MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Decision Cover Letter

Decision of the licensing authority to:

accept change(s) to the agreed paediatric investigation plan and to the deferral

MHRA-100329-PIP01-21-M01

Scope of the Application

Active Substance(s)

EDOXABAN TOSYLATE

Condition(s)

Treatment of venous thromboembolism, Prevention of arterial thromboembolism, Prevention of Venous thromboembolism

Pharmaceutical Form(s)

Film coated tablets; Age-appropriate oral dosage form

Route(s) of Administration

Oral use

Name / Corporate name of the PIP applicant

Daiichi Sankyo UK Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Daiichi Sankyo UK Limited submitted to the licensing authority on 30/11/2021 22:25 GMT an application for a

The procedure started on 10/08/2022 21:34 BST

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to accept change(s) to the agreed paediatric investigation plan and to the deferral

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This decision is forwarded to the applicant, together with its annex and appendix.

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Final Decision Letter

MHRA-100329-PIP01-21-M01

Of 16/09/2022 19:55 BST

On the adopted decision for EDOXABAN TOSYLATE (MHRA-100329-PIP01-21-M01) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on modification of a paediatric investigation plan (including modification of a waiver or deferral included in that paediatric investigation plan)

This decision applies to a for EDOXABAN TOSYLATE, Film coated tablets; Age-appropriate oral dosage form , Oral use .

This decision is addressed to Daiichi Sankyo UK Limited, Zielstattstrasse 48, Munich, Germany, 81379

ANNEX I

1. Waiver

1.1 Condition:

Not applicable

2. Paediatric Investigation Plan:

2.1 Condition(s):

Condition 1: Prevention of arterial thromboembolism, Condition 2: Treatment of venous thromboembolism Condition 3: Prevention of venous thromboembolism,

2.2 Indication(s) targeted by the PIP:

Condition 1: Prevention of arterial thromboembolism in paediatric cardiac patients at risk of thrombotic events Condition 2: Acute treatment and secondary prevention of symptomatic recurrent venous thrombotic events (VTE) in paediatric patients at risk Condition 3: Acute treatment and secondary prevention of symptomatic recurrent venous thrombotic events (VTE) in paediatric patients at risk

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

(For Conditions 1 2 and 3) The paediatric population from birth to less than 18 years of age

2.4 Pharmaceutical Form(s):

(For Conditions 1 2 and 3): Film coated tablets; Age-appropriate oral dosage form

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	1	(Same Study for Conditions 1, 2 and 3) Study 1 Development of an age-appropriate oral dosage form (granules for oral suspension).
Non-Clinical Studies	6	(Same Studies for Conditions 1, 2 and 3) 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	5	(Same Studies for Conditions 1, 2 and 3) 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 for Condition 1 only) 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) (Same Studies for Conditions 2 and 3 only) 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. (Same Study for Conditions 1, 2 and 3) 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, Modeling & Simulation Studies	1	(Same Study for Conditions 1, 2 and 3) 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

3. Follow-up, completion and deferral of a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	31/12/2022
Deferral of one or more studies contained in the paediatric investigation plan:	Yes