EMA/521972/2021

European Medicines Agency decision

P/0406/2021

of 30 September 2021

on the acceptance of a modification of an agreed paediatric investigation plan for tezacaftor / ivacaftor (Symkevi), (EMEA-001640-PIP01-14-M07) 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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

European Medicines Agency decision

P/0406/2021

of 30 September 2021

on the acceptance of a modification of an agreed paediatric investigation plan for tezacaftor / ivacaftor (Symkevi), (EMEA-001640-PIP01-14-M07) 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 European Medicines Agency's decision P/0098/2015 issued on 8 May 2015, decision P/0193/2016 issued on 15 July 2016, decision P/0193/2017 issued 3 July 2017, decision P/0311/2017 issued on 31 October 2017, decision P/0069/2018 issued on 16 March 2018, decision P/0250/2019 issued on 17 July 2019, and decision P/0193/2020 issued on 15 May 2020,

Having regard to the application submitted by Vertex Pharmaceuticals (Ireland) Limited on 4 June 2021 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 10 September 2021, in accordance with Article 22 of Regulation (EC) No 1901/2006 and Article 13 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 acceptance of changes to the agreed paediatric investigation plan and to the deferral and on the granting 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 granting a waiver.

[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 tezacaftor / ivacaftor (Symkevi), film-coated tablet, age-appropriate oral solid dosage form, 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

A waiver for tezacaftor / ivacaftor (Symkevi), 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 the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

This decision is addressed to Vertex Pharmaceuticals (Ireland) Limited, 28-32 Pembroke Upper Street, Dublin 2, D02 EK84 – Dublin, Ireland.

EMA/PDCO/347091/2021
Amsterdam, 10 September 2021

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

EMEA- 001640-PIP01-14-M07

Scope of the application

Active substance(s):

Tezacaftor / ivacaftor

Invented name:

Symkevi

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 4 June 2021 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, decision P/0193/2016 issued on 15 July 2016, decision P/0193/2017 issued 3 July 2017, decision P/0311/2017 issued on 31 October 2017, decision P/0069/2018 issued on 16 March 2018, decision P/0250/2019 issued on 17 July 2019, and decision P/0193/2020 issued on 15 May 2020.

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

The procedure started on 12 July 2021.

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified. A waiver for a new paediatric subset has been added.

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 grant a waiver for one or more subsets of the paediatric population concluded in accordance with Article 11(1)(a) of said Regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population.
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 1 year 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 ineffective or unsafe in part or all of the paediatric population.

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 1 year 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** 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	11	**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 (VX16-661-115) Randomised, double-blind, placebo and active-controlled, parallel, multicentre study to evaluate the efficacy, safety and pharmacokinetics of 8 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, 12 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 1 year to less than 2 year 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. **Study 18** (**VX17-661-116)** Open-label rollover study to evaluate the safety and efficacy of long-term treatment in subjects who were 6 to less than 12 years of age at the beginning of Study 12 and who are homozygous or heterozygous for the F508del mutation in the CFTR protein
Extrapolation, modelling and simulation studies	1	**Study 17** Modelling and simulation study for dose selection in children from 1 year 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 December 2024

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	Yes
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):

Treatment of cystic fibrosis

Authorised indication(s):

- Treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

Authorised pharmaceutical form(s):

Film-coated tablet

Authorised route(s) of administration:

Oral use