality		
No deaths occurred in the course of the study.		
Morbidity		
Successful transition to GPB while maintaining ammonia levels (see supplementary information)	*16*	*16 (100)*
Hyperammonaemic crises (HACs) during the transition period (days 1 to 7)		
Children with HAC	16	0
HACs during the safety extension		
HAC rate per child and day[a]	16	0.003
Children with 1 HAC	16	3 (18.8)
Children with 2 HACs	16	2 (12.5)
Children with 3 or more HACs	16	0
Health-related quality of life		
No quality of life data was collected		
Side effects		
AEs	16	16 (100)
AEs with a severity grade of ≥ 3	16	6 (37.5)
SAEs	16	11 (68.8)
AE that led to discontinuation of the trial drug	16	1 (6.3)
UE as specified for MedDRA[b] SOC Preferred Term[c]		
Blood and lymphatic system disorders	16	6 (37.5)
Anaemia	16	3 (18.8)
Neutropenia	16	2 (12.5)

[1] Data from the dossier evaluation by the G-BA (published on 15 April 2019) unless indicated otherwise.
[2] The data of patients aged < 2 months at inclusion in the study are presented

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Thrombocytopenia	16	2 (12.5)
Thrombocytosis	16	2 (12.5)
Congenital, familial and genetic diseases	16	2 (12.5)
Plagiocephaly	16	2 (12.5)
Gastrointestinal disorders	16	14 (87.5)
Gastroesophageal reflux disease	16	6 (37.5)
Vomiting	16	6 (37.5)
Diarrhoea	16	5 (31.3)
Flatulence	16	3 (18.8)
Teething	16	3 (18.8)
Constipation	16	2 (12.5)
General disorders and administration site conditions	16	4 (25.0)
Fever	16	2 (12.5)
Infections and infestations	16	13 (81.3)
Upper respiratory tract infections	16	5 (31.3)
Nasopharyngitis	16	4 (25.0)
Ear infection	16	3 (18.8)
Renal infection	16	3 (18.8)
Oral candidiasis	16	2 (12.5)
Respiratory syncytial virus infection	16	2 (12.5)
Investigations	16	7 (43.8)
Hepatic enzyme increased	16	2 (12.5)
Metabolism and nutrition disorders	16	10 (62.5)
Hyperammonaemia	16	6 (37.5)
Dehydration	16	3 (18.8)
Metabolic acidosis	16	2 (12.5)
Nervous system disorders	16	2 (12.5)

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Lethargy	16	2 (12.5)
Respiratory, thoracic and mediastinal disorders	16	7 (43.8)
Coughing	16	4 (25.0)
Nasal congestion	16	2 (12.5)
Oropharyngeal pain	16	2 (12.5)
Skin and subcutaneous tissue disorders	16	9 (56.3)
Nappy rash	16	6 (37.5)
Rash	16	5 (31.3)

a) Calculated for the first 6 months of the safety extension phase as the sum of (number of HACs) / sum of (number of days during the first 6 months starting on day 8, or number of days under GPB, depending on which was smaller) divided by the number of children in the corresponding group.
b) Use of MedDRA version 19.0.
c) Adverse events classified according to MedDRA system organ classes (SOC) and Preferred Terms (PT) with an incidence of ≥ 10%.

Abbreviations: HAC: hyperammonaemic crisis; MedDRA Medical Dictionary for Regulatory Activities; N: number of patients evaluated; n: number of patients with (at least one) event; PT: Preferred Terms; (S)UE: (Serious) Adverse Event; SOC System Organ Class

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

Approx. 10–18 patients

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.

4. Treatment costs

Annual treatment costs:

The average costs for the first two months of life are shown.

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Designation of the therapy	Annual treatment costs/patient
Glycerol phenylbutyrate	€1,247.96 – €2,096.58

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2019)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 4 July 2019.

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

Berlin, 4 July 2019

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

Prof Hecken

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