EMA/130877/2019 Corr

European Medicines Agency decision

P/0090/2019

of 22 March 2019

on the agreement of a paediatric investigation plan and on the granting of a deferral for ivacaftor / tezacaftor/ potassium (benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl)cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide (VX-659) (EMEA-002191-PIP02-17) 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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on the agreement of a paediatric investigation plan and on the granting of a deferral for ivacaftor / tezacaftor/ potassium (benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl)cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide (VX-659) (EMEA-002191-PIP02-17) 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 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 application submitted by Vertex Pharmaceuticals (Europe) Ltd. on 20 April 2018 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 1 February 2019, in accordance with Article 17 of Regulation (EC) No 1901/2006 and Article 21 of said Regulation,

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 agreement of a paediatric investigation plan and on the granting of a deferral.

(2) It is therefore appropriate to adopt a decision agreeing a paediatric investigation plan.

(3) It is therefore appropriate to adopt a decision granting a 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

A paediatric investigation plan for ivacaftor / tezacaftor/ potassium (benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl)cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide (VX-659), film-coated tablet, age-appropriate oral solid dosage form, oral use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A deferral for ivacaftor / tezacaftor/ potassium (benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl)cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide (VX-659), film-coated tablet, age-appropriate oral solid dosage form, oral use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

This decision is addressed to Vertex Pharmaceuticals (Europe) Ltd, 2 Kingdom Street, 9th Floor, W2 6BD – London, United Kingdom.

EMA/PDCO/796672/2018 Corr
London, 1 February 2019

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral

EMEA-002191-PIP02-17

Scope of the application

Active substance(s):

ivacaftor / tezacaftor/ potassium (benzenesulfonyl)({[6-(3-{2-[1-(trifluoromethyl)cyclopropyl]ethoxy}-1H-pyrazol-1-yl)-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridin-3-yl]carbonyl})azanide (VX-659)

Condition(s):

Treatment of cystic fibrosis

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate oral solid dosage form

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Vertex Pharmaceuticals (Europe) Ltd.

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Vertex Pharmaceuticals (Europe) Ltd. submitted for agreement to the European Medicines Agency on 20 April 2018 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation.

The procedure started on 29 May 2018.

Supplementary information was provided by the applicant on 26 October 2018. The applicant proposed modifications to the paediatric investigation plan.

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Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree the paediatric investigation plan in accordance with Article 17(1) of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation.

   The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the agreed 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 from birth to less than 18 years of age either heterozygous for the F508del-CFTR mutation and a mutation that results in minimal function of the CFTR protein (F/MF) or homozygous for the F508del-CFTR mutation (F/F)

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 solid dosage form

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	2	**Study 1 (Q-1)** Development of an age-appropriate fixed-dose combination (FDC) film-coated tablet for children aged 6 to less than 12 years old. **Study 2 (Q-2)** Development of an age appropriate oral solid dosage form for use in children from birth to less than 6 years of age.
Non-clinical studies	1	**Study 3 (N-1)** Oral (gavage) toxicity and toxicokinetics study in juvenile rats.
Clinical studies	7	**Study 4 (C-1)** Randomized, double-blind, placebo-controlled, parallel group, multi-centre study to assess the efficacy and safety of the FDC of VX-659/TEZ(tezacaftor)/IVA(Ivacaftor) in subjects 12 to less than 18 years of age (and adults) with cystic fibrosis (CF) who are heterozygous for F508del and a CFTR mutation of minimal function (F/MF genotypes).

		Study 5 (C-2) Randomized, double-blind, active-controlled, parallel group, multicenter study to assess the efficacy and safety of the FDC of VX-659/TEZ/IVA in subjects with CF who are homozygous for F508del mutation (F/F genotype). **Study 6 (C-3)** Rollover open-label, 96-week long-term safety and efficacy study in subjects with CF, 12 to less than 18 years of age (and adults) who have completed study 4 or 5. **Study 7 (C-4)** Two-part, single-arm, multicenter study to evaluate the safety, PK, PD and efficacy of VX-659/TEZ/IVA in subjects with CF who are 6 to less than 12 years of age and who have F/MF or F/F genotypes. **Study 8 (C-5)** Rollover open-label 96-week long-term safety and efficacy study in subjects with CF, 6 to less than 12 years of age who have completed part B of study 7. **Study 9 (C-6)** Two-part, single-arm, multicenter study to evaluate the safety, PK, PD and efficacy of VX-659/TEZ/IVA in subjects with CF who are 2 to less than 6 years of age and who have F/MF or F/F genotypes. **Study 10 (C-7)** Two-part, single-arm, multicenter study to evaluate the safety, PK, PD and efficacy of VX-659/TEZ/IVA in subjects with CF from birth to less than 2 years of age and who have F/MF or F/F genotypes.
Extrapolation, modelling and simulation studies	2	**Study 11 (M-1)** Modelling and simulation study for dose selection in children from birth to less than 12 years of age. **Study 12 (E-1)** Extrapolation study by modeling and simulation of efficacy and pharmacodynamic endpoints using data obtained in adolescents and adults to support extrapolation of efficacy to patients less than 12 years of age.
Other studies	2	**Study 13 (C-9)** Meta-analysis of VX-659/TEZ/IVA and TEZ/IVA study data to provide comparative 24-week efficacy data in CF subjects with the F/F genotype. **Study 14 (C-10)** Descriptive comparison of efficacy and safety outputs for 2 studies evaluating the respective triple combination regimen (TC) in CF subjects with an F/MF genotype (Studies 445 102 and 659 102).
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 January 2029
Deferral for one or more measures contained in the paediatric investigation plan:	Yes