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-101008-PIP01-23-M01

Scope of the Application

Active Substance(s)

AMBRISENTAN

Condition(s)

Pulmonary Arterial Hypertension

Pharmaceutical Form(s)

Film-coated tablet

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

GlaxoSmithKline UK Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, GlaxoSmithKline UK Limited submitted to the licensing authority on 25/05/2023 12:26 BST an application for a Modification

The procedure started on 14/11/2023 11:03 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

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-101008-PIP01-23-M01

Of 08/12/2023 10:55 GMT

On the adopted decision for AMBRISENTAN (MHRA-101008-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:

AAgreement 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 AMBRISENTAN, Film-coated tablet , ORAL USE .

This decision is addressed to GlaxoSmithKline UK Limited, 980 Great West Road, Brentford, UNITED KINGDOM, TW8 9GS

ANNEX I

1. Waiver

1.1 Condition:

Treatment of pulmonary arterial hypertension 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 Route(s) of administration: ORAL USE Reason for granting waiver: On the grounds the specific medicinal product is likely to be unsafe

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of pulmonary arterial hypertension

2.2 Indication(s) targeted by the PIP:

Treatment of idiopathic (IPAH) and familial (FPAH) pulmonary hypertension; treatment of associated pulmonary hypertension (APAH).

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

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1 Development of film coated tablets 2.5 mg for oral use. Study 2 Development of film-coated tablets 1.25 mg for oral use.
Non-Clinical Studies	2	Study 3 2-week juvenile animal study to determine tolerability and toxicokinetics of ambrisentan. Study 4 8-week juvenile animal study to determine oral toxicology and toxicokinetic of ambrisentan including an 8 weeks recovery period.
Clinical Studies	2	Study 5 (AMB112529) 24 weeks randomised, open label, multi-centre, comparative trial to evaluate safety, efficacy and population PK of ambrisentan low and high dose for the treatment of children from 8 years of age to less than 18 years of age with Pulmonary Arterial Hypertension. Study 7 (AMB112530) 24 weeks randomised, open-label, multi-centre, comparative trial to evaluate safety, efficacy and PK of ambrisentan low and high dose for the treatment of children from 2 years of age to less than 8 years of age with Pulmonary Arterial Hypertension.
Extrapolation, Modeling & Simulation Studies	2	Study 8 (This study was added during procedure EMEA-00434-PIP01-08-M05) Pharmacokinetic (PK) and exposure-response

		(ER) modelling and simulation study to support ambrisentan dose recommendation for treatment of paediatric PAH. Study 9 (This study was added during procedure EMEA-00434-PIP01-08-M05) Extrapolation study to evaluate the efficacy of ambrisentan in paediatric PAH based on the change in 6-minute walk distance (6MWD) observed in study AMB112529.
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:	30/04/2021
Deferral of one or more studies contained in the paediatric investigation plan:	Yes