



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/724148/2017

European Medicines Agency decision

P/0347/2017

of 1 December 2017

on the refusal of a modification of an agreed paediatric investigation plan for tolvaptan (Samsca and associated names), (EMA-001231-PIP02-13-M05) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Only the English text is authentic.



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on the refusal of a modification of an agreed paediatric investigation plan for tolvaptan (Samsca and associated names), (EMA-001231-PIP02-13-M05) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004¹,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency²,

Having regard to the European Medicines Agency's decision P/0221/2013 issued on 9 September 2013, the decision P/0336/2014 issued on 22 December 2014, the decision P/0045/2016 issued on 26 February 2016, the decision P/0161/2016 issued on 15 June 2016 and the decision P/0294/2016 issued on 4 November 2016,

Having regard to the application submitted by Otsuka Pharmaceutical Europe Ltd. on 24 July 2017 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 13 October 2017, in accordance with Article 22 of Regulation (EC) No 1901/2006, and of its own motion in accordance with Article 12 of said Regulation,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

- (1) The Paediatric Committee of the European Medicines Agency has given an opinion on the refusal of changes to the agreed paediatric investigation plan and to the deferral and on the granting of a waiver.
- (2) It is therefore appropriate to adopt a decision on the refusal of changes to the agreed paediatric investigation plan, including changes to the deferral.
- (3) It is therefore appropriate to adopt a decision on the granting of a waiver.

¹ OJ L 378, 27.12.2006, p.1.

² OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for tolvaptan (Samsca and associated names), tablet, oral suspension, oral use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, are hereby refused.

Article 2

A waiver for tolvaptan (Samsca and associated names), tablet, oral suspension, oral use, the details of which are set out in the opinion of the Paediatric Committee the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

This decision is addressed to Otsuka Pharmaceutical Europe Ltd., Gallions, Wexham Springs, Framewood Road, SL3 6PJ – Wexham, United Kingdom.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/PDCO/501579/2017

London, 13 October 2017

Opinion of the Paediatric Committee on the refusal of a modification of an agreed Paediatric Investigation Plan and on the granting of a product-specific waiver

EMA-001231-PIP02-13-M05

Scope of the application

Active substance(s):

Tolvaptan

Invented name:

Samsca and associated names

Condition(s):

Treatment of dilutional hyponatraemia

Treatment of polycystic kidney disease

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Tablet

Oral suspension

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Otsuka Pharmaceutical Europe Ltd.

Information about the authorised medicinal product:

See Annex II



Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Otsuka Pharmaceutical Europe Ltd. submitted to the European Medicines Agency on 24 July 2017 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/0221/2013 issued on 9 September 2013, the decision P/0336/2014 issued on 22 December 2014, the decision P/0045/2016 issued on 26 February 2016, the decision P/0161/2016 issued on 15 June 2016 and the decision P/0294/2016 issued on 4 November 2016.

The application for modification proposed changes to the agreed paediatric investigation plan and to the deferral.

The procedure started on 15 August 2017.

Opinion

The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to refuse the changes proposed by the applicant regarding the paediatric investigation plan and the deferral;

And in accordance with Article 12 of Regulation (EC) No 1901/2006 as amended, recommends:

- to grant a product-specific waiver on its own motion for one or more subsets of the paediatric population concluded in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annexes and appendix.

Annex I

The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)

1. Waiver

1.1. Condition

Treatment of dilutional hyponatraemia

The waiver applies to:

- preterm and term newborn infants from birth to less than 28 days of age;
- tablet, oral suspension, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

And to:

- the paediatric population from 28 days to less than 18 years of age;
- tablet, oral suspension, oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.

1.2. Condition

Treatment of polycystic kidney disease

The waiver applies to:

- preterm and term newborn infants from birth to less than 28 days of age;
- tablet, oral suspension, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric investigation plan

2.1. Condition

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)

2.2.1. Subset(s) of the paediatric population concerned by the paediatric development

From 28 days to less than 18 years of age

2.2.2. Pharmaceutical form(s)

Tablet

Oral suspension

2.2.3. Measures

Area	Number of measures	Description
Quality-related studies	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	2	<i>Study 3 for condition "treatment of dilutional hyponatraemia" was deleted as a result of procedure EMEA-001231-PIP02-13-M05</i> <i>Study 4 for condition "treatment of dilutional hyponatraemia" was deleted as a result of procedure EMEA-001231-PIP02-13-M05</i> <i>Study 5 for condition "treatment of dilutional hyponatraemia" was deleted as a result of procedure EMEA-001231-PIP02-13-M05</i> Study 6 Double-blind, randomised, placebo controlled trial to assess the effects of titrated oral tolvaptan on renal size, pharmacokinetics and safety in children from 4 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 (156-12-298) Study 7 Open-label study to assess safety and activity of tolvaptan in children from 4 weeks to less than 18 years of age diagnosed with autosomal recessive polycystic kidney disease (156-12-204)
Extrapolation, modelling and simulation studies	0	Not applicable
Other studies	0	Not applicable
Other measures	0	Not applicable

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By November 2020
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of dilutional hyponatraemia

Authorised indication(s):

- Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

2. Treatment of polycystic kidney disease

- Treatment of adult patients with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD).

Authorised pharmaceutical form(s):

Tablet

Authorised route(s) of administration:

Oral use