EMA/107971/2022

European Medicines Agency decision

P/0060/2022

of 7 March 2022

on the agreement of a paediatric investigation plan and on the granting of a deferral for L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride (EMEA-003049-PIP01-21) 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.

European Medicines Agency decision

P/0060/2022

of 7 March 2022

on the agreement of a paediatric investigation plan and on the granting of a deferral for L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride (EMEA-003049-PIP01-21) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

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 Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency[2],

Having regard to the application submitted by Iperboreal Pharma S.r.l. on 4 June 2021 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 21 January 2022, in accordance with Article 17 of Regulation (EC) No 1901/2006 and Article 21 of said Regulation,

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

Whereas:

(1) The Paediatric Committee of the European Medicines Agency following a re-examination procedure of the Paediatric Committee's opinion according to Article 25(3) of Regulation (EC) No 1901/2006, has given an opinion on the agreement of a paediatric investigation plan and on the granting of a deferral.

(2) It is therefore appropriate to adopt a decision agreeing a paediatric investigation plan.

(3) It is therefore appropriate to adopt a decision granting a deferral.

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

Has adopted this decision:

Article 1

A paediatric investigation plan for L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride, solution for peritoneal dialysis, intraperitoneal use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A deferral for L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride, solution for peritoneal dialysis, intraperitoneal use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

This decision is addressed to Iperboreal Pharma Srl, Via Piave 110, 65122 – Pescara, Italy.

EMA/83427/2022
Amsterdam, 25 February 2022

Final opinion of the Paediatric Committee on the agreement of a Paediatric Investigation plan and a deferral

EMEA-003049-PIP01-21

Scope of the application

Active substance(s):

L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride

Condition(s):

Treatment of renal failure with carnitine deficiency

Pharmaceutical form(s):

Solution for peritoneal dialysis

Route(s) of administration:

Intraperitoneal use

Name/corporate name of the PIP applicant:

Iperboreal Pharma S.r.l.

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Iperboreal Pharma S.r.l. submitted for agreement to the European Medicines Agency on 4 June 2021 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation.

An Opinion was adopted by the Paediatric Committee on 21 January 2021 for the above mentioned product. Iperboreal Pharma S.r.l. received the Paediatric Committee Opinion on 31 January 2022.

On 9 February 2022 Iperboreal Pharma S.r.l. submitted to the European Medicines Agency a written request, including detailed grounds for re-examination of the Opinion.

The re-examination procedure started on 10 February 2022.

A meeting with the Paediatric Committee took place on 23 February 2022.

Final Opinion

1. The PDCO, having considered the matter as set out in the appended summary report, by 16 out of 27 votes, did not reach an absolute majority in favour of granting a deferral as per Annex I. Therefore, the Paediatric Committee, having assessed the detailed grounds for re-examination, in accordance with Article 25(3) of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   1.1. to maintain its opinion and

   - to agree the paediatric investigation plan in accordance with Article 17(1) of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation, as per Annex I.

The divergent position is appended to this opinion.

The Norwegian Paediatric Committee member does not agree with the above-mentioned recommendation of the Paediatric Committee. The Norwegian divergent position is appended to this opinion.

2. The measures and timelines of the agreed 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 annex and appendixes.

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 renal failure with carnitine deficiency

2.1.1. Indication(s) targeted by the PIP

Treatment of secondary carnitine deficiency in patients with acute and chronic renal failure in peritoneal dialysis

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)

Solution for peritoneal dialysis

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable
Non-clinical studies	0	Not applicable
Clinical studies	1	Open-label, uncontrolled trial to evaluate safety and efficacy of L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride for peritoneal dialysis in children from birth to less than 18 years of age with end stage renal disease (ESRD) and secondary carnitine deficiency (IP-001-2021)
Extrapolation, modelling and simulation studies	1	Extrapolation study to evaluate the use of L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride for peritoneal dialysis in children with end stage renal disease (ESRD) and secondary carnitine deficiency
Other studies	0	Not applicable
Other measures	0	Not applicable

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	By June 2024
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Appendix

Divergent position statement

Divergent position statement dated 25 February 2022

L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride, (EMEA-003049-PIP01-21)

The undersigned members of the PDCO did not agree with the PDCO's negative opinion on the acceptance of a deferral for the initiation of Study 1 for L-carnitine / glucose / calcium chloride dihydrate / magnesium chloride hexahydrate / sodium lactate / sodium chloride, (EMEA-003049-PIP01-21).

The reasons for divergent opinion were the following:

- Not granting a deferral for the start of the paediatric trial would delay the marketing authorisation (MA) in adults.
- As the adult MA is not expected to be granted before starting the paediatric trial, there should be no risk of off-label use in children and feasibility of the paediatric trial is not expected to be affected.
- It doesn't seem that deferring the start of the paediatric trial will delay the availability of paediatric data, provided the applicant will run the study as planned.
- End stage renal disease (ESRD) prevalence is very rare in children (estimated prevalence 18-100 per million according to IPPN Registry). In addition, alternative treatments are available to children with renal failure and secondary carnitine deficiency who undergo peritoneal dialysis.

Marleen Renard

Zena Gunther

Tereza Bazantova

Nanna Borup Johansen

Jana Lass

Pauliina Lehtolainen-Dalkilic

Dina Apele-Freimane

Herbert Lenicker

Marek Migdal

Peter Sisovsky

Stefan Grosek

Eva Agurell

Dana Gabriela Marin

Dimitrios Athanasiou

Fernando Cabanas

Siri Wang, the Norwegian Paediatric Committee member

A concern raised by some PDCO members was that patients in a paediatric trial might be difficult to recruit if the product is already available in adults and therefore could be used off-label in paediatrics. However, I would agree with the applicant's view, that even if the MAA is not blocked by validation due to not deferring initiation of the paediatric trial, availability would still be quite delayed, as a marketing authorisation procedure takes more than a year plus more time to put the product on the market. At

this time recruitment would likely be completed, if keeping the timelines as proposed in the PIP (completion by Dec 2023).

In conclusion I do not see sufficient scientific ground why now at a time when the applicant has the intention to submit the adult MAA to CHMP, a delay of such a step would be justified. In practice: even if PDCO denied granting a deferral, this would only ensure that one patient has to be included into a trial, based on which action a positive compliance and subsequent MAA submission would be validated. Therefore, granting a deferral would in the worst case cause some delay in this first patient first dose approach, but could not really ensure that such a trial would be compliant until completion. In both cases the outcome would have to be followed by a full compliance check at the end of the study anyway. Therefore, in my opinion, a negative decision at this time will not provide any benefit to children, but will delay access to adults.

Karl-Heinz Huemer