EMA/403996/2018

European Medicines Agency decision

P/0191/2018

of 17 July 2018

on the acceptance of a modification of an agreed paediatric investigation plan for glycerol phenylbutyrate (Ravicti), (EMEA-000297-PIP02-12-M02) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Disclaimer

This decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

Only the English text is authentic.

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The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0214/2013 issued on 4 September 2013 and the decision P/0068/2014 issued on 14 March 2014,

Having regard to the application submitted by Horizon Pharma Ireland Limited on 9 March 2018 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 1 June 2018, in accordance with Article 22 of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the acceptance of changes to the agreed paediatric investigation plan.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for glycerol phenylbutyrate (Ravicti), oral liquid, oral use, gastroenteral use, are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

This decision is addressed to Horizon Pharma Ireland Limited, Connaught House, 1st Floor, 1 Burlington Road, D04C5Y6 - Dublin 4, Ireland.

EMA/PDCO/186961/2018
London, 1 June 2018

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-000297-PIP02-12-M02

Scope of the application

Active substance(s):

Glycerol phenylbutyrate

Invented name:

Ravicti

Condition(s):

Treatment of urea cycle disorders

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Oral liquid

Route(s) of administration:

Oral use

Gastroenteral use

Name/corporate name of the PIP applicant:

Horizon Pharma Ireland Limited

Information about the authorised medicinal product:

See Annex II

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Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Horizon Pharma Ireland Limited submitted to the European Medicines Agency on 9 March 2018 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0214/2013 issued on 4 September 2013 and the decision P/0068/2014 issued on 14 March 2014.

The application for modification proposed changes to the agreed paediatric investigation plan.

The procedure started on 3 April 2018.

Scope of the modification

Some measures of the Paediatric Investigation Plan have been modified.

Opinion

1. The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree to changes to the paediatric investigation plan in the scope set out in the Annex I of this opinion.

   The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annexes and appendix.

Annex I

The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)

1. Waiver

Not applicable.

2. Paediatric Investigation Plan

2.1. Condition: treatment of urea cycle disorders

2.1.1. Indication(s) targeted by the PIP

Adjunctive therapy for children age with urea cycle disorders involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (HHH deficiency)

2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Oral liquid

2.1.4. Studies

Area	Number of studies	Description
Quality	1	**Study 1** Development of an age-appropriate liquid form of glycerol phenylbutyrate (GPB).
Non-clinical	0	Not applicable.
Clinical	5	**Study 2** Fixed sequence, open-label, switch-over study of *g*lycerol phenylbutyrate with a long-term safety extension to evaluate the safety, tolerability, PK characteristics, and activity of GPB in children aged from 6 years to less than 18 years for the treatment of urea cycle disorders as compared with sodium phenylbutyrate (NaPBA). HPN-100-005 (switch-over) **Study 3** Open label safety extension study to evaluate the long-term safety of GPB and its control of blood ammonia in paediatric patients aged from 6 years to less than 18 years with urea cycle disorders. HPN-100-005 (Safety Extension)

Area	Number of studies	Description
		Study 4 Fixed sequence, open-label, switch-over study of glycerol phenylbutyrate with a long-term safety extension to evaluate the safety, tolerability, PK characteristics, and activity of GPB in children aged from 1 month to less than 6 years for the treatment of urea cycle disorders as compared to sodium phenylbutyrate (NaPBA). HPN-100-012 (Switch-Over) **Study 5** Open label safety extension study to evaluate the long-term safety of GPB and its control of blood ammonia in paediatric patients aged from 1 month to less than 6 years with urea cycle disorders. HPN-100-012 (Safety Extension) **Study 6** Open-label, multi-centre, multiple dose, non-randomised trial to evaluate pharmacokinetics, safety, efficacy, acceptability/palatability of glycerol phenylbutyrate as add-on to best standard of care compared to sodium phenylbutyrate (NaPBA) in children from birth to less than 2 months of age with urea cycle disorders with an extension phase until the age of 24 months. HPN-100-009

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By December 2018
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of urea cycle disorders

Authorised indication(s):

- RAVICTI is indicated for use as adjunctive therapy for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia 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).

Authorised pharmaceutical form(s):

Oral liquid

Authorised route(s) of administration:

Oral or gastroenteral use.