EMA/568797/2021

European Medicines Agency decision

P/0423/2021

of 29 October 2021

on the acceptance of a modification of an agreed paediatric investigation plan for edoxaban (tosylate) (Lixiana), (EMEA-000788-PIP02-11-M11) 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) (Lixiana), (EMEA-000788-PIP02-11-M11) 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, the decision P/0244/2013 issued on 4 October 2013, the decision P/0028/2014 issued on 27 January 2014, the decision P/0250/2014 issued on 30 September 2014, the decision P/0302/2015 issued on 21 December 2015, the decision P/0012/2017 issued on 31 January 2017, the decision P/0322/2017 issued on 31 October 2017, the decision P/0141/2018 issued on 7 May 2018, the decision P/0368/2018 issued on 7 December 2018, the decision P/0013/2020 issued on 6 January 2020 and the decision P/0393/2020 issued on 23 October 2020,

Having regard to the application submitted by Daiichi Sankyo Europe GmbH on 4 June 2021 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 10 September 2021, 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 edoxaban (tosylate) (Lixiana), film-coated tablet, age-appropriate oral dosage form, oral 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 Daiichi Sankyo Europe GmbH, Zielstattstrasse 48, 81379 – Munich, Germany.

EMA/PDCO/325790/2021 Corr
Amsterdam, 10 September 2021

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

EMEA-000788-PIP02-11-M11

Scope of the application

Active substance(s):

Edoxaban (tosylate)

Invented name:

Lixiana

Condition(s):

Prevention of arterial thromboembolism

Treatment of venous thromboembolism

Prevention of venous thromboembolism

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate oral dosage form

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Daiichi Sankyo Europe GmbH

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 4 June 2021 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 decision P/0244/2013 issued on 4 October 2013, the decision P/0028/2014 issued on 27 January 2014, the decision P/0250/2014 issued on 30 September 2014, the decision P/0302/2015 issued on 21 December 2015, the decision P/0012/2017 issued on 31 January 2017, the decision P/0322/2017 issued on 31 October 2017, the decision P/0141/2018 issued on 7 May 2018, the decision P/0368/2018 issued on 7 December 2018, the decision P/0013/2020 issued on 6 January 2020 and the decision P/0393/2020 issued on 23 October 2020.

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

The procedure started on 12 July 2021.

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

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

Age-appropriate oral dosage form

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of an age appropriate oral dosage form (granules for oral suspension)
Non-clinical studies	6	**Study 2** Dose-range finding study of edoxaban (tosylate) in juvenile rats. (SBL314-516) **Study 3** Dose-range finding study of edoxaban (tosylate) metabolite (D21-2393) in juvenile rats. (SBL314-517) **Study 4** Repeated-dose toxicity study of edoxaban (tosylate) in juvenile rats. (SBL314-562) **Study 5** Repeated-dose toxicity study of edoxaban (tosylate) metabolite (D21-2393) in juvenile rats. (SBL314-563)

		Study 6 Single dose study in juvenile and adult rats to evaluate pharmacokinetics of edoxaban (tosylate). (B100897) **Study 7** Single dose study in juvenile and adult rats to evaluate pharmacokinetics of edoxaban (tosylate) metabolite (D21-2393). (B100896)
Clinical studies	4	**Study 8** Open-label, randomised, cross-over, single dose trial to determine the bioequivalence of edoxaban (tosylate) paediatric age appropriate formulation compared to tablets and food effect in healthy adults. (DU176b-A-U154) **Study 9** Ex vivo assessment of coagulation assays in paediatric and adult subjects. (TMCP-Peds-001) **Study 10** Open-label, randomised, multicentre, parallel-group observational trial to evaluate safety and efficacy of edoxaban (tosylate) in children from 38 weeks gestational age to less than 18 years of age with cardiac diseases at risk of thrombotic events. (DU176b-C-U313) **Study 13** Open-label, single-dose, non-randomised trial to evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of edoxaban in paediatric patients. (DU176b-A-U157; 2015-005732-18)
Extrapolation, modelling and simulation studies	1	**Study 14** Population-based pharmacokinetic (PopPK) model to predict the dose in the single-dose study.
Other studies	0	Not applicable
Other measures	0	Not applicable

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

Age-appropriate oral dosage form

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** (Same study as for condition "Prevention of arterial thromboembolism")
Non-clinical studies	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 studies	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** Randomised, open-label, blinded-endpoint (PROBE), multicentre, controlled trial to evaluate pharmacokinetics and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban to standard of care anticoagulant therapy in children from birth to less than 18 years with confirmed venous thromboembolism (VTE). (DU176B-D-U312) *Study 12 deleted in procedure EMEA-000788-PIP02-11-M04.* **Study 13** (Same study as for condition "Prevention of arterial thromboembolism")
Extrapolation, modelling and simulation studies	1	**Study 14** (Same study as for condition "Prevention of arterial thromboembolism")
Other studies	0	Not applicable
Other measures	0	Not applicable

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

Age-appropriate oral dosage form

2.3.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** (Same study as for condition "Prevention of arterial thromboembolism")
Non-clinical studies	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 studies	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 deleted in procedure EMEA-000788-PIP02-11-M04.* **Study 13** (Same study as for condition "Prevention of arterial thromboembolism")

Extrapolation, modelling and simulation studies	1	**Study 14** (Same study as for condition "Prevention of arterial thromboembolism")
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:	No
Date of completion of the paediatric investigation plan:	By December 2022
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. Prevention of arterial thromboembolism

Authorised indication(s):

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

2. Treatment of venous thromboembolism and prevention of venous thromboembolism

Authorised indication(s):

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

Authorised pharmaceutical form(s)

Film-coated tablet

Authorised route(s) of administration

Oral use