EMA/170272/2023

European Medicines Agency decision

P/0160/2023

of 12 May 2023

on the acceptance of a modification of an agreed paediatric investigation plan for bupivacaine / meloxicam (Zynrelef), (EMEA-002246-PIP01-17-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/0013/2019 issued on 3 January 2019, the decision P/0088/2020 issued on 18 March 2020 and the decision P/0182/2021 issued on 10 May 2021,

Having regard to the application submitted by Heron Therapeutics B.V. on 16 December 2022 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 31 March 2023, 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 and to the deferral.

(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.

[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 bupivacaine / meloxicam (Zynrelef), prolonged-release wound solution, intralesional 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

This decision is addressed to Heron Therapeutics B.V., Herengracht 500, 1017 CB – Amsterdam, The Netherlands.

EMA/PDCO/4985/2023 Corr[1]
Amsterdam, 31 March 2023

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

EMEA-002246-PIP01-17-M03

Scope of the application

Active substance(s):

Bupivacaine / meloxicam

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of acute postoperative pain

Pharmaceutical form(s):

Prolonged-release wound solution

Route(s) of administration:

Intralesional use

Name/corporate name of the PIP applicant:

Heron Therapeutics B.V.

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Heron Therapeutics B.V. submitted to the European Medicines Agency on 16 December 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/0013/2019 issued on 3 January 2019, the decision P/0088/2020 issued on 18 March 2020 and the decision P/0182/2021 issued on 10 May 2021.

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

The procedure started on 30 January 2023.

[1] 2 May 2023

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified.

Pharmaceutical form and route of administration were amended.

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.

   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 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 acute postoperative pain

2.1.1. Indication(s) targeted by the PIP

Treatment of acute postoperative pain

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)

Prolonged-release wound solution

2.1.4. Measures

Area	Description
Quality-related studies	Not applicable
Non-clinical studies	**Study 1** Definitive juvenile toxicity study to assess the potential general toxicity of meloxicam including the development of kidney, liver, lung, and testes in neonatal animals (HTX-011-nonclinical-2) **Study 2** Definitive juvenile toxicity study to assess the potential toxicity of the dimethyl sulfoxide excipient on the CNS via histopathology, long-term functional and cognitive assessments and ophthalmic examinations (HTX-011-nonclinical-1)
Clinical studies	**Study 3** Randomised, double-blind, active controlled, multicentre study to evaluate the PK, PD, and safety and tolerability of a single-dose administration into the surgical site of HTX-011 compared with bupivacaine HCl 0.25% (without epinephrine) in adolescents and children from 3 to less than 18 years of age undergoing unilateral open inguinal herniorrhaphy (HTX-011-clinical-1)

	Study 4 Randomised, double-blind, active controlled, multicentre study to evaluate the PK, safety and pharmacodynamics of a single-dose administration into the surgical site of HTX-011 compared with bupivacaine HCl 0.25% in children from birth to less than 3 years of age undergoing unilateral open inguinal herniorrhaphy (HTX-011-clinical-2)
Extrapolation, modelling and simulation studies	**Study 5** Step-up (physiologically based) pharmacokinetic (PBPK) Modelling and Simulation to support dose selection for adolescents (12 to less than 18 years of age) (HTX-011-PBPK-1) **Study 6** Step-up (physiologically based) PBPK Modelling and Simulation to support dose selection for children (6 to less than 12 years of age) (HTX-011-PBPK-2) **Study 7** Step-up (physiologically based) PBPK Modelling and Simulation to support dose selection for children (3 to less than 6 years of age) (HTX-011-PBPK-3) **Study 8** Step-up (physiologically based) PBPK Modelling and Simulation to support dose selection for neonates and infants (from birth to less than 3 years of age) (HTX-011-PBPK-4) **Study 9** Step-down Population PK model (assumption: Linear PK) (HTX-011-PPK-1) **Study 10** Step-down Population PK model (assumption: Linear PK) (HTX-011-PPK-2) **Study 11** Step-down Population PK model (assumption: Linear PK) (HTX-011-PPK-3) **Study 12** Step-down Population PK model (assumption: Linear PK) (HTX-011-PPK-4)
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 May 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:

Condition(s) and authorised indication(s)

1. Treatment of acute postoperative pain

Authorised indication(s):

- Zynrelef is indicated for treatment of somatic postoperative pain from small- to medium-sized surgical wounds in adults
  - Invented name(s): Zynrelef
  - Authorised pharmaceutical form(s): Prolonged-release wound solution
  - Authorised route(s) of administration: Intralesional use
  - Authorised via centralised procedure