EMADOC-1700519818-1853205

European Medicines Agency decision

EMA/PE/0000227394

of 28 January 2025

on the acceptance of a modification of an agreed paediatric investigation plan for ivacaftor / tezacaftor (Symkevi) 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 acceptance of a modification of an agreed paediatric investigation plan for ivacaftor / tezacaftor (Symkevi) 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 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/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, decision P/0193/2020 issued on 15 May 2020 and the decision P/0406/2021 issued on 30 September 2021,

Having regard to the application submitted by Vertex Pharmaceuticals (Ireland) Limited on 3 September 2024 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 13 December 2024, 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 and to the 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 and to the waiver.

[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 ivacaftor / tezacaftor (Symkevi), including changes to the deferral and to the waiver, 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 5, Northwood Court, Northwood Crescent, D09 - T665 Dublin 9, Ireland.

EMADOC-1700519818-1709326
Amsterdam, 13 December 2024

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

EMA/PE/0000227394

Scope of the application

Active substance(s):

Ivacaftor / tezacaftor

Invented name and authorisation status:

See Annex II

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 (Ireland) Limited

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 3 September 2024 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/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, decision P/0193/2020 issued on 15 May 2020 and the decision P/0406/2021 issued on 30 September 2021.

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

The procedure started on 14 October 2024.

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified. The waiver has been extended to cover an additional paediatric population.

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 and to the waiver in the scope set out in the Annex I of this opinion.

   The Paediatric Committee members of Liechtenstein and Norway agree with the above-mentioned recommendation of the Paediatric Committee.

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;
- the paediatric population from 2 to less than 6 years of age;
- film-coated tablet, age-appropriate oral solid dosage form, oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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 2 years of age and from 6 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** 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 2 years of age.
Non-clinical studies	**Study 3** Fertility and early embryonic development oral (gavage) toxicity study with VX-661 in rat.

Area	Description
	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	**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)**

Area	Description
	Randomised, double-blind, placebo- and active controlled, parallel, multicentre study to evaluate the efficacy, safety and PK of 8 weeks treatment with VX-661 co-formulated with Ivacaftor (Study C, part B; VX16-661-115). **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** Study deleted in EMA/PE/0000227394 of 13/12/2024. **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	**Study 17** Modelling and simulation study for dose selection in children from 1 year to less than 12 years of age.
Other studies	Not applicable.
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 December 2024
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Information provided by the applicant:

Condition(s) and authorised indication(s)

1. Treatment of cystic fibrosis

Authorised indication(s):

- Symkevi is indicated in a combination regimen with ivacaftor tablets for the 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.
  - Invented name(s): Symkevi
  - Authorised pharmaceutical form(s): film-coated tablets.
  - Authorised route(s) of administration: oral use.
  - Authorised via centralised procedure