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 and to the deferral

MHRA-100844-PIP01-23-M01

Scope of the Application

Active Substance(s)

IVACAFTOR

Condition(s)

Treatment of cystic fibrosis.

Pharmaceutical Form(s)

Film-coated tablet; Granules in sachet

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

Vertex Pharmaceuticals (Europe) Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Vertex Pharmaceuticals (Europe) Limited submitted to the licensing authority on 10/01/2023 15:28 GMT an application for a Modification

The procedure started on 09/05/2023 11:34 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 accept change(s) to the agreed paediatric investigation plan and to the deferral.

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-100844-PIP01-23-M01

Of 22/05/2023 13:56 BST

On the adopted decision for IVACAFTOR (MHRA-100844-PIP01-23-M01) 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, Film-coated tablet; Granules in sachet , ORAL USE .

This decision is addressed to Vertex Pharmaceuticals (Europe) Limited, 2 Kingdom Street, Paddington, UNITED KINGDOM, w2 6BD

ANNEX I

1. Waiver

1.1 Condition:

Not applicable.

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 birth to less than 18 years of age.

2.4 Pharmaceutical Form(s):

Film-coated tablet Age-appropriate oral solid formulation (Granules in sachet)

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	1	Study 1 Development of an age-appropriate oral solid formulation for children below 6 years of age with acceptability, palatability, and compatibility testing.
Non-Clinical Studies	1	Study 2 An oral (gavage) toxicity and toxicokinetics study in juvenile rats, with recovery.
Clinical Studies	9	Study 3 (Study 102) A randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor (VX-770) in adolescents 12 years to less than 18 years old (and adults) with Cystic Fibrosis (CF) and G551D mutation. Study 4 (Study 103) A randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor (VX-770) in children with cystic fibrosis (CF) and G551D Mutation aged 6 years to less than 12 years. Study 5 (Study 110) A randomised, double-blind, placebo-controlled, multicentre study in patients with CF with at least 1 Allele of a R117H-CFTR mutation, aged 6 years and older. Study 6 (Study 104) A randomised, double-blind, placebo-controlled, multicentre study in adults and children with CF with the $_{\Delta}$F508/$_{\Delta}$F508-CFTR mutation, aged 12 years to less than 18 years. Study 7 (Study 105) Rollover long-term safety and

		efficacy study in adults and children with CF aged 6 years and older with at least one allele of G551D-CFTR mutation. Study 8 (Study 106) A randomised, double-blind, placebo-controlled, crossover study to evaluate the effect of ivacaftor (VX-770) on lung clearance index in subjects with cystic fibrosis with the G551D mutation and a FEV1 above 90% predicted, aged 6 years and older. Study 9 (Study 108) A 2-part open-label study to evaluate the safety, PK, and PD of ivacaftor (VX-770) in subjects with cystic fibrosis and a CFTR gating mutation, aged 2 years to less than 6 years. Study 10 (Study H (Study 124 (VX15-770-12)) A 2-part open-label study to evaluate the safety, PK, and PD of ivacaftor in subjects with cystic fibrosis who are less than 24 months of age and have a CFTR gating mutation. Study 11 (Study 111) A two-part, randomised, double-blind, placebo-controlled, crossover study with an open-label period to evaluate the efficacy and safety of ivacaftor in patients with cystic fibrosis aged 6 years or older, who have a non-G551D CFTR mutation.
Extrapolation, Modeling & Simulation Studies	0	Not applicable.
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:	31/12/2022
Deferral of one or more studies contained in the paediatric investigation plan:	Yes