EMA/816613/2018

European Medicines Agency decision

P/0407/2018

of 19 December 2018

on the acceptance of a modification of an agreed paediatric investigation plan for lumacaftor / ivacaftor (Orkambi), (EMEA-001582-PIP01-13-M08) 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/0118/2014 issued on 6 May 2014, the decision P/0337/2014 issued on 22 December 2014, the decision P/0185/2015 issued on 24 August 2015, the decision P/0220/2016 issued on 26 August, 2016, the decision P/0086/2017 issued on 16 March 2017, the decision P/0198/2017 issued on 14 July 2017 and the decision P/0005/2018 issued on 15 January 2018,

Having regard to the application submitted by Vertex Pharmaceuticals (Europe) Limited on 31 July 2018 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 16 November 2018, 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.

(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.

[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 lumacaftor / ivacaftor (Orkambi), film-coated tablet, granules, oral 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

This decision is addressed to Vertex Pharmaceuticals (Europe) Limited, 2 Kingdom Street, W2 6BD – London, United Kingdom.

EMA/PDCO/599831/2018
London, 16 November 2018

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

EMEA-001582-PIP01-13-M08

Scope of the application

Active substance(s):

Lumacaftor / ivacaftor

Invented name:

Orkambi

Condition(s):

Treatment of cystic fibrosis

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Granules

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Vertex Pharmaceuticals (Europe) Limited

Information about the authorised medicinal product:

See Annex II

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Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Vertex Pharmaceuticals (Europe) Limited submitted to the European Medicines Agency on 31 July 2018 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0118/2014 issued on 6 May 2014, the decision P/0337/2014 issued on 22 December 2014, the decision P/0185/2015 issued on 24 August 2015, the decision P/0220/2016 issued on 26 August 2016, the decision P/0086/2017 issued on 16 March 2017, the decision P/0198/2017 issued on 14 July 2017 and the decision P/0005/2018 issued on 15 January 2018.

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

The procedure started on 18 September 2018.

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.

   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 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 cystic fibrosis

2.1.1. Indication(s) targeted by the PIP

Treatment of cystic fibrosis

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)

Film-coated tablet

Granules

2.1.4. Measures

Area	Number of studies	Description
Quality-related studies	2	• Development of an age-appropriate fixed-dose combination film-coated tablet for children aged 6 to less than 12 years old; • Development of an age appropriate oral solid formulation for children below 6 years of age (fixed-dose combination granules).
Non-clinical studies	7	• Six-month oral (gavage) toxicity and toxicokinetics study with lumacaftor and VRT-0995096 in rats with a 1-month recovery (VX-809-TX-012); • 3-month oral (gavage) toxicity and toxicokinetics study with lumacaftor, ivacaftor, and VRT-0995096 in rats with a 1-month recovery (VX-809-TX-013); • 12-month oral (gavage) toxicity and toxicokinetics study with lumacaftor in Beagle dogs with a 1-month recovery (VX-809-TX-014); • Developmental and Perinatal/Postnatal Reproduction Toxicity Study in Rats, Including a Postnatal Behavioral/Functional Evaluation (VX-809-TX-017); • Fertility and early embryonic development study in rats with lumacaftor and VRT-0995096 (VX-809-TX-016);

		• Oral (gavage) dose range finding study in juvenile rats; • Oral (gavage) toxicity and toxicokinetics study in juvenile rats with 4-week recovery.
Clinical studies	10	• Open-label, multi-dose study to evaluate the pharmacokinetics (PK) and safety of lumacaftor in combination with ivacaftor and their respective major circulating metabolites in subjects with Cystic Fibrosis (CF) who are homozygous for the F508del-CFTR mutation aged 6 to less than 12 years (VX13-809-011 Part A); • Randomised, double-blind, placebo-controlled study to evaluate efficacy and safety and PK in subjects with CF homozygous for the F508del-CFTR mutation aged 6 to less than 12 years (VX14-809-109); • Randomised, double-blind, placebo-controlled study to evaluate efficacy and safety in subjects with CF who are homozygous for the F508del-CFTR mutation aged 12 to less than 18 years (and adults) (VX12-809-103); • Randomised, double-blind, placebo-controlled study to evaluate efficacy and safety in subjects with CF who are homozygous for the F508del-CFTR mutation aged 12 to less than 18 years (and adults) (VX12-809-104); • Rollover open-label long-term safety and efficacy study in subjects with CF who are homozygous for the F508del-CFTR mutation aged 12 to less than 18 years (and adults) (VX12-809-105); • Pharmacokinetic and safety study in subjects with CF who are homozygous for the F508del-CFTR mutation aged 2 to less than 6 years (VX15-809-115); • Pharmacokinetic and safety study in subjects with CF who are homozygous for the F508del-CFTR mutation from 1 year to less than 2 years of age; • Relative bioavailability study to characterize the PK of the paediatric age appropriate formulation relative to the tablet formulation in healthy adults; • Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation (VX15-809-110). • Pharmacokinetic and safety study in subjects with CF who are homozygous for the F508del-CFTR mutation from birth to less than 1 year of age.
Extrapolation, modelling and simulation studies	0	Not applicable

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:	Yes
Date of completion of the paediatric investigation plan:	By December 2024
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of cystic fibrosis

Authorised indication(s):

- Treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene

Authorised pharmaceutical form(s):

Film-coated tablet

Authorised route(s) of administration:

Oral use