EMA/586778/2019

European Medicines Agency decision

P/0364/2019

of 4 November 2019

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for remimazolam (as besylate) (EMEA-001880-PIP02-19) 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/0364/2019

of 4 November 2019

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for remimazolam (as besylate) (EMEA-001880-PIP02-19) 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 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 application submitted by PAION Deutschland GmbH on 25 March 2019 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 18 October 2019, 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.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

A paediatric investigation plan for remimazolam (as besylate), powder for solution for injection or infusion, nasal powder, intravenous use, intranasal 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 remimazolam (as besylate), powder for solution for injection or infusion, nasal powder, intravenous use, intranasal 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 remimazolam (as besylate), powder for solution for injection or infusion, nasal powder, intravenous use, intranasal 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 PAION Deutschland GmbH, Martinstrasse 10-12, 52062 – Aachen, Germany.

EMA/PDCO/419973/2019
Amsterdam, 18 October 2019

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

EMEA-001880-PIP02-19

Scope of the application

Active substance(s):

Remimazolam (as besylate)

Conditions:

General anaesthesia

Sedation

Pharmaceutical form(s):

Powder for solution for injection or infusion

Nasal powder

Route(s) of administration:

Intravenous use

Intranasal use

Name/corporate name of the PIP applicant:

PAION Deutschland GmbH

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, PAION Deutschland GmbH submitted for agreement to the European Medicines Agency on 25 March 2019 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 30 April 2019.

Supplementary information was provided by the applicant on 15 July 2019.

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)(a) of said Regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population, and 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 Norwegian Paediatric Committee member 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 annex 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:

General anaesthesia

The waiver applies to:

- the paediatric population from birth to less than 6 months of age
- powder for solution for injection or infusion, intravenous use;
- on the grounds that the specific medicinal product is likely to be unsafe;

And

- the paediatric population from birth to less than 18 years of age;
- nasal powder; intranasal 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.

2. Paediatric investigation plan

2.1. Condition:

Sedation

2.1.1. Indication(s) targeted by the PIP

Procedural sedation

Sedation of mechanically ventilated patients

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)

Powder for solution for injection or infusion

Nasal powder

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	2	**Study 1** (Intranasal formulation finding): Development of a paediatric formulation for intranasal use **Study 2** (Intranasal device finding): Development of a device for delivery of the paediatric formulation for intranasal use
Non-clinical studies	3	**Study 3** (Juvenile minipigs intranasal formulation study): Juvenile minipigs study of pharmacokinetics, pharmacodynamics, bioavailability and local tolerability of candidate intranasal formulations of remimazolam intended for paediatric use. **Study 4** (Juvenile minipigs intranasal efficacy study): Juvenile minipigs repeated administration study to assess pharmacokinetics; pharmacodynamics, bioavailability, efficacy and local tolerability of the final remimazolam formulation for intranasal paediatric use, loaded into the chosen delivery device. **Study 5** (Juvenile minipigs intravenous toxicity study): Juvenile minipigs study to assess toxicity, pharmacodynamics (level of sedation) and pharmacokinetics of remimazolam after single prolonged administration as continuous intravenous infusion. *This study is the same as Study 5 in the condition general anaesthesia.*
Clinical studies	4	**Study 6** (Paediatric trial of intravenous sedation for short procedures): Open-label, multicentre uncontrolled trial to assess efficacy, safety and pharmacokinetics of intravenous (IV) remimazolam in paediatric patients undergoing sedation for diagnostic or therapeutic mixed medical procedures. **Study 7** (Randomized controlled trial of intravenous sedation for short procedures): Randomized, double-blind, active-controlled multicentre trial to establish superiority of intravenous (IV) remimazolam over dexmedetomidine in paediatric patients undergoing sedation for painless or minimally painful procedures. **Study 8** ***(Paediatric trial of intranasal sedation for short procedures:*** Open-label, multicentre uncontrolled trial to assess effect, safety and pharmacokinetics of intranasal (IN) remimazolam in paediatric patients undergoing sedation for painless procedures. **Study 9** (Paediatric Intravenous Intensive Care Unit Sedation Trial): Open-label, randomized, active controlled, parallel group, trial comparing remimazolam with midazolam in paediatric patients requiring sedation in the intensive care unit (ICU).

Extrapolation, modelling and simulation studies	1	**Study 10:** PK/PD modelling and simulation study to evaluate the use of the intravenous and the intranasal formulation of remimazolam in the paediatric population. *This study is the same as study 10 in the condition general anaesthesia*
Other studies	0	Not applicable.
Other measures	0	Not applicable.

2.2. Condition:

General anaesthesia

2.2.1. Indication(s) targeted by the PIP

General anaesthesia

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

From 6 months to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Powder for solution for injection or infusion

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable.
Non-clinical studies	1	**Study 5** (Juvenile minipigs intravenous toxicity study): Juvenile minipigs study to assess toxicity, pharmacodynamics (level of sedation) and pharmacokinetics of remimazolam after single prolonged administration as continuous intravenous infusion. *This study is the same as study 5 in the condition sedation*
Clinical studies	1	**Study 11** (Paediatric Intravenous General Anaesthesia Trial): Open-label, randomized, active controlled, parallel group, multicentre trial comparing remimazolam with propofol for induction and maintenance of general anaesthesia in paediatric patients undergoing elective mixed surgical procedures
Extrapolation, modelling and simulation studies	1	**Study 10** (Paediatric pharmacokinetic/pharmacodynamics model): PK/PD modelling and simulation study to evaluate the use of the intravenous and the intranasal formulation of remimazolam in the paediatric population.

		This study is the same as study 10 in the condition sedation
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 2031
Deferral for one or more measures contained in the paediatric investigation plan:	Yes