EMA/71025/2022

European Medicines Agency decision

P/0071/2022

of 11 March 2022

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for (14S)-8-[3-(2-{dispiro[2.0.2^(4).1^(3)]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl- 2lambda^(6)-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.1^(11,14).0^(5,10)] tetracosa- 1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate / tezacaftor / deutivacaftor (VX-121/ TEZ/D-IVA) (EMEA-003052-PIP01-21) 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 and on the granting of a waiver for (14S)-8-[3-(2-{dispiro[2.0.2^(4).1^(3)]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl- 2lambda^(6)-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.1^(11,14).0^(5,10)] tetracosa- 1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate / tezacaftor / deutivacaftor (VX-121/ TEZ/D-IVA) (EMEA-003052-PIP01-21) 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 application submitted by Vertex Pharmaceuticals (Ireland) Limited on 4 June 2021 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 21 January 2022, in accordance with Article 17 of Regulation (EC) No 1901/2006 and Article 21 of said Regulation 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 agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver.

(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.

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

A paediatric investigation plan for (14S)-8-[3-(2-{dispiro[2.0.2^(4).1^(3)]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl- 2lambda^(6)-thia-3,9,11,18,23-penta-azatetracyclo [17.3.1.1^(11,14).0^(5,10)]tetracosa- 1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate / tezacaftor / deutivacaftor (VX-121/ TEZ/D-IVA), 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 (14S)-8-[3-(2-{dispiro[2.0.2^(4).1^(3)]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl- 2lambda^(6)-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.1^(11,14).0^(5,10)]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate / tezacaftor / deutivacaftor (VX-121/ TEZ/D-IVA), 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

A waiver for (14S)-8-[3-(2-{dispiro[2.0.2^(4).1^(3)]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl- 2lambda^(6)-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.1^(11,14).0^(5,10)]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate / tezacaftor / deutivacaftor (VX-121/ TEZ/D-IVA), 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 4

This decision is addressed to Vertex Pharmaceuticals (Ireland) Limited, Unit 49, Block F2, Northwood Court, Santry, D09 T665 - Dublin 9, Ireland.

EMA/PDCO/605072/2021
Amsterdam, 21 January 2022

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

EMEA-003052-PIP01-21

Scope of the application

Active substance(s):

(14S)-8-[3-(2-{dispiro[2.0.2^(4).1^(3)]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lambda^(6)-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.1^(11,14).0^(5,10)]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate / tezacaftor / deutivacaftor (VX-121/ TEZ/D-IVA)

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 16(1) of Regulation (EC) No 1901/2006 as amended, Vertex Pharmaceuticals (Ireland) Limited submitted for agreement to the European Medicines Agency on 4 June 2021 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 12 July 2021.

Supplementary information was provided by the applicant on 15 October 2021.

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;
   - to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and 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.

   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 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 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

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 tablets, 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

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 (Study Q-1)*** Development of an age-appropriate oral formulation for children from 1 year to less than 6 years of age ***Study 2 (Study Q-2)*** Development of a fixed dose combination (FDC) film-coated tablet with lower strength for all 3 active components (VX-121, TEZ, and D-IVA) and with a maximum dimension of 14 mm for children aged from 6 years to less than 12 years of age

Non-clinical studies	1	***Study 3 (Study N-1)*** Definitive toxicity and toxicokinetics study in juvenile rats to support clinical evaluation of VX-121/TEZ/D-IVA in children from 1 year to less than 6 years of age with cystic fibrosis (CF)
Clinical studies	4	***Study 4 (Study C-1)*** Randomized, double-blind, controlled study to assess efficacy and safety of the fixed-dose combination (FDC) of VX-121/tezacaftor/ deutivacaftor (VX-121/TEZ/D-IVA) in adolescents from 12 years 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 genotype) ***Study 5 (Study C-2)*** Randomized, double-blind, controlled study to assess efficacy and safety of the fixed-dose combination (FDC) of VX-121/TEZ/D-IVA in adolescents from 12 years to less than 18 years of age (and adults) with cystic fibrosis (CF) who are homozygous for F508del (F/F genotype) or have other F508del-anchored genotypes with responsive alleles ***Study 6 (Study C-3)*** Rollover, open-label, long-term safety study of VX-121/TEZ/D-IVA in children from 12 years to less than 18 years of age ***Study 7 (Study C-4)*** Two-part single-arm study to evaluate safety and pharmacokinetics (PK) of VX-121/TEZ/D-IVA in children from 1 year to less than 12 years of age with CF who have at least one F508del allele.
Extrapolation, modelling and simulation studies	2	***Study 8 (Study M-1)*** Modelling and simulation study for dose selection in children from 1 year of age to less than 12 years of age ***Study 9 (Study E-1)*** Modelling and simulation study of efficacy and pharmacodynamic endpoints in children from 1 year of age 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:	No
Date of completion of the paediatric investigation plan:	By December 2030
Deferral for one or more measures contained in the paediatric investigation plan:	Yes