MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

accept of change(s) to the agreed paediatric investigation plan and to the deferral

MHRA-100553-PIP01-22-M01

Scope of the Application

Active Substance(s)

REMIMAZOLAM BESYLATE

Condition(s)

Sedation, General Anaesthesia

Pharmaceutical Form(s)

Orodispersible film; Powder for solution for injection/infusion; Age-appropriate formulation

Route(s) of Administration

BUCCAL USE; INTRAVENOUS USE

Name / Corporate name of the PIP applicant

PAION UK LIMITED

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, PAION UK LIMITED submitted to the licensing authority on 07/06/2022 12:25 BST an application for a Modification

The procedure started on 09/02/2023 14:24 GMT

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to accept change(s) to the agreed paediatric investigation plan and to the deferral

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This decision is forwarded to the applicant, together with its annex and appendix.

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Final Decision Letter

MHRA-100553-PIP01-22-M01

Of 29/03/2023 09:28 BST

On the adopted decision for REMIMAZOLAM BESYLATE (MHRA-100553-PIP01-22-M01) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on modification of a paediatric investigation plan (including modification of a waiver or deferral included in that paediatric investigation plan)

This decision applies to a Modification for REMIMAZOLAM BESYLATE, Powder for solution for injection/infusion; Orodispersible film; Age-appropriate formulation , BUCCAL USE; INTRAVENOUS USE .

This decision is addressed to PAION UK LIMITED, Heussstrasse 25, Aachen, GERMANY, 52078

ANNEX I

1. Waiver

1.1 Condition:

General anaesthesia The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 6 months of age Pharmaceutical form(s): Powder for solution for injection or infusion Route(s) of administration: INTRAVENOUS USE Reason for granting waiver: on the grounds that the specific medicinal product is likely to be unsafe The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 18 years of age Pharmaceutical form(s): Orodispersible film Route(s) of administration: BUCCAL USE Reason for granting waiver: 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(s):

Sedation, General anaesthesia

2.2 Indication(s) targeted by the PIP:

Procedural sedation; Sedation of mechanically ventilated patients. General anaesthesia

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

The paediatric population from birth to less than 18 years of age. The paediatric population from 6 months to less than 18 years of age.

2.4 Pharmaceutical Form(s):

Powder for solution for injection or infusion Orodispersible film Age-appropriate formulation

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1 Development of a paediatric formulation for buccal use. Study 2 This study was deleted in procedure MHRA-100553-PIP01-22-M01. Study 12 Development of a formulation suitable for use in paediatric patients from birth to less than 18 years of age. This study was added in procedure MHRA-100553-PIP01-22-M01.
Non-Clinical Studies	2	Study 3 Juvenile minipigs study of pharmacokinetics, pharmacodynamics, bioavailability and local tolerability of candidate buccal formulations of remimazolam intended for paediatric use. Study 4 This study was deleted in procedure MHRA-100553-PIP01-22-M01. Study 5 Juvenile rat study to assess toxicity, pharmacodynamics (level of sedation) and pharmacokinetics of remimazolam after single exposure during the brain growth spurt. This study is the same as Study 5 in the condition: general anaesthesia.
Clinical Studies	5	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 Randomised, 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, randomised, active controlled, parallel group, trial comparing remimazolam with midazolam in paediatric patients requiring sedation in the intensive care unit (ICU). Study 11 Open-label, randomised, 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, Modeling & 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.

3. Follow-up, completion and deferral of a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	30/06/2031
Deferral of one or more studies contained in the paediatric investigation plan:	Yes