MHRA
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Canary Wharf
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United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

accept of change(s) to the agreed paediatric investigation plan

MHRA-100377-PIP01-21-M01

Scope of the Application

Active Substance(s)

ACALABRUTINIB

Condition(s)

Treatment of mature B cell neoplasms

Pharmaceutical Form(s)

Capsule hard; Film-coated tablet; Age-appropriate oral liquid dosage form; Age-appropriate oral solid dosage form

Route(s) of Administration

Oral use

Name / Corporate name of the PIP applicant

AstraZeneca UK Ltd

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, AstraZeneca UK Ltd submitted to the licensing authority on 05/12/2021 15:24 GMT an application for a Modification

The procedure started on 18/07/2022 15:58 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-100377-PIP01-21-M01

Of 03/08/2022 17:27 BST

On the adopted decision for ACALABRUTINIB (MHRA-100377-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 ACALABRUTINIB, Capsule hard; Film-coated tablet; Age-appropriate oral liquid dosage form; Age-appropriate oral solid dosage form , Oral use .

This decision is addressed to AstraZeneca UK Ltd, 600 Capability Green, Luton, United Kingdom, LU1 3LU

ANNEX I

1. Waiver

1.1 Condition:

Treatment of mature B cell neoplasms The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 1 year of age Pharmaceutical form(s): Capsule hard; Film-coated tablet; Age-appropriate oral liquid dosage form; Age-appropriate oral solid dosage form Route(s) of administration: Oral use Reason for granting waiver: on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of mature B cell neoplasms

2.2 Indication(s) targeted by the PIP:

Treatment of children from 1 year to less than 18 years of age with newly-diagnosed and relapsed/ refractory mature B-cell lymphoma, that is, diffuse large B-cell lymphoma or Burkitt lymphoma or primary mediastinal lymphoma.

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):

Capsule, hard; Film-coated tablet; Age-appropriate oral liquid dosage form; 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 oral liquid formulation to be used in children from 1 year to less than 18 years of age. Study 2 Development of an age-appropriate oral solid dosage form (minitablets or dispersible tablets or granules) to be used in children from 1 year to less than 18 years of age.
Non-Clinical Studies	2	Study 3 Efficacy study in mouse xenograft models of paediatric (and adult) B cell malignancies. Study 4 Efficacy study in mouse models of CNS lymphoma.
Clinical Studies	2	Study 5 Open-label, single arm dose-escalation (phase 1) trial to evaluate the pharmacokinetics, pharmacodynamics, safety and anti-tumour activity of acalabrutinib as add-on to rituximab, ifosfamide, carboplatin and etoposide (R-ICE) or rituximab, vincristine, ifosfamide, carboplatin, idarubicin and dexamethasone (R-VICI) regimens in paediatric patients from 1year to less than 18 years of age (and young adults) with a relapsed or refractory mature B-cell neoplasm and an expansion cohort (phase 2). Study 6 Open-label, single arm trial to evaluate the pharmacokinetics, pharmacodynamics, safety and anti-

		tumour activity of acalabrutinib as add-on to multi-agent Lymphoma-Malins-B (LMB) chemotherapy + rituximab in paediatric patients from 1year to less than 18 years of age (and young adults) with a newly-diagnosed mature B-cell neoplasm.
Extrapolation, Modeling & Simulation Studies	2	Study 7 Modelling and simulation study to better define the dose of acalabrutinib to be used in children from 1 year to less than 18 years of age with a refractory or relapsed mature B-cell neoplasm. Study 8 Extrapolation study to support and evaluate the use of acalabrutinib in children from 1 year to less than 18 years of age with a newly-diagnosed mature B-cell neoplasm.
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:	30/09/2028
Deferral of one or more studies contained in the paediatric investigation plan:	Yes