



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/273210/2012

European Medicines Agency decision P/0096/2012

of 30 May 2012

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate (LCZ696) (EMEA-000316-PIP02-11) 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.



European Medicines Agency decision

P/0096/2012

of 30 May 2012

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate (LCZ696) (EMEA-000316-PIP02-11) 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 application submitted by Novartis Europharm Ltd. on 23 December 2011 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 13 April 2012, 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 trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate (LCZ696), film-coated tablet, age-appropriate solid oral dosage form, 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 trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate (LCZ696), film-coated tablet, age-appropriate solid oral dosage form, 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 trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate (LCZ696), film-coated tablet, age-appropriate solid oral dosage form, 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 Novartis Europharm Ltd., Wimblehurst Road, RH12 5AB - Horsham, West Sussex, United Kingdom.

Done at London, 30 May 2012

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/PDCO/249277/2012

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

EMA-000316-PIP02-11

Scope of the application

Active substance(s):

Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate (LCZ696)

Condition(s):

Treatment of heart failure

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate solid oral dosage form

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Novartis Europharm Ltd.

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Novartis Europharm Ltd. submitted for agreement to the European Medicines Agency on 23 December 2011 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 15 February 2012.



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 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(es) and appendix.

London, 13 April 2012

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

Not applicable.

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)

Film-coated tablet

Age-appropriate solid oral dosage form

2.1.4. Studies

Area	Number of studies	Description
Quality	1	Study 1: Development of an age-appropriate solid oral dosage form
Non-clinical	4	Study 2: Mechanistic <i>in-vitro</i> study (1107517) Study 3: 4-week dose range-finding juvenile rabbit bone toxicity study (1170514) Study 4: 26-week juvenile rabbit bone toxicity study (1170515) Study 5: 4-week juvenile rat bone toxicity study (1170516)

Area	Number of studies	Description
Clinical	5	Study 6: Open-label, randomized, single-dose, multiple treatment period study to determine the relative bioavailability of Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate (hereinafter: LCZ696) paediatric formulations relative to the LCZ696 200 mg Final Market Image (FMI) tablet in healthy adult subjects (CLCZ696 BXXXX) Study 7: Open label, randomized, three period, single-dose, crossover study to determine the bioavailability of the 200 mg LCZ696 paediatric formulation relative to the 200 mg LCZ696 FMI tablet under fasted condition and to evaluate the effect of food on the pharmacokinetics of 200 mg LCZ696 paediatric formulation in healthy adult subjects (CLCZ696 BYYYY) Study 8: Open-label, single-dose, multi-centre study to evaluate the safety/tolerability and pharmacokinetics of LCZ696 in paediatric patients from birth to less than 18 years of age with heart failure (CLCZ696 B22PK) Study 9: Double-blind, randomized, multi-centre, active controlled, parallel-group study to evaluate the safety and efficacy of LCZ696 vs. enalapril in paediatric patients from birth to less than 18 years of age with symptomatic left ventricular systolic dysfunction and heart failure (CLCZ696 B23HF) Study 10: Multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of LCZ696 in paediatric patients from birth to less than 18 years of age with chronic heart failure resulting from left ventricular systolic dysfunction (CLCZ696 B23HF-E1)

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety or efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By November 2021
Deferral for one or more studies contained in the paediatric investigation plan:	Yes