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-100166-PIP01-21-M01

Scope of the Application

Active Substance(s)

ENTRECTINIB

Condition(s)

Treatment of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms).

Pharmaceutical Form(s)

Capsule, hard; Coated granules

Route(s) of Administration

Oral use; Gastric use

Name / Corporate name of the PIP applicant

Roche Products Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Roche Products Limited submitted to the licensing authority on 12/07/2021 22:37 BST an application for a Modification

The procedure started on 09/05/2022 11:41 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

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-100166-PIP01-21-M01

Of 19/05/2022 14:57 BST

On the adopted decision for ENTRECTINIB (MHRA-100166-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 ENTRECTINIB, Capsule, hard; Coated granules , Oral use; Gastric use .

This decision is addressed to Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, United Kingdom, AL7 1TW

ANNEX I

1. Waiver

1.1 Condition:

Not applicable

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms).

2.2 Indication(s) targeted by the PIP:

Treatment of NTRK fusion-positive locally advanced or metastatic solid tumours paediatric patients from birth to less than 18 years of age, who have either progressed following prior therapies or who have no acceptable standard therapies.

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):

Capsule, hard; Coated granules

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1 Development of an age-appropriate solid dosage form (coated granules) suitable for children unable to swallow the already available capsules. Study 6 (added in procedure EMEA-002096-PIP01-16-M02) Assessment of the administration of the content of the hard capsules and of the coated granules via naso-gastric and gastric tube.
Non-Clinical Studies	2	Study 2 Dose range-finding juvenile toxicity study Study 3 Definitive juvenile toxicity study.
Clinical Studies	1	Study 4 (STARTRK-NG; NCT02650401) Open-label trial to evaluate the pharmacokinetic, safety and anti-tumour activity of entrectinib in paediatric patients with relapsed or refractory extracranial solid tumours from 2 to less than 18 years of age (dose escalation part) and to evaluate the anti-cancer activity of entrectinib in an expansion cohort of paediatric patients from birth to less than 18 years of age with solid tumours harbouring NTRK1/2/3 fusions who have either progressed following prior therapies or who have no acceptable standard therapy (expansion part).

Extrapolation, Modeling & Simulation Studies	1	Study 5 Modelling and simulation, and partial extrapolation study to evaluate the use and support the dosing regimen of entrectinib in paediatric patients from birth to less than 18 years of age with solid tumours harbouring NTRK1/2/3 fusions.
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