EMA/579644/2013

European Medicines Agency decision

P/0244/2013

of 4 October 2013

on the acceptance of a modification of an agreed paediatric investigation plan for edoxaban (tosylate) (EMEA-000788-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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on the acceptance of a modification of an agreed paediatric investigation plan for edoxaban (tosylate) (EMEA-000788-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/136/2011 issued on 10 June 2011,

Having regard to the application submitted by Daiichi Sankyo Development Limited on 21 June 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 13 September 2013, in accordance with Article 22 of Regulation (EC) No 1901/2006, and Article 21 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 acceptance of changes to the agreed paediatric investigation plan and on the granting of a deferral.

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

(3) It is therefore appropriate to adopt a decision on the granting of a 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 edoxaban (tosylate), film-coated tablet, age-appropriate oral solid 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

A deferral for edoxaban (tosylate), film-coated tablet, age-appropriate oral solid dosage form, oral use, the details of which are set out in the opinion of the Paediatric Committee the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

This decision is addressed to Daiichi Sankyo Development Limited, Chiltern Place, Chalfont Park, SL9 0BG Gerrards Cross, Buckinghamshire, United Kingdom.

Done at London, 4 October 2013

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

EMA/579644/2013 Corr

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

EMEA-000788-PIP02-11-M01

Scope of the application

Active substance(s):

Edoxaban (tosylate)

Condition(s):

Prevention of arterial thromboembolism

Treatment of venous thromboembolism

Prevention of venous thromboembolism

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate oral solid dosage form

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Daiichi Sankyo Development Limited

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Daiichi Sankyo Development Limited submitted to the European Medicines Agency on 21 June 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/136/2011 issued on 10 June 2011.

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

The procedure started on 17 July 2013.

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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 in the scope set out in the Annex I of this opinion;
   - to grant a deferral, the details of which are 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, 13 September 2013

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: Prevention of arterial thromboembolism

2.1.1. Indication(s) targeted by the PIP

Prevention of arterial thromboembolism in paediatric cardiac patients at risk of thrombotic events.

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 and age-appropriate oral solid dosage form.

2.1.4. Measures

Area	Number of measures	Description
Quality	1	**Measure 1**: Development of an age appropriate oral powder or powder/granules for oral suspension.
Non-clinical	6	**Measure 2**: 18-day dose-range finding study of edoxaban tosylate in juvenile rats **Measure 3**: 18-day dose-range finding study of edoxaban tosylate metabolite (D21-2393) in juvenile rats. **Measure 4**: 38-day repeated-dose toxicity study of edoxaban tosylate in juvenile rats **Measure 5**: 38-day repeated-dose toxicity study of edoxaban tosylate metabolite (D21-2393) in juvenile rats. **Measure 6**: Single dose study in juvenile and adult rats to evaluate pharmacokinetics of edoxaban tosylate. **Measure 7:** Single dose study in juvenile and adult rats to evaluate pharmacokinetics of

		edoxaban tosylate metabolite (D21-2393).
Clinical	3	**Measure 8:** Open-label, randomised, cross-over, and single dose trial to determine the bioequivalence of edoxaban tosylate paediatric age appropriate formulation compared to tablets and food effect in healthy adults. **Measure 9:** Ex vivo assessment of coagulation assays in paediatric and adult subjects. **Measure 10:** Open-label, randomised, multicentre, parallel-group observational trial to evaluate safety (primary objective) and efficacy (secondary objective) of edoxaban tosylate in children from 36 weeks gestational age to less than 18 years of age with cardiac diseases at risk of thrombotic events.

2.2. Condition: Treatment of venous thromboembolism

2.2.1. Indication(s) targeted by the PIP

Acute treatment and secondary prevention of symptomatic recurrent venous thrombotic events (VTE) in paediatric patients at risk.

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

From birth to less than 18 years of age.

2.2.3. Pharmaceutical form(s)

Film-coated tablet and age-appropriate oral solid dosage form.

2.2.4. Measures

Area	Number of measures	Description
Quality	1	**Measure 1**: (Same study as for condition “Prevention of arterial thromboembolism”)
Non-clinical	6	**Measure 2**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 3**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 4**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 5**: (Same study as for condition “Prevention of arterial thromboembolism”)

		Measure 6: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 7:** (Same study as for condition “Prevention of arterial thromboembolism”)
Clinical	4	**Measure 8:** (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 9:** (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 11:** Open-label, multicentre, sequential design trial to evaluate pharmacokinetics and pharmacodynamics of edoxaban tosylate in children from birth to less than 18 years of age with deep vein thrombosis treated initially with standard of care. **Measure 12:** Open-label, randomised, multicentre, active controlled trial to compare the efficacy of low molecular weight heparin (LMWH) / unfractionated heparin (UFH) followed by edoxaban tosylate with LMWH / UFH followed by vitamin K antagonists (VKA) or LMWH / UFH only in children from 38 weeks gestational age to less than 18 years of age with confirmed venous thromboembolic diseases.

2.3. Condition: Prevention of venous thromboembolism

2.3.1. Indication(s) targeted by the PIP

Acute treatment and secondary prevention of symptomatic recurrent venous thrombotic events (VTE) in paediatric patients at risk.

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

From birth to less than 18 years of age.

2.3.3. Pharmaceutical form(s)

Film-coated tablet and age-appropriate oral solid dosage form.

2.3.4. Measures

Area	Number of measures	Description
Quality	1	**Measure 1**: (Same study as for condition “Prevention of arterial thromboembolism”)
Non-clinical	6	**Measure 2**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 3**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 4**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 5**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 6**: (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 7:** (Same study as for condition “Prevention of arterial thromboembolism”)
Clinical	4	**Measure 8:** (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 9:** (Same study as for condition “Prevention of arterial thromboembolism”) **Measure 11:** (Same study as for condition “Treatment of venous thromboembolism”) **Measure 12:** (Same study as for condition “Treatment of venous thromboembolism”)

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	By March 2018
Deferral for one or more measures contained in the paediatric investigation plan:	Yes