EMA/256562/2023

European Medicines Agency decision

P/0214/2023

of 14 June 2023

on the acceptance of a modification of an agreed paediatric investigation plan for cenobamate (Ontozry), (EMEA-002563-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.

European Medicines Agency decision

P/0214/2023

of 14 June 2023

on the acceptance of a modification of an agreed paediatric investigation plan for cenobamate (Ontozry), (EMEA-002563-PIP02-19-M02) 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 Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0120/2020 issued on 18 March 2020 and the decision P/0300/2021 issued on 13 August 2021,

Having regard to the application submitted by Angelini Pharma S.p.A on 20 January 2023 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and proposing a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 26 April 2023, 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 and to the deferral and on the refusal of a waiver.

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

(3) It is therefore appropriate to adopt a decision refusing a waiver.

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

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for cenobamate (Ontozry), tablet, film-coated tablet, age-appropriate oral liquid dosage form, age-appropriate dosage form for parenteral use, oral use, parenteral use, gastric use, including changes to the deferral, 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

A waiver for cenobamate (Ontozry), tablet, film-coated tablet, age-appropriate oral liquid dosage form, age-appropriate dosage form for parenteral use, oral use, parenteral use, gastric use, the details of which are set out in the opinion of the Paediatric Committee the European Medicines Agency annexed hereto, together with its appendices, is hereby refused.

Article 3

This decision is addressed to Angelini Pharma S.p.A, 70 Viale Amelia, 00181 – Rome, Italy.

EMA/PDCO/50616/2023 Corr[1]
Amsterdam, 26 April 2023

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

EMEA-002563-PIP02-19-M02

Scope of the application

Active substance(s):

Cenobamate

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of epilepsy

Pharmaceutical form(s):

Tablet

Film-coated tablet

Age-appropriate oral liquid dosage form

Age-appropriate dosage form for parenteral use

Route(s) of administration:

Oral use

Parenteral use

Gastric use

Name/corporate name of the PIP applicant:

Angelini Pharma S.p.A

[1] 22 May 2023

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Angelini Pharma S.p.A submitted to the European Medicines Agency on 20 January 2023 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0120/2020 issued on 18 March 2020 and the decision P/0300/2021 issued on 13 August 2021.

The application for modification proposed changes to the agreed paediatric investigation plan and to the deferral and proposed a waiver.

The procedure started on 27 February 2023.

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 and to the deferral in the scope set out in the Annex I of this opinion;
    - to refuse the granting of a waiver for some of the subsets of the paediatric population and the above mentioned condition as it does not meet the grounds detailed in Article 11(1) of said Regulation.
2. The measures and timelines of the paediatric investigation plan 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

Not applicable

2. Paediatric investigation plan

2.1. Condition:

Treatment of epilepsy

2.1.1. Indication(s) targeted by the PIP

Treatment of epilepsy

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)

Tablet

Film-coated tablet

Age-appropriate oral liquid dosage form

Age-appropriate dosage form for parenteral use

2.1.4. Measures

Area	Description
Quality-related studies	**Study 1** Development of an oral liquid suspension with minimum loading of 10 mg/ml (CMC0X1) **Study 2** Development of a parenteral formulation with appropriate dose load, volume, dispensing accuracy and excipients that are suitable for the neonatal population (CMC0X2)
Non-clinical studies	**Study 3** Non-clinical study to evaluate the local tolerance of the intravascular and perivascular administration of the parenteral formulation (NC0X1)
Clinical studies	**Study 4** 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 (C0X39/C0X40) **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 - *deleted in procedure EMEA-002563-PIP02-19-M02*** **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 - *deleted in procedure EMEA-002563-PIP02-19-M02*** **Study 16 - *added in procedure EMEA-002563-PIP02-19-M02*** Randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of cenobamate as adjunctive therapy in subjects equal to and above 12 years of age with primary generalized tonic-clonic (PGTC) seizures in the setting of idiopathic generalized epilepsy (IGE). (COX25) **Study 17 - *added in procedure EMEA-002563-PIP02-19-M02*** Open-label extension study to evaluate the long-term safety of cenobamate adjunctive therapy in children equal to and above 12 years of age with primary generalized tonic-clonic (PGTC) seizures in the setting of idiopathic generalised epilepsy. (COX33) **Study 18 - *added in procedure EMEA-002563-PIP02-19-M02*** Open label, single arm study to evaluate safety, PK and activity of cenobamate in children from 2 years to less than 12 years of age

	with primary generalized tonic-clonic (PGTC) seizures in the setting of idiopathic generalized epilepsy (IGE) (COX10)
Extrapolation, modelling and simulation studies	**Study 11** 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 (MS1) **Study 12 – *deleted in procedure EMEA-002563-PIP02-19-M02*** **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 1 month to less than 12 years of age with epilepsy with focal-onset seizures (MS3)
Other studies	**Study 19 - *added in procedure EMEA-002563-PIP02-19-M02*** Long term safety observation within the compassionate use program
Other measures	Not applicable

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By January 2031
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Information provided by the applicant:

Condition(s) and authorised indication(s):

1. Treatment of epilepsy

Authorised indication(s):

- Adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic medicinal products
  - Invented name(s): Ontozry
  - Authorised pharmaceutical form(s): Tablet, film-coated tablet
  - Authorised route(s) of administration: Oral use
  - Authorised via centralised procedure