EMA/314188/2016

European Medicines Agency decision

P/0161/2016

of 15 June 2016

on the acceptance of a modification of an agreed paediatric investigation plan for tolvaptan (Samsca and associated names), (EMEA-001231-PIP02-13-M03) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Disclaimer

This Decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

Only the English text is authentic.

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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 726/2004[1],

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 Agency[2],

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, and the decision P/0045/2016 issued on 26 February 2016,

Having regard to the application submitted by Otsuka Pharmaceutical Europe Ltd. on 8 February 2016 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 29 April 2016, in accordance with Article 22 of Regulation (EC) No 1901/2006,

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 acceptance of changes to the agreed paediatric investigation plan.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.

[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, are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

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

Done at London, 15 June 2016

For the European Medicines Agency
Zaïde Frias
Head of Division
Human Medicines Research and Development Support
(Signature on file)

EMA/PDCO/159185/2016
London, 29 April 2016

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-001231-PIP02-13-M03

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

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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 8 February 2016 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, and the decision P/0045/2016 issued on 26 February 2016.

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

The procedure started on 1 March 2016.

Scope of the modification

Some measures of the Paediatric Investigation Plan have been modified.

Opinion

1. 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 agree to changes to the paediatric investigation plan in the scope set out in the Annex I of this opinion.

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

2. The measures and timelines of the paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver are set out in the Annex I.

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;
- for tablet and for oral suspension for oral use;
- on the grounds that the specific medicinal product is likely to be unsafe; and
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

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;
- for tablet and for oral suspension for oral use;
- on the grounds that the specific medicinal product is likely to be unsafe; and
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

2. Paediatric investigation plan

2.1. Condition:

Treatment of dilutional hyponatraemia

2.1.1. Indication(s) targeted by the PIP

Treatment of chronic (greater than 48 hours) dilutional hyponatraemia resistant to fluid restriction (i.e., euvolaemic and hypervolaemic hyponatraemia) associated with heart failure, cirrhosis or SIADH

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

From 28 days to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Tablet

Oral suspension

2.1.4. 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	3	**Study 3** Randomised, double-blind, placebo-controlled pilot trial to evaluate safety, efficacy and pharmacokinetics of tolvaptan in children from 4 weeks to less than 18 years of age with chronic (greater than 48 hours) dilutional hyponatraemia resistant to fluid restriction (156-13-207). **Study 4** Multicentre, randomised, double-blind, placebo-controlled trial to evaluate safety, efficacy and pharmacokinetics of tolvaptan in children from 4 weeks to less than 18 years of age with chronic (greater than 48 hours) dilutional hyponatraemia resistant to fluid restriction (156-12-205). **Study 5** Open-label extension trial to evaluate long-term safety of multiple doses of tolvaptan in children and adolescents with chronic (greater than 48 hours) dilutional hyponatraemia resistant to fluid restriction (156-11-294).
Extrapolation, modelling and simulation studies	0	Not applicable.
Other studies	0	Not applicable.
Other measures	0	Not applicable.

2.2. Condition:

Treatment of polycystic kidney disease

2.3. Indication(s) targeted by the PIP

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

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

From 28 days to less than 18 years of age

2.3.2. Pharmaceutical form(s)

Tablet

Oral suspension

2.3.3. 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. (Same study as for condition “Treatment of dilutional hyponatraemia”)
Non-clinical studies	1	**Study 2** Study to evaluate the toxicity and toxicokinetics of tolvaptan in juvenile rats. (Same study as for condition “Treatment of dilutional hyponatraemia”)
Clinical studies	2	**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).
   - 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