EMA/251327/2021

European Medicines Agency decision

P/0180/2021

of 10 May 2021

on the acceptance of a modification of an agreed paediatric investigation plan for remimazolam (as besylate), (Byfavo), (EMEA-001880-PIP02-19-M02) 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 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 European Medicines Agency's decision P/0364/2019 issued on 4 November 2019,

Having regard to the application submitted by PAION Deutschland GmbH on 21 December 2020 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 26 March 2021, 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.

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

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

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for remimazolam (as besylate), (Byfavo), powder for solution for injection or infusion, orodispersible film, age-appropriate formulation, intravenous use, buccal use, 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 PAION Deutschland GmbH, Martinstrasse 10-12, 52062 – Aachen, Germany.

EMA/PDCO/24425/2021
Amsterdam, 26 March 2021

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

EMEA-001880-PIP02-19-M02

Scope of the application

Active substance(s):

Remimazolam (as besylate)

Invented name:

Byfavo

Condition(s):

General Anaesthesia

Sedation

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Powder for solution for injection or infusion

Orodispersible film

Age-appropriate formulation

Route(s) of administration:

Intravenous use

Buccal use

Name/corporate name of the PIP applicant:

PAION Deutschland GmbH

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, PAION Deutschland GmbH submitted to the European Medicines Agency on 21 December 2020 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/0364/2019 issued on 4 November 2019.

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

The procedure started on 26 January 2021.

Scope of the modification

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

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 in the scope set out in the Annex I of this opinion.

   The Norwegian Paediatric Committee member 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:

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;
- orodispersible film, buccal use;
- age-appropriate formulation, buccal 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

Orodispersible film

Age-appropriate formulation

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	2	**Study 1** Development of a paediatric formulation for buccal use **Study 2** *Study 2 deleted in procedure EMEA-001880-PIP02-19-M02* **Study 12** Development of a formulation suitable for use in paediatric patients from 6 months to less than 18 years of age *Study 12 added in procedure EMEA-001880-PIP02-19-M02*
Non-clinical studies	3	**Study 3** Juvenile minipigs study of pharmacokinetics, pharmacodynamics, bioavailability and local tolerability of candidate buccal formulations of remimazolam intended for paediatric use **Study 4** Juvenile minipigs repeated administration study to assess pharmacokinetics; pharmacodynamics, bioavailability, efficacy and local tolerability of the remimazolam orodispersible film **Study 5** 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** (CNS7056-026 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, 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** Open-label, multicentre uncontrolled trial to assess effect, safety and pharmacokinetics of buccal remimazolam in paediatric patients undergoing sedation for painless procedures **Study 9** 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 buccal 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 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** 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** PK/PD modelling and simulation study to evaluate the use of the intravenous and the buccal 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

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Procedural sedation

Authorised indication(s):

- Remimazolam is indicated in adults for procedural sedation.

Authorised pharmaceutical form(s):

Powder for solution for injection

Authorised route(s) of administration:

Intravenous use