EMA/169104/2014

European Medicines Agency decision

P/0106/2014

of 5 May 2014

on the acceptance of a modification of an agreed paediatric investigation plan for octadecasodium hexakis(4-{[(1*S*,3*R*)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate) hexakis(*N*-pentanoyl-*N*-{[2´-(1*H*-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15) (LCZ696) (EMEA-000316-PIP02-11-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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European Medicines Agency decision

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on the acceptance of a modification of an agreed paediatric investigation plan for octadecasodium hexakis(4-{[(1*S*,3*R*)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate) hexakis(*N*-pentanoyl-*N*-{[2´-(1*H*-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15) (LCZ696) (EMEA-000316-PIP02-11-M01) 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 726/2004[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/0096/2012 issued on 30 May 2012,

Having regard to the application submitted by Novartis Europharm Ltd. on 17 December 2013 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 21 March 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 octadecasodium hexakis(4-{[(1*S*,3*R*)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate) hexakis(*N*-pentanoyl-*N*-{[2´-(1*H*-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15) (LCZ696), film-coated tablet, age-appropriate solid oral dosage form, 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 Novartis Europharm Ltd., Wimblehurst Road, RH12 5AB - Horsham, West Sussex, United Kingdom.

Done at London, 5 May 2014

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

EMA/PDCO/39160/2014

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

EMEA-000316-PIP02-11-M01

Scope of the application

Active substance(s):

Octadecasodium hexakis(4-{[(1*S*,3*R*)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate) hexakis(*N*-pentanoyl-*N*-{[2´-(1*H*-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15) (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 22 of Regulation (EC) No 1901/2006 as amended, Novartis Europharm Ltd. submitted to the European Medicines Agency on 17 December 2013 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0096/2012 issued on 30 May 2012.

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

The procedure started on 21 January 2014.

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Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified and the name of the substance updated to comply with the current naming conventions.

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 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, 21 March 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

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	3	**Study 2:** Mechanistic *in-vitro* study (1170517). **Study 3:** 4-week dose range-finding juvenile rabbit bone toxicity study (1170514). **Study 4:** 4-week investigative bone study in juvenile rats (1170516).
Clinical	4	**Study 5:** Open-label, randomized, single-dose, multiple treatment period study to determine the relative bioavailability of LCZ696 paediatric formulation relative to the LCZ696 200 mg Final Market Image (FMI) tablet in healthy adult subjects (CLCZ696 B2126). **Study 6:** 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).

Area	Number of studies	Description
		Study 7: 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 8:** 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