MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Decision Cover Letter

Decision of the licensing authority to:

agree a paediatric investigation plan and grant a deferral and grant a waiver

MHRA-100062-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

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 Pharmaceutics (Europe) Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Vertex Pharmaceutics (Europe) Limited submitted to the licensing authority on 04/06/2021 10:30 BST an application for a

The procedure started on 22/04/2022 07:19 BST

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to agree a paediatric investigation plan and grant a deferral and grant a waiver

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This decision is forwarded to the applicant, together with its annex and appendix.

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Final Decision Letter

MHRA-100062-PIP01-21

Of 27/05/2022 14:19 BST

On the adopted decision 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 (MHRA-100062-PIP01-21) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on a paediatric investigation plan

This decision applies to a 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, Film-coated tablet; Age-appropriate oral solid dosage form , Oral use .

This decision is addressed to Vertex Pharmaceutics (Europe) Limited, 2 Kingdom Street, London, United Kingdom, W2 6BD

ANNEX I

1. Waiver

1.1 Condition:

Treatment of cystic fibrosis The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 1 year of age Pharmaceutical form(s): Film-coated tablet; Age-appropriate oral solid dosage form Route(s) of administration: Oral use Reason for granting waiver: on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of cystic fibrosis

2.2 Indication(s) targeted by the PIP:

Treatment of cystic fibrosis

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

The paediatric population from 1 year to less than 18 years of age

2.4 Pharmaceutical Form(s):

Film-coated tablet; Age-appropriate oral solid dosage form

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	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 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 toxicokinetic study 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) Randomised, double-blind, controlled study to assess the 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 heterozygous for F508del and a CTFR mutation of minimal function (F/MF genotype). Study 5 (Study C-2) Randomised, double-blind, controlled study to assess the 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 (and adults). Study 7(Study C-4) Two-part, single-arm, study to evaluate the 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, Modeling & Simulation Studies	2	Study 8 (Study M-1) Modelling and simulation study for dose selection in children from 1 year to less than 12 years of age. Study 9 (Study E-1) Modelling and simulation study of efficacy and pharmacodynamics endpoints 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 a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	31/12/2030
Deferral of one or more studies contained in the paediatric investigation plan:	Yes