EMA/266985/2020

European Medicines Agency decision

P/0198/2020

of 20 May 2020

on the acceptance of a modification of an agreed paediatric investigation plan for apixaban (Eliquis), (EMEA-000183-PIP01-08-M08) 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/8/2009 issued on 27 January 2009, the decision P/210/2011 issued on 2 September 2011, the decision P/0078/2012 issued on 27 April 2012, the decision P/0110/2015 issued on 5 June 2015, the decision P/0254/2016 issued on 5 October 2016, the decision P/0196/2017 issued on 14 July 2017 and the decision P/0154/2018 issued on 25 May 2018,

Having regard to the application submitted by Bristol-Myers Squibb / Pfizer EEIG on 27 January 2020 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 30 April 2020, 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 waiver.

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

Changes to the agreed paediatric investigation plan for apixaban (Eliquis), film-coated tablet, age-appropriate oral liquid dosage form, age-appropriate dosage form, other, oral use, including changes to the waiver, 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 Bristol-Myers Squibb / Pfizer EEIG, Plaza 254 - Blanchardstown Corporate Park 2, D15 T867 - Dublin 15, Ireland.

EMA/PDCO/76752/2020
Amsterdam, 30 April 2020

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

EMEA-000183-PIP01-08-M08

Scope of the application

Active substance(s):

Apixaban

Invented name:

Eliquis

Condition(s):

Prevention of venous thromboembolism

Prevention of arterial thromboembolism

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate oral liquid dosage form

Age-appropriate dosage form, other

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Bristol-Myers Squibb / Pfizer EEIG

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Bristol-Myers Squibb / Pfizer EEIG submitted to the European Medicines Agency on 27 January 2020 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/8/2009 issued on 27 January 2009, the decision P/210/2011 issued on 2 September 2011, the decision P/0078/2012 issued on 27 April 2012, the decision P/0110/2015 issued on 5 June 2015, the decision P/0254/2016 issued on 5 October 2016, the decision P/0196/2017 issued on 14 July 2017 and the decision P/0154/2018 issued on 25 May 2018.

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

The procedure started on 2 March 2020.

Scope of the modification

Some measures of the Paediatric Investigation Plan have been modified. A waiver for a new paediatric subset has been added.

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 waiver 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 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 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

1.1. Condition:

Prevention of venous thromboembolism

The waiver applies to:

- neonates (from birth to less than 28 days);
- film-coated tablet, age-appropriate oral liquid dosage form, age-appropriate dosage form (other), oral use;
- on the grounds that the product does not represent a significant therapeutic benefit over existing treatments.

1.2. Condition:

Prevention of arterial thromboembolism

The waiver applies to:

- neonates (from birth to less than 28 days);
- film-coated tablet, age-appropriate oral liquid dosage form, age-appropriate dosage form (other), oral use;
- on the grounds that the product does not represent a significant therapeutic benefit over existing treatments.

2. Paediatric Investigation Plan

2.1. Condition:

Prevention of venous thromboembolism

2.1.1. Indication(s) targeted by the PIP

Prevention of VTE in paediatric patients with a newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoma, (T or B cell), a functioning central venous access device (CVAD) and receiving asparaginase during chemotherapy induction.

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

From 28 days to less than 18 years

2.1.3. Pharmaceutical form(s)

Film-coated tablet, age-appropriate oral liquid dosage form, age-appropriate dosage form (other)

2.1.4. Measures

Area	Number of studies	Description
Quality-related studies	1	**Study 8** Development of an age appropriate formulation of Apixaban **Study 9** Development of an age appropriate formulation of Apixaban for children < 5 years old
Non-clinical studies	2	**Study 1** Range-finding Juvenile toxicity study in rats, post-natal day 4-21 **Study 2** Definitive Juvenile toxicity study in rats, post-natal day 4-90
Clinical studies	3	**Study 3** Bioavailability of Apixaban Solution Formulation Relative to Apixaban Tablets in Healthy Subjects **Study 4** Single-Dose, Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Apixaban in Paediatric Subjects **Study 5** Multicentre, randomized, open-label, parallel-group trial in paediatric subjects to evaluate safety and efficacy of apixaban in children from 1 year to less than 18 years of age with a newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoma, (T or B cell), a functioning central venous access device (CVAD) and receiving asparaginase.
Extrapolation, modelling and simulation studies	1	**Study 7** Extrapolation Study Model-based analysis of pharmacokinetic data accrued from Study 4) Paediatric Pharmacokinetics Study (CV185118), and Study 5) Safety and Efficacy Study (CV185155).

2.2. Condition

Prevention of arterial thromboembolism

2.2.1. Indication(s) targeted by the PIP

Prevention of TE in paediatric patients (28 days to less than 18 years old) with cardiac disease

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

From 28 days to less than 18 years

2.2.3. Pharmaceutical form(s)

Film-coated tablet, age-appropriate oral liquid dosage form, age-appropriate dosage form (other)

2.2.4. Measures

Area	Number of studies	Description
Quality-related studies	1	**Study 8** Development of an age appropriate formulation of Apixaban **Study 9** Development of an age appropriate formulation of Apixaban for children < 5 years of age
Non-clinical studies	2	**Study 1** Range-finding Juvenile toxicity study in rats, postnatal day 4-21 **Study 2** Definitive Juvenile toxicity study in rats, postnatal day 4-90
Clinical studies	3	**Study 3** Bioavailability of Apixaban Solution Formulation Relative to Apixaban Tablets in Healthy Subjects **Study 4** Single-Dose, Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Apixaban in Paediatric Subjects **Study 6** Prospective, open label, non-comparative safety trial to evaluate prevention of thromboembolism in children (from 28 days to <18 years) with cardiac disease, with a reference comparison of VKA and low molecular weight heparin (LMWH).

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 March 2022
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Prevention of venous thromboembolic events

Authorised indication(s):

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

2. Prevention of arterial thromboembolic events

Authorised indication(s):

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

3. Treatment of venous thromboembolism

Authorised indication(s):

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and 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