MHRA
10 South Colonnade
Canary Wharf
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United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

accept change(s) to the agreed paediatric investigation plan

MHRA-100116-PIP01-21-M02

Scope of the Application

Active Substance(s)

IVACAFTOR; TEZACAFTOR; ELEXACAFTOR

Condition(s)

Treatment of cystic fibrosis

Pharmaceutical Form(s)

Film-coated tablet; Age-appropriate solid dosage form (Granules)

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

Vertex Pharmaceuticals Incorporated

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Vertex Pharmaceuticals Incorporated submitted to the licensing authority on 18/11/2022 12:08 GMT an application for a Modification

The procedure started on 28/11/2022 10:56 GMT

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 accept change(s) to the agreed paediatric investigation plan

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.

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Final Decision Letter

MHRA-100116-PIP01-21-M02

Of 14/12/2022 07:50 GMT

On the adopted decision for IVACAFTOR; TEZACAFTOR; ELEXACAFTOR (MHRA-100116-PIP01-21-M02) 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 modification of a paediatric investigation plan (including modification of a waiver or deferral included in that paediatric investigation plan)

This decision applies to a Modification for IVACAFTOR; TEZACAFTOR; ELEXACAFTOR, Film-coated tablet; Age-appropriate solid dosage form (Granules) , ORAL USE .

This decision is addressed to Vertex Pharmaceuticals Incorporated , 2 Kingdom Street, Paddington, 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 12 months of age Pharmaceutical form(s): Film-coated tablet. Age-appropriate solid dosage form (Granules). 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 (CF) in patients aged from 12 months to less than 18 years, either heterozygous for the F508del-CFTR mutation and a mutation that results in a minimal function of the CFTR protein (F/MF) or homozygous for the F508del-CFTR mutation (F/F).

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

The paediatric population from 12 months to less than 18 years of age

2.4 Pharmaceutical Form(s):

Film-coated tablet. Age-appropriate oral solid dosage form (Granules)

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	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 to less than 6 years of age.
Non-Clinical Studies	1	Study 3 (N-1) Oral (gavage) toxicity and toxicokinetics study in juvenile rats.
Clinical Studies	7	Study 4 (C-1) Randomised, 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 12years 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) Randomised, double-blind, active-controlled, parallel group, multicentre 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, 12years to less than 18 years of age (and adults) who have completed study 4 or 5. Study 7 (C-4) Two-part, single-arm, multicentre study to evaluate the safety, PK, PD and efficacy of VX-445/TEZ/IVA in subjects with CF who are 6 years 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 years to less than 12 years of age who have completed part B of study 7. Study 9 (C-6) Two-part, single-arm, multicentre study to evaluate the safety, PK, PD and efficacy of VX-445/TEZ/IVA in subjects with CF who are 2 years to less than 6 years of age and who have F/MF or F/F genotypes. Study 10 (C-7) Two-part, single-arm, multicentre study to evaluate the safety, PK, PD and efficacy of VX-445/TEZ/IVA in subjects with CF from 12months to less than 2 years of age and who have F/MF or F/F genotypes.
Extrapolation, Modeling & Simulation Studies	2	Study 11 (M-1) Modelling and simulation study for dose selection in children from 12 months 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 months to less than 12 years of age.
Other Studies	2	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	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:	Yes
Date of completion of the paediatric investigation plan:	31/01/2029
Deferral of one or more studies contained in the paediatric investigation plan:	Yes