EMA/711194/2014

European Medicines Agency decision

P/0336/2014

of 22 December 2014

on the acceptance of a modification of an agreed paediatric investigation plan for tolvaptan (Samsca) (EMEA-001231-PIP02-13-M01) 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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on the acceptance of a modification of an agreed paediatric investigation plan for tolvaptan (Samsca) (EMEA-001231-PIP02-13-M01) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

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,

Having regard to the application submitted by Otsuka Pharmaceutical Europe Ltd. on 26 August 2014 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 14 November 2014, 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), 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, 22 December 2014

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

EMA/PDCO/541126/2014

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

EMEA-001231-PIP02-13-M01

Scope of the application

Active substance(s):

Tolvaptan

Invented name:

Samsca

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 26 August 2014 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 application for modification proposed changes to the agreed paediatric investigation plan.

The procedure started on 16 September 2014.

Scope of the modification

Some timelines 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 Icelandic and the Norwegian Paediatric Committee members agree 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.

London, 14 November 2014

On behalf of the Paediatric Committee
Dr Dirk Mentzer, Chairman
(Signature on file)

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 (>48 hours) dilutional hyponatraemia resistant to fluid restriction (i.e., euvolemic 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 4 weeks 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 and efficacy of tolvaptan in children from 4 weeks to less than 18 years of age with chronic (>48 hours) dilutional hyponatraemia resistant to fluid restriction (156-13-207). **Study 4** Multicentre, randomised, double-blind, placebo-controlled trial to evaluate safety and efficacy of tolvaptan in children from 4 weeks to less than 18 years of age with chronic (>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 (>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

2.2.1. Indication(s) targeted by the PIP

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

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

From 4 weeks to less than 18 years of age.

2.2.3. Pharmaceutical form(s)

Tablet

Oral suspension

2.2.4. 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 (same as for the condition “Treatment of dilutional hyponatraemia”).
Non-clinical studies	1	**Study 2** Study to evaluate the toxicity and toxicokinetics of tolvaptan in juvenile rats (same as for the 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 December 2019
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).

Authorised pharmaceutical form(s):

Tablet

Authorised route(s) of administration:

Oral use