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-100646-PIP01-22-M01) and to the deferral

MHRA-100646-PIP01-22-M02

Scope of the Application

Active Substance(s)

TOLVAPTAN

Condition(s)

Treatment of dilutional hyponatraemia, Treatment of polycystic kidney disease

Pharmaceutical Form(s)

Tablet, Oral suspension

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

Otsuka Pharmaceutical Netherlands B.V.

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Otsuka Pharmaceutical Netherlands B.V. submitted to the licensing authority on 03/07/2023 18:09 BST an application for a Modification

The procedure started on 14/11/2023 16:54 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-100646-PIP01-22-M02

Of 13/02/2024 07:04 GMT

On the adopted decision for TOLVAPTAN (MHRA-100646-PIP01-22-M02) 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 TOLVAPTAN, Tablet, Oral suspension , ORAL USE .

This decision is addressed to Otsuka Pharmaceutical Netherlands B.V., Herikerbergweg 292, Amsterdam, NETHERLANDS, 1101 CT

ANNEX I

1. Waiver

1.1 Condition:

Treatment of dilutional hyponatraemia The waiver applies / applied to: Paediatric Subset(s): Preterm and term newborn infants from birth to less than 28 days of age The paediatric population from 28 days to less than 18 years of age Pharmaceutical form(s): Tablet Oral suspension Route(s) of administration: ORAL USE Reason for granting waiver: For preterm and term newborn infants from birth to less than 28 days of age - on the grounds that the specific medicinal product is likely to be unsafe. For the paediatric population from 28 days to less than 18 years of age - on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible. 1.2 Condition: Treatment of polycystic kidney disease The waiver applies / applied to: Paediatric Subset(s): Preterm and term newborn infants from birth to less than 28 days of age Pharmaceutical form(s): Tablet Oral suspension 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 polycystic kidney disease

2.2 Indication(s) targeted by the PIP:

Treatment of progression of autosomal dominant and of autosomal recessive polycystic kidney disease (ADPKD and ARPKD)

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

The paediatric population from 28 days to less than 18 years of age

2.4 Pharmaceutical Form(s):

Tablet Oral suspension

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	1	Study 1 Development of an oral suspension for use in children younger than 4 years or who are unable to swallow tablets.
Non-Clinical Studies	1	Study 2 Study to evaluate the toxicity and toxicokinetics of tolvaptan in juvenile rats.
Clinical Studies	3	Study 3 for condition “treatment of dilutional hyponatraemia” was deleted during procedure EMEA-001231-PIP02-13-M05. Study 4 for condition “treatment of dilutional hyponatraemia” was deleted during procedure EMEA-001231-PIP02-13-M05. Study 5 for condition “treatment of dilutional hyponatraemia” was deleted during procedure EMEA-001231-PIP02-13-M05. Study 6 (156-12-298) Double-blind, randomised, placebo controlled trial to assess the effects of titrated oral tolvaptan on renal size, pharmacokinetics and safety in children from 4 years to less than

		18 years of age diagnosed with autosomal dominant polycystic kidney disease followed by an open label extension phase to collect additional safety and efficacy data. Study 7 (156-12-204) Open-label study to assess tolvaptan in children from 28 days to less than 12 weeks of age diagnosed with autosomal recessive polycystic kidney disease. Study 8 (156-201-00307) (This study was added during procedure EMEA-001231-PIP02-13-M07) Open-label study to assess safety and activity of tolvaptan in children from 28 days to less than 18 years of age diagnosed with autosomal recessive polycystic kidney disease.
Extrapolation, Modeling & Simulation Studies	0	Not applicable.
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:	31/12/2026
Deferral of one or more studies contained in the paediatric investigation plan:	Yes