EMA/43448/2014

European Medicines Agency decision

P/0050/2014

of 7 March 2014

on the agreement of a paediatric investigation plan and on the refusal of a waiver for enalapril (maleate) (EMEA-001241-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 Proveca Limited on 5 July 2013 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 17 January 2014, in accordance with Article 18 of Regulation (EC) No 1901/2006, 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 refusal of a waiver.

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

(4) It is therefore appropriate to adopt a decision refusing 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 enalapril (maleate), oral solution, 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 waiver for enalapril (maleate), oral solution, 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 refused.

Article 2

This decision is addressed to Proveca Limited, Daresbury Innovation Centre, Keckwick Lane, Daresbury, Halton, Cheshire, WA4 4FS – Halton, United Kingdom.

Done at London, 7 March 2014

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

EMA/PDCO/676641/2013

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

EMEA-001241-PIP02-13

Scope of the application

Active substance(s):

Enalapril (maleate)

Condition(s):

Treatment of heart failure

Pharmaceutical form(s):

Oral solution

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Proveca Limited

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Proveca Limited submitted for agreement to the European Medicines Agency on 5 July 2013 an application for a paediatric investigation plan for the above mentioned medicinal product and a waiver under Article 13 of said Regulation.

The procedure started on 15 August 2013.

Supplementary information was provided by the applicant on 25 October 2013. The applicant proposed modifications to the paediatric investigation plan.

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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 refuse the granting of a waiver in accordance with Article 13 of said Regulation, for some of the subsets of the paediatric population and the above mentioned condition(s) as it does not meet the grounds detailed in Article 11(1) of said Regulation.

   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 agreed paediatric investigation plan 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 annex and appendix.

London, 17 January 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

1. Waiver

1.1. Condition: treatment of heart failure

The request for the waiver applied to:

- Preterm and term newborn infants from birth to less than 1 month of age;
- for oral solution for oral use.

The waiver request does not provide evidence to support the following grounds set out in Article 11(1) of Regulation (EC) No 1901/2006 that:

- (a) the specific medicinal product is likely to be ineffective or unsafe in the paediatric population;
- (b) the disease or condition for which the specific medicinal product is intended occurs only in adult populations;
- (c) the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Because:

- the PDCO disagreed with the applicant(s)' argumentation that the specific medicinal product is likely to be ineffective or unsafe;
- the disease or condition for which the specific medicinal product is intended, does occur in the paediatric population(s);
- measures would be justified by the expected therapeutic benefit and clinical trials may be feasible;
- the specific medicinal product may represent a significant therapeutic benefit as the needs are not met;
- and clinical studies may fulfil a therapeutic need of the paediatric population.

The waiver request is therefore refused by the PDCO.

2. Paediatric Investigation Plan

2.1. Condition: treatment of heart failure

2.1.1. Indication(s) targeted by the PIP

Treatment of heart failure

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

From birth to less than 18 years of age.

2.1.3. Pharmaceutical form(s)

Oral solution for oral use.

2.1.4. Measures

Area	Number of measures	Description
Quality	3	**Study 1:** Development of an enalapril-containing formulation suitable for administration via the oral route to the paediatric population from birth to less than 18 years of age (PRO/ENA/004) **Study 2:** An adult trained taste panel to assess the palatability of the enalapril oral formulation prior to its use in children (PRO/ENA/005) **Study 3:** Assessment of the in vitro stability of enalapril in the new formulation in combination with milk feed and simulated "gastric juices of an infant" plus in vitro assessment of parenteral feeding as used with nasogastric/gastronomy tubes in older children (PRO/GLY/ENA/007)
Non-clinical	0	Not applicable.
Clinical	6	**Study 4:** Bioequivalence / comparative bioavailability study in adult healthy volunteers comparing the new liquid formulation of enalapril with a licensed enalapril tablet (PRO/ENA/006) **Study 5:** Open label, single dose population pharmacokinetic study of oral enalapril administered to children from 1 month to less than 12 years of age, diagnosed with heart failure secondary to both high and low output disease (PRO/ENA/001) **Study 6:** Open label, 12 month safety study in children aged 1 to less than 12 months at entry to study receiving enalapril for heart failure (PRO/ENA/002) **Study 7:** Systematic literature review, data extrapolation and modeling (PRO/ENA/003) **Study 8:** Open label, single dose population pharmacokinetic study of oral enalapril administered to term neonates from birth to less than 1 month of age, diagnosed with heart failure **Study 9:** Open label, 12 month safety study in term neonates from birth to less than 1 month of age at entry to study receiving enalapril for heart failure

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By September 2019
Deferral for one or more measures contained in the paediatric investigation plan:	No