EMA/442341/2024

European Medicines Agency decision

P/0352/2024

of 25 October 2024

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for bitopertin (EMEA-000439-PIP03-23) 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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on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for bitopertin (EMEA-000439-PIP03-23) 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 Disc Medicine B.V. on 26 June 2023 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 6 September 2024, in accordance with Article 17 of Regulation (EC) No 1901/2006 and Article 21 of said Regulation and Article 13 of said Regulation,

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 agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver.

(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.

(4) It is therefore appropriate to adopt a decision granting a waiver.

[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 bitopertin, film-coated tablet, age-appropriate dosage form, oral 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 bitopertin, film-coated tablet, age-appropriate dosage form, oral 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

A waiver for bitopertin, film-coated tablet, age-appropriate dosage form, oral 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 4

This decision is addressed to Disc Medicine B.V., P.J. Oudweg 4, 1314 CH – Almere, The Netherlands.

EMA/PDCO/270199/2024
Amsterdam, 6 September 2024

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver

EMEA-000439-PIP03-23

Scope of the application

Active substance(s):

Bitopertin

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of erythropoietic protoporphyria

Treatment of X-linked protoporphyria

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate dosage form

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Disc Medicine B.V.

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Disc Medicine B.V. submitted for agreement to the European Medicines Agency on 26 June 2023 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 14 August 2023.

Supplementary information was provided by the applicant on 3 June 2024. The applicant proposed modifications to the paediatric investigation plan.

Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - 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;
   - to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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

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

1.1. Condition:

Treatment of erythropoietic protoporphyria

The waiver applies to:

- the paediatric population from birth to less than 1 year of age;
- film-coated tablet and age-appropriate dosage form; oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

1.2. Condition:

Treatment of X-linked protoporphyria

The waiver applies to:

- the paediatric population from birth to less than 1 year of age;
- film-coated tablet and age-appropriate dosage form; oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

2. Paediatric investigation plan

2.1. Condition:

Treatment of erythropoietic protoporphyria

2.1.1. Indication(s) targeted by the PIP

Treatment of erythropoietic protoporphyria

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

From 1 year to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Film-coated tablet and age-appropriate dosage form

2.1.4. Measures

Area	Description
Quality-related studies	Study 1 Generation of data on suitability of crushing existing film-coated tablets for use in the paediatric population from 1

	year to less than 12 years and children not able to swallow the existing film-coated tablets. Study 2 Development of an age-appropriate dosage form (oral solid dosage form or oral liquid dosage form) for use in the paediatric population from 1 year to less than 12 years of age and children not able to swallow the existing film-coated tablets and results of study 1 demonstrate that crushing existing film-coated tablets is not appropriate.
Non-clinical studies	Study 3 Definitive juvenile rat toxicity study (1054421) Study 4 Oral gavage lactational transfer study of bitopertin in rats (2024-011-DISC-1459-R-PK)
Clinical studies	Study 5 Randomised, open-label, parallel-arm study of bitopertin to evaluate safety, tolerability, efficacy, and protoporphyrin IX (PPIX) concentrations in adolescents from 12 years to less than 18 years of age (and adults) with erythropoietic protoporphyria or X-linked protoporphyria (DISC-1459-202) Study 6 Randomised, double-blind, placebo-controlled, parallel-group study of bitopertin to evaluate the efficacy, safety, and tolerability in adolescents from 12 years to less than 18 years of age (and adults) with erythropoietic protoporphyria or X-linked protoporphyria (DISC-1459-301) Study 7 Open-label, single-treatment-arm study to evaluate the safety, tolerability, preliminary efficacy, pharmacokinetics, and pharmacodynamics in paediatric participants from 1 year to less than 12 years of age with erythropoietic protoporphyria or X-linked protoporphyria (DISC-1459-401)
Modelling and simulation analyses	Study 8 Use of physiologically-based PK (PBPK) to predict initial paediatric doses to be used in clinical studies Study 9 Use of Population Pharmacokinetic/Pharmacodynamic model to confirm or modify the paediatric posology compared to the regimen used in clinical trials
Other studies	Not applicable

Extrapolation plan	Study 10 Analysis of existing in-house data on bitopertin to support efficacy assumptions in the paediatric population from 1 year to less than 12 years of age based on extrapolation

2.2. Condition:

Treatment of X-linked protoporphyria

2.2.1. Indication(s) targeted by the PIP

Treatment of X-linked protoporphyria

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

From 1 year to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Film-coated tablet and age-appropriate dosage form

2.2.4. Measures

Area	**Description**
Quality-related studies	Study 1 Generation of data on suitability of crushing existing film-coated tablets for use in the paediatric population from 1 year to less than 12 years and children not able to swallow the existing film-coated tablets. *(Same study as for the condition "Treatment of erythropoietic protoporphyria")* Study 2 Development of an age-appropriate dosage form (oral solid dosage form or oral liquid dosage form) for use in the paediatric population from 1 year to less than 12 years and children not able to swallow the existing film-coated tablets and results of study 1 demonstrate that crushing existing film-coated tablets is not appropriate. *(Same study as for the condition "Treatment of erythropoietic protoporphyria")*
Non-clinical studies	Study 3 Definitive juvenile rat toxicity study (1054421) *(Same study as for the condition "Treatment of erythropoietic protoporphyria")* Study 4 Oral gavage lactational transfer study of bitopertin in rats

	(2024-011-DISC-1459-R-PK *) (Same study as for the condition "Treatment of erythropoietic protoporphyria")*
Clinical studies	Study 5 Randomised, open-label, parallel-arm trial of bitopertin to evaluate safety, tolerability, efficacy, and protoporphyrin IX (PPIX) concentrations in adolescents from 12 years to less than 18 years of age (and adults) with erythropoietic protoporphyria or X-linked protoporphyria (DISC-1459-202) *(Same study as for the condition "Treatment of erythropoietic protoporphyria")* Study 6 Randomised, double-blind, placebo-controlled, parallel-group study of bitopertin to evaluate the efficacy, safety, and tolerability in adolescents from 12 years to less than 18 years of age (and adults) with erythropoietic protoporphyria or X-linked protoporphyria (DISC-1459-301) *(Same study as for the condition "Treatment of erythropoietic protoporphyria")* Study 7 Open-label, single-treatment-arm study to evaluate the safety, tolerability, preliminary efficacy, pharmacokinetics, and pharmacodynamics in paediatric participants from 1 year to less than 12 years of age with erythropoietic protoporphyria or X-linked protoporphyria (DISC-1459-401) *(Same study as for the condition "Treatment of erythropoietic protoporphyria")*
Modelling and simulation analyses	Study 8 Use of physiologically-based PK (PBPK) to predict initial paediatric doses to be used in clinical studies *(Same study as for the condition "Treatment of erythropoietic protoporphyria")* Study 9 Use of Population Pharmacokinetic/Pharmacodynamic model to confirm or modify the paediatric posology compared to the regimen used in clinical trials *(Same study as for the condition "Treatment of erythropoietic protoporphyria")*
Other studies	Not applicable
Extrapolation plan	Study 10 Analysis of existing in-house data on bitopertin to support efficacy assumptions in the paediatric population from 1 year to less than 12 years of age based on extrapolation *(Same study as for the condition "Treatment of erythropoietic protoporphyria")*

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 December 2029
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Information provided by the applicant:

The product is not authorised anywhere in the European Community.