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 changes to the agreed paediatric investigation plan and to the deferral

MHRA-100046-PIP01-21-M01

Scope of the Application

Active Substance(s)

cenobamate; cenobamate

Condition(s)

Treatment of epilepsy

Pharmaceutical Form(s)

Film-coated tablet, Tablet, Oral suspension, Solution for injection

Route(s) of Administration

Oral use; Parenteral use; Gastric use;

Name / Corporate name of the PIP applicant

Arvelle Therapeutics Netherlands B.V.

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Arvelle Therapeutics Netherlands B.V. submitted to the licensing authority on 22/02/2021 20:29 GMT an application for a Modification

The procedure started on 18/03/2021 10:45 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 changes 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-100046-PIP01-21-M01

Of 19/03/2021 13:01 GMT

On the adopted decision for cenobamate (MHRA-100046-PIP01-21-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 cenobamate, Film-coated tablet, Tablet, Oral suspension, Solution for injection , Oral use, Parenteral use .

This decision is addressed to Arvelle Therapeutics Netherlands B.V., Johannes Vermeerplein 9, Amsterdam, Netherlands, 1071DV

ANNEX I

1. Waiver

1.1 Condition:

Not applicable

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of epilepsy

2.2 Indication(s) targeted by the PIP:

Treatment of epilepsy

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

The paediatric population from birth to less than 18 years

2.4 Pharmaceutical Form(s):

Film-coated tablet; Tablet; Oral suspension; Solution for injection

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1: Development of an oral liquid suspension with minimum loading of 10 mg/ml. (CMC0X1) Study 2: Development of parenteral formulation with appropriate dose load, volume, dispensing accuracy and excipients that are suitable for the neonate population. (CMC0X2)
Non-Clinical Studies	1	Study 3: Local tolerance test: local tolerance related to intravascular and perivascular administration of the parenteral formulation (NC0X1)
Clinical Studies	7	Study 4 Open-label study to evaluate pharmacokinetics, safety and exploratory efficacy of cenobamate as adjunctive therapy in the paediatric population from 2 to less than 18 years of age with epilepsy with focal onset seizures. (C0X1) Study 5 Open-label study to evaluate pharmacokinetics, safety and exploratory efficacy of cenobamate as adjunctive therapy in the paediatric population from 1 month to less than 2 years of age with epilepsy with focal onset seizures. (C0X2) Study 6 Randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of cenobamate as adjunctive therapy in the paediatric population from 1 month to less than 4 years of age with

		epilepsy with focal onset seizures. (C0X3) Study 7 Open-label study to evaluate pharmacokinetics, safety and efficacy of cenobamate in the paediatric population from 2 years to less than 18 years of age with a range of paediatric epilepsy syndromes with generalized seizures. (C0X5) Study 8 Randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study C0X5. (C0X6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (C0X8) Study 10 Long-term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies C0X1, C0X2, C0X3, C0X5, C0X6 and C0X8 (C0X9)
Extrapolation, Modeling & Simulation Studies	5	Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X1. PopPK study to predict initial paediatric doses to be used in studies C0X2 and C0X5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be used in studies C0X8

		and paediatric doses to be used in study C0X3 (MS2) Study 13 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X8 (MS4) Study 14 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X5 (MS5) Study 15 Extrapolation study for paediatric patients from 4 to less than 12 years of age with epilepsy with focal-onset seizures (MS3)
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:	Yes
Date of completion of the paediatric investigation plan:	31/10/2029
Deferral of one or more studies contained in the paediatric investigation plan:	Yes