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-100183-PIP01-21-M03)

MHRA-100183-PIP01-21-M04

Scope of the Application

Active Substance(s)

AZILSARTAN MEDOXOMIL

Condition(s)

Treatment of hypertension

Pharmaceutical Form(s)

Granules for oral suspension ; Tablet

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

Takeda UK Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Takeda UK Limited submitted to the licensing authority on 28/01/2025 14:24 GMT an application for a Modification

The procedure started on 05/03/2025 17:23 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

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-100183-PIP01-21-M04

Of 04/06/2025 08:38 BST

On the adopted decision for AZILSARTAN MEDOXOMIL (MHRA-100183-PIP01-21-M04) 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 AZILSARTAN MEDOXOMIL, Granules for oral suspension ; Tablet , ORAL USE .

This decision is addressed to Takeda UK Limited, 1 Kingdom Street, London, UNITED KINGDOM, W26BD

ANNEX I

1. Waiver

1.1 Condition:

Treatment of hypertension The waiver applies / applied to: Paediatric Subset(s): Preterm newborn infants Term newborn infants (from birth to less than 28 days) Infants and children (from 28 days to less than 24 months) Pharmaceutical form(s): Granules for oral suspension Tablet Route(s) of administration: ORAL USE Reason for granting waiver: on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of hypertension

2.2 Indication(s) targeted by the PIP:

Treatment of essential (primary) hypertension Treatment of secondary hypertension

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

The paediatric population from 2 years to less than 18 years of age

2.4 Pharmaceutical Form(s):

Tablet Granules for oral suspension

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	1	Study 1 Development of age appropriate formulation (granules for oral suspension).
Non-Clinical Studies	4	Study 2 Repeat-dose range-finding toxicity study in neonatal rats Study 3 Repeat-dose toxicity study with recovery in neonatal rats. Study 4 A detailed comparative analysis of the toxicity profile of azilsartan compared to candesartan. Study 5 Repeat dose toxicity with recovery in juvenile rats.
Clinical Studies	5	Study 6 Relative bioavailability, safety, and tolerability study in adults. Study 7 Single-dose PK, safety, and tolerability of azilsartan medoxomil in children and adolescents. Study 8 Randomised, double-blind, active-controlled, 6-week dose-ranging safety and efficacy study with a 2-week, randomised, double-blind, placebo-controlled withdrawal phase and 44-week open-label extension in children aged 6 years to less than 18 years with essential and secondary hypertension. Study 9 (AR14.002) Randomised, open-label, uncontrolled, dose-ranging, parallel-group, safety, pharmacokinetic (PK) and exposure-response study

		with a 10-week treatment period and a 2-week safety follow-up period of azilsartan medoxomil in children with primary or secondary hypertension from 2 years to less than 6 years of age and with a weight of less than 25 kg. Study 10 (AR14.003) (added during procedure MHRA-100183-PIP01-21-M03) Long-term, multi-centre, open-label, safety study of azilsartan medoxomil in children with primary and secondary hypertension from 2 years to 6 years of age.
Extrapolation, Modeling & Simulation Studies	3	Study 11 (added during procedure MHRA-100183-PIP01-21-M03) Development of a population PK model to support the appropriate dose and the extrapolation of the use of azilsartan medoxomil in patients from 2 years of age. Study 12 (added during procedure MHRA-100183-PIP01-21-M03) Development of a model to characterise the PK/PD relationship between individual TAK-536 exposure (AUC) and blood pressure in adults and children with a focus on weight and age-related changes, to support the extrapolation of the use of azilsartan medoxomil in patients from 2 years of age. Extrapolation Plan Studies TAK-491CLD_309, TAK-491CLD_302, TAK-491_103, 01-05-TL-491-008, 01-06-TL-491-011, and 01-06-TL-491-019, TAK-491_109, AR14.001, and AR14.002 are part of an extrapolation plan covering the paediatric population from 2 years to less than 18 years of age, as agreed by the Regulatory Agency.
Other Studies	0	Not applicable.
Other Measures	1	Study 13 (added in procedure MHRA-100183-PIP01-21-M03) Review and analysis of available data (compounds of the same class, data from different age ranges) to further substantiate efficacy as well as the safety database.

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:	30/04/2029
Deferral of one or more studies contained in the paediatric investigation plan:	Yes