

EMA/387124/2016

European Medicines Agency decision

P/0193/2016

of 15 July 2016

on the acceptance of a modification of an agreed paediatric investigation plan for 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide (VX-661) / ivacaftor (EMEA-001640-PIP01-14-M01) 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 726/2004¹,

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 Agency²,

Having regard to the European Medicines Agency's decision P/0098/2015 issued on 8 May 2015,

Having regard to the application submitted by Vertex Pharmaceuticals (Europe) Ltd. on 7 March 2016 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 27 May 2016, 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 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide (VX-661) / ivacaftor, film-coated tablet, age appropriate oral formulation, 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) Ltd, 2 Kingdom Street, W2 6BD - London, United Kingdom.

Done at London, 15 July 2016

For the European Medicines Agency
Zaïde Frias
Head of Division
Human Medicines Research and Development Support
(Signature on file)

EMA/PDCO/192455/2016

London, 27 May 2016

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan EMA-001640-PIP01-14-M01

Scope of the application

Active substance(s):

1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide (VX-661) / ivacaftor

Condition(s):

Treatment of cystic fibrosis

Pharmaceutical form(s):

Film-coated tablet

Age appropriate oral formulation

Route(s) of administration:

Oral use

Name / corporate name of the PIP applicant:

Vertex Pharmaceuticals (Europe) Ltd.

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Vertex Pharmaceuticals (Europe) Ltd. submitted to the European Medicines Agency on 7 March 2016 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0098/2015 issued on 8 May 2015.

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

The procedure started on 29 March 2016.

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 annex 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 in patients who have at least 1 allele of the F508del mutation in the CFTR gene

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

Age-appropriate oral formulation

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	2	Study 1 Development of an age-appropriate film-coated tablet for children aged 6 to less than 12 years old. Study 2 Development of an age appropriate oral formulation for children below 6 years of age.
Non-clinical studies	4	Study 3 Fertility and early embryonic development oral (gavage) toxicity study with VX-661 in rat. Study 4 Peri and post natal development reproductive toxicology study with VX-661 in rats. Study 5 Oral (gavage) dose-range finding study in juvenile rats.

		Study 6 Oral (gavage) toxicity and toxicokinetics study in juvenile rats with recovery.
Clinical studies	10	Study 7 (VX14-661-106) Randomised, double-blind, placebo-controlled, parallel group, multicenter study to assess the efficacy and long-term safety of VX-661 in combination with ivacaftor in subjects 12 to less than 18 years of age (and adults) with CF who are homozygous for the F508del-CFTR mutation. Study 8 (VX14-661-107) Double-blind, placebo controlled, multicenter study to assess the efficacy and safety of VX-661 co-formulated with Ivacaftor in F508del-CFTR heterozygous subjects with an Ivacaftor- and VX-661 nonresponsive mutation on the second allele, 12 years to less than 18 years of age (and adults). Study 9 (VX14-661-108) Double-blind, placebo and active treatment controlled, 6-sequence, 8 week cross-over study to assess the efficacy and safety of VX-661 co-formulated with ivacaftor in F508del-CFTR heterozygous subjects with a residual function mutation that is potentially ivacaftor responsive on the second allele, 12 years to less than 18 years of age (and adults). Study 10 (VX14-661-109) Double-blind, active-controlled, multicenter study, parallel arm study to assess the efficacy and safety of VX-661 co-formulated with ivacaftor in F508del-CFTR heterozygous subjects with a clinically proven ivacaftor-responsive mutation with a gating defect on the second allele, 12 years to less than 18 years of age (and adults). Study 11 Open-label, multicenter study, to assess the safety and pharmacokinetics of two weeks treatment with single oral doses of VX-661 and ivacaftor in subjects with cystic fibrosis who are homozygous or heterozygous for F508del-CFTR mutation, 6 years to less than 12 years of age. Study 12 Randomised, double-blind, placebo-controlled, parallel, multicentre study to evaluate the efficacy, safety and pharmacokinetics of 24 weeks treatment with VX-661 coformulated with ivacaftor in subjects with cystic fibrosis who are homozygous or heterozygous for F508-del-CFTR mutation, 6 to less than 12 years of age. Study 13 Rollover open-label long-term safety and efficacy study in subjects with CF, 6 to less than 18 years of age (and adults).

		Study 14 Two-part, uncontrolled, multi-centre study to evaluate the safety, PK, PD and efficacy of VX-661 and ivacaftor in subjects with CF who are homozygous or heterozygous for the F508del-CFTR mutation, aged 2 years to less than 6 years. Study 15 Two-part, uncontrolled, multi-centre study to assess the long-term safety and pharmacokinetics in subjects from birth to less than 2 years of age with CF who are homozygous or heterozygous for the F508del CFTR mutation. Study 16 Randomized, single dose, cross-over, relative bioavailability study in healthy adults to characterize PK of age appropriate paediatric formulation relative to the adult formulation.
Extrapolation, modelling and simulation studies	1	Study 17 Modelling and simulation study for dose selection in children from birth to less than 12 years of age.
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 March 2024
Deferral for one or more measures contained in the paediatric investigation plan:	Yes