EMA/356126/2011

European Medicines Agency decision

P/136/2011

of 10 June 2011

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the refusal of a waiver for edoxaban (tosylate) (EMEA-000788-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.

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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 Daiichi Sankyo Development Limited on 13 January 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 20 April 2011, 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 refusal 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 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 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 of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

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 of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

A waiver 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 of the European Medicines Agency annexed hereto, together with its appendices, is hereby refused.

Article 4

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

Done at London, 10 June 2011

For the European Medicines Agency
Andreas Pott
Acting Executive Director
(Signature on file)

EMA/PDCO/257648/2011

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

EMEA-000788-PIP02-11

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 16(1) of Regulation (EC) No 1901/2006 as amended, Daiichi Sankyo Development Limited submitted for agreement to the European Medicines Agency on 13 January 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 23 February 2011.

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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 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 Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the agreed paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver 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, 20 April 2011

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: 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. Studies

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

		edoxaban tosylate metabolite (D21-2393).
Clinical	3	**Study 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. **Study 9:** Ex vivo assessment of coagulation assays in paediatric and adult subjects. **Study 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. Studies

Area	Number of studies	Description
Quality	1	**Study 1**: (Same study as for condition "Prevention of arterial thromboembolism")
Non-clinical	6	**Study 2**: (Same study as for condition "Prevention of arterial thromboembolism") **Study 3**: (Same study as for condition "Prevention of arterial thromboembolism") **Study 4**: (Same study as for condition "Prevention of arterial thromboembolism") **Study 5**: (Same study as for condition "Prevention of arterial thromboembolism") **Study 6**: (Same study as for condition "Prevention of arterial thromboembolism") **Study 7:** (Same study as for condition "Prevention of arterial thromboembolism")
Clinical	4	**Study 8:** (Same study as for condition "Prevention of arterial thromboembolism") **Study 9:** (Same study as for condition "Prevention of arterial thromboembolism") **Study 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. **Study 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. Studies

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

3. Follow-up, completion and deferral of PIP

Measures to address long term follow-up of potential 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 studies contained in the paediatric investigation plan:	Yes