EMA/241894/2019

European Medicines Agency decision

P/0176/2019

of 15 May 2019

on the acceptance of a modification of an agreed paediatric investigation plan for asfotase alfa (Strensiq), (EMEA-000987-PIP01-10-M04) 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 European Medicines Agency's decision P/0052/2013 issued on 1 March 2013, the decision P/0306/2013 issued on 5 December 2013, the decision P/0176/2014 issued on 2 July 2014 and the decision P/0204/2017 issued on 9 August 2017,

Having regard to the application submitted by Alexion Europe SAS on 20 December 2018 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 29 March 2019, 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 and to the deferral.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan, including changes to the deferral.

[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 asfotase alfa (Strensiq), solution for injection, subcutaneous use, including changes to the deferral, 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 Alexion Europe SAS, 1-15 avenue Edouard Belin, 92500 - Rueil-Malmaison, France.

EMA/PDCO/908839/2019
Amsterdam, 29 March 2019

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

EMEA-000987-PIP01-10-M04

Scope of the application

Active substance(s):

Asfotase alfa

Invented name:

Strensiq

Condition(s):

Treatment of hypophosphatasia

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Solution for injection

Route(s) of administration:

Subcutaneous use

Name/corporate name of the PIP applicant:

Alexion Europe SAS

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Alexion Europe SAS submitted to the European Medicines Agency on 20 December 2018 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0052/2013 issued on 1 March 2013, the decision P/0306/2013 issued on 5 December 2013, the decision P/0176/2014 issued on 2 July 2014 and the decision P/0204/2017 issued on 9 August 2017.

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

The procedure started on 29 January 2019.

Scope of the modification

Some measures and 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 and to the deferral in the scope set out in the Annex I of this opinion.

   The Norwegian Paediatric Committee member agrees 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 annexes and appendix.

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

Not applicable

2. Paediatric investigation plan

2.1. Condition:

Treatment of hypophosphatasia

2.1.1. Indication(s) targeted by the PIP

Treatment of hypophosphatasia

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)

Solution for injection

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of appropriate strengths solution of asfotase alfa for subcutaneous use for all subsets of the paediatric population: 40 mg/mL and 100 mg/mL
Non-clinical studies	0	Not applicable
Clinical studies	7	**Study 3** Open label, single arm, exploratory trial to evaluate the safety, tolerability, pharmacokinetics and pharmacology of asfotase alfa intravenous infusion and subcutaneous injection in children from birth to less than 4 years of age with severe hypophosphatasia (ENB-002-08) **Study 4** Open label, single arm, exploratory extension study of Measure 3 to evaluate the safety, tolerability, pharmacokinetics and pharmacology of asfotase alfa intravenous infusion and subcutaneous injection in children with severe hypophosphatasia (ENB-003-08)

		Study 5 Open-label trial to evaluate safety, efficacy, survival, growth, development and pharmacokinetics of asfotase alfa subcutaneous injection in children from birth to less than 6 years of age with severe hypophosphatasia (ENB-0010-10) **Study 6** Retrospective, non-interventional epidemiologic study of the natural history to evaluate overall survival in patients with severe perinatal and infantile hypophosphatasia and compare outcomes to those of the interventional studies with asfotase alfa of Measure 3 / 4 and 5 (ENB-011-10) **Study 7** Open-label, dose-ranging, historical control study to evaluate the safety, activity, pharmacokinetics and pharmacodynamics of asfotase alfa subcutaneous injection in paediatric hypophosphatasia patients from 5 to less than 13 years and Tanner stage of 2 or less (prepubescent) with open growth plates with perinatal/infantile and childhood onset (ENB-006-09) **Study 8** Open-label, dose-ranging, historical control, extension study of Measure 7 to evaluate the long-term safety, activity, pharmacokinetics and pharmacodynamics of asfotase alfa subcutaneous injection in paediatric hypophosphatasia patients with perinatal/infantile and childhood onset (ENB-008-09) **Study 9** Randomized, open-label, dose-ranging concurrent control study to evaluate the safety, pharmacokinetics, pharmacodynamics and activity of asfotase alfa in adolescents (and adults) with perinatal/infantile and childhood onset hypophosphatasia (ENB-009-10) **Study 10** *This study was deleted as a result of procedure EMEA-000987-PIP01-10-M04.*
Extrapolation, modelling and simulation studies	2	**Study 2** Population pharmacokinetics and exposure-response modelling to quantify the population pharmacokinetics of asfotase-alfa, to quantify the relationship between asfotase-alfa exposure and plasma inorganic pyrophosphate and Pyridoxal 5' phosphate biomarkers and to integrate the pharmacokinetic model and exposure-

		response relationships to support dosing recommendations for asfotase-alfa in specific hypophosphatasia treatment populations **Study 11** Measure to extrapolate efficacy to children from 6 months to below 3 years of age with juvenile onset HPP. Analysis of existing in house data on paediatric patients 6 months to below 3 years of age with perinatal/infantile onset HPP and children aged 3 years and above with juvenile onset hypophosphatasia
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 2016
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 hypophosphatasia

Authorised indication(s):

- Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease

Authorised pharmaceutical form(s):

Solution for injection

Authorised route(s) of administration:

Subcutaneous use