EMA/901112/2022

European Medicines Agency decision

P/0535/2022

of 30 December 2022

on the acceptance of a modification of an agreed paediatric investigation plan for lefamulin (Xenleta) (EMEA-002075-PIP01-16-M03) 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 Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0241/2017 issued on 4 September 2017 and the decision P/0066/2019 issued on 22 March 2019,

Having regard to the application submitted by Nabriva Therapeutics DAC on 28 July 2022 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and proposing a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 11 November 2022, in accordance with Article 22 of Regulation (EC) No 1901/2006 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 acceptance of changes to the agreed paediatric investigation plan and to the deferral and on the granting of a waiver.

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

(3) 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

Changes to the agreed paediatric investigation plan for lefamulin (Xenleta), concentrate for solution for infusion, coated tablet, age-appropriate oral solid dosage form, intravenous use, oral use, including changes to the deferral, 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

A waiver for lefamulin (Xenleta), concentrate for solution for infusion, coated tablet, age-appropriate oral solid dosage form, intravenous use, oral use, the details of which are set out in the opinion of the Paediatric Committee the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

This decision is addressed to Nabriva Therapeutics DAC, Alexandra House, Office 225/227, The Sweepstakes, Ballsbridge, D04 C7H2 - Dublin, Ireland.

EMA/PDCO/690304/2022
Amsterdam, 11 November 2022

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

EMEA-002075-PIP01-16-M03

Scope of the application

Active substance(s):

Lefamulin

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of bacterial community-acquired pneumonia

Pharmaceutical form(s):

Concentrate for solution for infusion

Coated tablet

Age-appropriate oral solid dosage form

Route(s) of administration:

Intravenous use

Oral use

Name/corporate name of the PIP applicant:

Nabriva Therapeutics DAC

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Nabriva Therapeutics DAC submitted to the European Medicines Agency on 28 July 2022 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0241/2017 issued on 4 September 2017 and the decision P/0066/2019 issued on 22 March 2019.

The application for modification proposed changes to the agreed paediatric investigation plan and to the deferral and proposed a waiver.

The procedure started on 12 September 2022.

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified. A waiver for a new paediatric subset has been added.

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 and to the deferral in the scope set out in the Annex I of this opinion;
   - to grant a waiver for one or more subsets of the paediatric population concluded in accordance with Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, 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 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 bacterial community-acquired pneumonia

The waiver applies to:

- the paediatric population from birth to less than 2 months of age;
- concentrate for solution for infusion, coated tablet, age-appropriate oral solid dosage form, intravenous use, oral use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

2. Paediatric investigation plan

2.1. Condition

Treatment of bacterial community-acquired pneumonia

2.1.1. Indication(s) targeted by the PIP

Treatment of community-acquired pneumonia

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

From 2 months to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Concentrate for solution for infusion

Coated tablet

Age-appropriate oral solid dosage form

2.1.4. Measures

Area	Description
Quality-related studies	**Study 1 - NAB-BC-3781-FDF-Oral Pediatric** Development of age-appropriate oral solid dosage form for use in children 2 months to less than 12 years of age
Non-clinical studies	**Study 2 - Dose range-finding juvenile toxicity study AB21557** Pharmacokinetic and tolerability dose range finding juvenile toxicity study in Sprague-Dawley rat testing the oral, intravenous (IV) and subcutaneous (SC) route

	Study 3 - Reprotox: (enhanced) pre- and postnatal develop AB21312 Pre- and post-natal development study via intravenous route in the rat **Study 4 - Dose range-finding juvenile toxicity study AB21770** Pharmacokinetic and tolerability dose range finding juvenile toxicity study in Sprague-Dawley rat testing the oral route **Study 5 - Pharmacology: *in vitro* binding study NAB-BC-3781-PKPD-PPB** *In vitro* protein binding in plasma of paediatric subjects using equilibrium dialysis to determine the *in vitro* plasma protein binding of different age groups **Study 6 - Definitive juvenile toxicity study AB21568** Repeated dose toxicity study in juvenile Sprague-Dawley rats
Clinical studies	**Study 7 - NAB-BC-3781-1201** Open-label, randomised, crossover study to evaluate the absolute and relative bioavailability and pharmacokinetics (PK) of a 600 mg oral paediatric formulation of lefamulin in comparison to lefamulin 150 mg administered intravenously and 600 mg IR tablet administered orally in healthy adult volunteers **Study 8 - NAB-BC-3781-1202_IV** Open-label, non-controlled trial to evaluate PK and safety of intravenous lefamulin in children from 2 months to less than 18 years of age with suspected or confirmed bacterial infection **Study 9 - NAB-BC-3781-1203_PO** Open-label, non-controlled trial to evaluate PK and safety of oral lefamulin in children from 2 months to less than 18 years of age with suspected or confirmed bacterial infection **Study 10 - NAB-BC-3781-2201** Open-label, randomised, active-control trial to evaluate safety, pharmacokinetics and efficacy of lefamulin in children from 2 months to less than 18 years of age with community-acquired bacterial pneumonia (CABP)
Extrapolation, modelling and simulation studies	**Study 11 - NAB-BC-3781-1202-PopPK** Population PK model to establish the appropriate dose of lefamulin in children in Study 8 and Study 9 **Study 12 - NAB-BC-3781-1202-PBPK**

	PK / PD model to confirm the appropriate dose of lefamulin in children less than 2 years of age in Part B of Study 8 and Study 9 **Study 13 - NAB-BC-3781-2201-popPK** Update of population PK model after Study 10 with confirmation of dose recommendations for lefamulin in paediatric patients with suspected or confirmed bacterial infection
Other studies	Not applicable
Other measures	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 2027
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:

Condition(s) and authorised indication(s)

1. Treatment of bacterial community-acquired pneumonia

Authorised indication(s):

- Xenleta is indicated for the treatment of community-acquired pneumonia (CAP) in adults when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP or when these have failed (see section 5.1).
  - Invented name(s): Xenleta
  - Authorised pharmaceutical form(s): concentrate for solution for intravenous infusion, film-coated tablet
  - Authorised route(s) of administration: intravenous use, oral use
  - Authorised via centralised procedure