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 change(s) to the agreed paediatric investigation plan (MHRA-100046-PIP01-21-M04) and to the deferral

MHRA-100046-PIP01-21-M05

Scope of the Application

Active Substance(s)

CENOBAMATE

Condition(s)

Treatment of epilepsy

Pharmaceutical Form(s)

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

Route(s) of Administration

ORAL USE GASTRIC USE PARENTERAL USE

Name / Corporate name of the PIP applicant

Angelini Pharma UK-I Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Angelini Pharma UK-I Limited submitted to the licensing authority on 01/08/2024 11:51 BST an application for a Modification

The procedure started on 06/09/2024 11:12 BST

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-100046-PIP01-21-M05

Of 08/11/2024 07:14 GMT

On the adopted decision for CENOBAMATE (MHRA-100046-PIP01-21-M05) 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, Tablet, Film-coated tablet, Oral suspension, Solution for injection , ORAL USE; GASTRIC USE; PARENTERAL USE .

This decision is addressed to Angelini Pharma UK-I Limited, 6th Floor, Napier House, 24 High Holborn, London, UNITED KINGDOM, WC1V 6AZ

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 of age

2.4 Pharmaceutical Form(s):

Tablet Film-coated tablet Oral suspension Solution for injection

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1 (CMC0X1) Development of an oral liquid suspension with minimum loading of 10 mg/ml. Study 2 (CMC0X2) Development of parenteral formulation with appropriate dose load, volume, dispensing accuracy and excipients that are suitable for the neonatal population.
Non-Clinical Studies	1	Study 3 (NC0X1) Non-clinical study to evaluate the local tolerance related to intravascular and perivascular administration of the parenteral formulation.
Clinical Studies	4	Study 4 (C0X39/C0X40) Open-label study consisting of two linked clinical protocols (C0X39/C0X40) to evaluate the pharmacokinetics, safety and exploratory efficacy of cenobamate as adjunctive therapy in the paediatric population from 2 years to less than 18 years of age with epilepsy with focal onset seizures. Study 5 (C0X2) 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. Study 6 (COX3) Deleted during procedure MHRA-100046-PIP01-21-M04. Study 7 (C0X5) Deleted during procedure MHRA-100046-PIP01-21-

		M05 Study 8 (C0X6) 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. Study 9 (C0X8) 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. Study 10 (COX9) Deleted during procedure MHRA-100046-PIP01-21-M04.
Extrapolation, Modeling & Simulation Studies	5	Study 11 (MS1) PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X39/40. PopPK study to predict initial paediatric doses to be used in studies C0X2 and C0X5. Study 12 (MS2) Deleted during procedure MHRA-100046-PIP01-21-M04. Study 13 (MS4) PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X8. Study 14 (MS5) Deleted during procedure MHRA-100046-PIP01-21-M05 Study 15 (MS3) Extrapolation study for paediatric patients from 1 month to less than 12 years of age with epilepsy with focal-onset seizures. Study 20 (MS6) Added during procedure MHRA-100046-PIP01-21-M05 Population PK model aimed at the characterization of the pharmacokinetics of cenobamate in the paediatric population with epilepsy from 1 month to less than 18 years of age. Extrapolation Plan Added during procedure MHRA-100046-PIP01-21-M05 Studies 4, 5, 11 and 15 are part of the extrapolation plan of efficacy data from adult and adolescent patients to the paediatric population from 1 month to less than 18 years of age with focal onset seizures. Studies 16, 17, 18 and 20 are part of the

		extrapolation plan of efficacy data from adult and adolescent patients to the paediatric population from 2 years to less than 18 years of age with primary generalized tonic-clonic (PGTC) seizures in the setting of idiopathic generalized epilepsy (IGE).
Other Studies	4	Studies added during procedure MHRA-100046-PIP01-21-M04 Study 16 (COX25) Randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of cenobamate as adjunctive therapy in subjects from 12 years of age with primary generalised tonic-clinic (PGTC) seizures in the setting of idiopathic generalised epilepsy. Study 17 (COX33) Open-label extension study to evaluate the long-term safety of cenobamate adjunctive therapy in subjects from 12 years of age with primary generalised tonic-clinic (PGTC) seizures in the setting of idiopathic generalised epilepsy. Study 18 (COX10) Open-label, single arm study to evaluate safety, PK and activity of cenobamate in children from 2 years of age to < 12 years of age with primary generalised tonic-clinic (PGTC) seizures in the setting of idiopathic generalised epilepsy (IGE). Study 19 Long term safety observation within the compassionate use program.
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:	31/01/2034
Deferral of one or more studies contained in the paediatric investigation plan:	Yes