MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
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-100119-PIP01-21-M01) and to the deferral and waiver

MHRA-100119-PIP01-21-M02

Scope of the Application

Active Substance(s)

TEZACAFTOR; IVACAFTOR

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 Incorporated

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Vertex Pharmaceuticals Incorporated submitted to the licensing authority on 04/03/2025 09:44 GMT an application for a Modification

The procedure started on 26/03/2025 16:33 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 and to the deferral and to the 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.

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Final Decision Letter

MHRA-100119-PIP01-21-M02

Of 03/04/2025 09:46 BST

On the adopted decision for TEZACAFTOR; IVACAFTOR (MHRA-100119-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 TEZACAFTOR; IVACAFTOR, Film-coated tablet; AGE-APPROPRIATE ORAL SOLID DOSAGE FORM , ORAL USE .

This decision is addressed to Vertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, UNITED STATES OF AMERICA, 02210

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. The paediatric population from 2 years to less than 6 years 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 does not represent a significant therapeutic benefit over existing treatments.

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of Cystic Fibrosis.

2.2 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.

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

The paediatric population from 1 year to less than 2 years of age and from 6 years 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 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	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	8	Study 7 (VX14-661-106) Study 8 (VX14-661-107) Study 9 (VX14-661-108) Study 10 (VX14-661-109) Study 11 Study 12 (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, deleted in procedure MHRA-100119-PIP01-21-M02. 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 years 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, Modeling & 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 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:	31/12/2024
Deferral of one or more studies contained in the paediatric investigation plan:	Yes