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 include a wavier for a new paediatric subset

MHRA-100119-PIP01-21-M01

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 (Europe) Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Vertex Pharmaceuticals (Europe) Limited submitted to the licensing authority on 04/06/2021 17:55 BST an application for a Modification

The procedure started on 09/12/2021 11:33 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 including the addition of a waiver for a new paediatric subset

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-M01

Of 22/12/2021 17:33 GMT

On the adopted decision for TEZACAFTOR; IVACAFTOR (MHRA-100119-PIP01-21-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 TEZACAFTOR; IVACAFTOR, Film-coated tablet, Age-appropriate oral solid dosage form , Oral use .

This decision is addressed to Vertex Pharmaceuticals (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 ineffective or unsafe in part of all of the paediatric population.

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 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 years to less than 12 years old. Study 2 Development of an age appropriate oral formulation for children below 6 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	4	Study 7 (VX14-661-106) Randomised, double-blind, placebo-controlled, parallel group, multicentre study to assess the efficacy and long-term safety of VX-661 in combination with ivacaftor in subjects 12 years to less than 18 years of age (and adults) with CF who are homozygous for the F508del-CFTR mutation. Study 8 (VX14-661-107) Double-blind, placebo controlled, multicentre study to assess the efficacy and safety of VX-661 co-formulated with Ivacaftor in F508del-CFTR heterozygous subjects with an Ivacaftor- and VX-661 nonresponsive mutation on the second allele, 12 years to less than 18 years of age (and

		adults). Study 9 (VX14-661-108) Double-blind, placebo and active treatment controlled, 6-sequence, 8 week cross-over study to assess the efficacy and safety of VX-661 co-formulated with ivacaftor in F508del-CFTR heterozygous subjects with a residual function mutation that is potentially ivacaftor responsive on the second allele, 12 years to less than 18 years of age (and adults). Study 10 (VX14-661-109) Double-blind, active-controlled, multicentre study, parallel arm study to assess the efficacy and safety of VX-661 co-formulated with ivacaftor in F508del-CFTR heterozygous subjects with a clinically proven ivacaftor-responsive mutation with a gating defect on the second allele, 12 years to less than 18 years of age (and adults).
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	7 (other clinical studies)	Study 11 Open-label, multicentre study, to assess the safety and pharmacokinetics of two weeks treatment with single oral doses of VX-661 and ivacaftor in subjects with cystic fibrosis who are homozygous or heterozygous for F508del-CFTR mutation, 6 years to less than 12 years of age. Study 12 (VX16-661-115) Randomised, double-blind, placebo-controlled, parallel, multicentre study to evaluate the efficacy, safety and pharmacokinetics of 24 weeks treatment with VX-661 co-formulated with ivacaftor in subjects with cystic fibrosis who are homozygous or heterozygous for F508-del-CFTR mutation, 6 years to less than 12 years of age. Study 13 Rollover open-label long-term safety and efficacy study in subjects with CF, 12 years to less than 18 years of age (and adults). Study 14 Two-part, uncontrolled, multi-centre study to evaluate the safety, PK, PD and efficacy of VX-661 and ivacaftor in subjects with CF who are homozygous or heterozygous for

		the F508del-CFTR mutation, aged 2 years to less than 6 years. 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 Randomised, single dose, cross-over, relative bioavailability study in healthy adults to characterise 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 years 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
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