EMA/493083/2013

European Medicines Agency decision

P/0221/2013

of 9 September 2013

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for tolvaptan (Samsca), (EMEA-001231-PIP02-13) 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 application submitted by Otsuka Pharmaceutical Europe Ltd. on 11 January 2013 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 9 August 2013, in accordance with Article 18 of Regulation (EC) No 1901/2006, and Article 21 of said Regulation and Article 13 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 agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver.

(2) It is therefore appropriate to adopt a decision agreeing a paediatric investigation plan.

(3) It is therefore appropriate to adopt a decision granting a deferral.

(4) It is therefore appropriate to adopt a decision granting 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

A paediatric investigation plan for tolvaptan (Samsca), 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, is hereby agreed.

Article 2

A deferral for tolvaptan (Samsca), 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, is hereby granted.

Article 3

A waiver for tolvaptan (Samsca), 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, is hereby granted.

Article 4

This decision is addressed to Otsuka Pharmaceutical Europe Ltd., Hunton House, Highbridge Business Park, Oxford Road, UB8 1HU – Uxbridge, United Kingdom.

Done at London, 9 September 2013

For the European Medicines Agency
Guido Rasi
Executive Director
(Signature on file)

EMA/PDCO/232054/2013

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver

EMEA-001231-PIP02-13

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 16(1) of Regulation (EC) No 1901/2006 as amended, Otsuka Pharmaceutical Europe Ltd. submitted for agreement to the European Medicines Agency on 11 January 2013 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 13 February 2013.

Supplementary information was provided by the applicant on 20 May 2013. The applicant proposed modifications to the paediatric investigation plan.

Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree the paediatric investigation plan in accordance with Article 18 of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation;
   - to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(a) of said Regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population; and 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.

2. The measures and timelines of the agreed 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, 9 August 2013

On behalf of the Paediatric Committee
Dr Daniel Brasseur, 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

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 and oral suspension for oral use

2.1.4. Measures

Area	Number of measures	Description
Quality	1	**Measure 1** Development of an oral suspension for use in children younger than 4 years or who are unable to swallow tablets (1368432667269).
Non-clinical	1	**Measure 2** Study to evaluate the toxicity and toxicokinetics of tolvaptan in juvenile rats (1368433234582).
Clinical	3	**Measure 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. **Measure 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 (1368433274766; 156-12-205). **Measure 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 (1368970631896; 156-11-294).

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 and oral suspension for oral use.

2.2.4. Measures

Area	Number of measures	Description
Quality	1	**Measure 1** Development of an oral suspension for use in children younger than 4 years or who are unable to swallow tablets (1368432667269) (same as for the condition “Treatment of dilutional hyponatraemia”).
Non-clinical	1	**Measure 2** Study to evaluate the toxicity and toxicokinetics of tolvaptan in juvenile rats (1368433234582) (same as for the condition “Treatment of dilutional hyponatraemia”).
Clinical	2	**Measure 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 (1368532113287; 156-12-298). **Measure 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 (1368964587970; 156-12-204).

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety and 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