EMA/624974/2022

European Medicines Agency decision

P/0265/2022

of 22 July 2022

on the acceptance of a modification of an agreed paediatric investigation plan for elexacaftor / tezacaftor/ ivacaftor (Kaftrio), (EMEA-002324-PIP01-17-M03) 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 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/0091/2019 issued on 22 March 2019, the decision P/0397/2020 issued on 23 October 2020 and the decision P/0416/2021 issued on 29 October 2021.

Having regard to the application submitted by Vertex Pharmaceuticals (Ireland) Limited on 18 March 2022 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 24 June 2022, 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.

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

[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 elexacaftor / tezacaftor/ ivacaftor (Kaftrio), film-coated tablet, age-appropriate oral solid dosage form, oral use, 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 (Ireland) Limited, Unit 49, Block F2, Northwood Court, Santry D09 T665 - Dublin 9, Ireland.

EMA/PDCO/183178/2022
Amsterdam, 24 June 2022

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

EMEA-002324-PIP01-17-M03

Scope of the application

Active substance(s):

Elexacaftor / tezacaftor/ ivacaftor

Invented name:

Kaftrio

Condition(s):

Treatment of Cystic Fibrosis

Authorised indication(s):

See Annex II

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 (Ireland) Limited

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Vertex Pharmaceuticals (Ireland) Limited submitted to the European Medicines Agency on 18 March 2022 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European

Medicines Agency's decision P/0091/2019 issued on 22 March 2019, the decision P/0397/2020 issued on 23 October 2020 and the decision P/0416/2021 issued on 29 October 2021.

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

The procedure started on 25 April 2022.

Scope of the modification

Some measures 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 in the scope set out in the Annex I of this opinion.
2. The measures and timelines of the paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver 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

1.1. Condition:

Treatment of cystic fibrosis

The waiver applies to:

- the paediatric population from birth to less than 12 months of age;
- film-coated tablet, age-appropriate oral solid dosage form, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

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 12 months of age 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 12 months of age 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	Description
Quality-related studies	**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 12 months of age to less than 6 years of age
Non-clinical studies	**Study 3 (N-1)** Oral (gavage) toxicity and toxicokinetics study in juvenile rats

Clinical studies	**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-445/TEZ/IVA in subjects 12 to less than 18 years of age (and adults) with cystic fibrosis (CF) who are heterozygous for F508del and a minimal CFTR function mutation (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-445/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-445/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-445/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-445/TEZ/IVA in subjects with CF from 12 months of age to less than 2 years of age and who have F/MF or F/F genotypes
Extrapolation, modelling and simulation studies	**Study 11 (M-1)** Modelling and simulation study for dose selection in children from 12 months of age to less than 12 years of age **Study 12 (E-1)** Extrapolation study by modelling and simulation of efficacy and pharmacodynamic endpoints using data obtained in adolescents and adults to support extrapolation of efficacy to patients from 12 of age months to less than 12 years of age

Other studies	**Study 13 (C-9)** Meta-analysis of VX-445/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	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

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of Cystic Fibrosis

Authorised indication(s):

- Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Authorised pharmaceutical form(s):

Film-coated tablet

Authorised route(s) of administration:

Oral use