EMA/585767/2016

European Medicines Agency decision

P/0254/2016

of 5 October 2016

on the acceptance of a modification of an agreed paediatric investigation plan for apixaban (Eliquis), (EMEA-000183-PIP01-08-M04) 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Contact EMA www.ema.europa.eu/contact

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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 and the decision P/0110/2015 issued on 5 June 2015,

Having regard to the application submitted by Bristol-Myers Squibb / Pfizer EEIG on 27 May 2016 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 19 August 2016, 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 apixaban (Eliquis), film-coated tablet, Oral liquid, 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 Bristol-Myers Squibb / Pfizer EEIG, Uxbridge Business Park - Sanderson Road, UB8 1DH – Uxbridge United Kingdom.

EMA/PDCO/399233/2016
London, 19 August 2016

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

EMEA-000183-PIP01-08-M04

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

Oral liquid

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
Send a question via our website www.ema.europa.eu/contact

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 May 2016 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 and the decision P/0110/2015 issued on 5 June 2015.

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

The procedure started on 21 June 2016.

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 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

This covers:

- prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as knee or hip replacement surgery.

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- film-coated tablet, oral liquid, for oral use;

on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.

1.2. Condition:

Prevention of arterial thromboembolism

This covers:

- secondary prevention of arterial thrombosis in patients with a recent history of acute coronary syndromes (ACS);
- prevention of ischemic stroke and other thromboembolic complications associated with atrial fibrillation (AF).

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- film-coated tablet, oral liquid, oral use;

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subsets.

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 leukemia (ALL) or lymphoma, (T or B cell), a functioning central venous access device (CVAD) and receiving PEG L-asparaginase during chemotherapy induction.

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

From birth to less than 18 years.

2.1.3. Pharmaceutical form(s)

Film-coated tablet, oral liquid

2.1.4. Studies

Area	Number of studies	Description
Quality	1	Development of an age appropriate formulation of Apixaban
Non-clinical	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	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 with a newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoma,(T or B cell), a functioning central venous access device (CVAD) and receiving PEG L-asparaginase.
Extrapolation	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 pediatric patients (birth to below 18 years old) with cardiac disease

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

From birth to less than 18 years

2.2.3. Pharmaceutical form(s)

Film-coated tablet, oral liquid

2.2.4. Studies

Area	Number of studies	Description
Quality	1	Development of an age appropriate formulation of Apixaban
Non-clinical	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	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 (newborn 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 issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	By March 2021
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

6. Reminder

Interventional clinical trials have to be registered with the EudraCT database.

All investigational medicinal products used in the studies or trials must be registered in the EudraVigilance Medicinal Product Dictionary by the sponsor.

Studies or trials which are inconclusive or not interpretable will be considered non-compliant.

The Clinical trials should be performed in accordance with Good Clinical Practice. Those conducted outside the community should be carried out in accordance with the ethical standards of Directive 2001/20/EC and those conducted within the community should be carried out in accordance with Directive 2001/20/EC.

Applicants are reminded that it is their responsibility to submit a request for modification of an agreed paediatric investigation plan, if they encounter difficulties with its implementation which render the plan unworkable or no longer appropriate.

Applicants are also reminded that in order to verify compliance with the agreed PIP, the study report must be submitted for any study that had to be completed (see Commission Guideline 2014/C338/01 of 27 September 2014 and EMA procedural advice). This is part of the validation of the application for marketing authorisation, variation or line extension. Applicants are therefore advised to consider the time necessary to produce the appropriate report for their planned date of submission. For authorised medicinal products, reports need to be submitted to the competent authority within 6 months of completion of the studies, according to article 46 of Regulation (EC) No 1901/2006.

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Prevention of venous thromboembolic events

Authorised indication(s):

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

Authorised pharmaceutical form(s):

Film-coated tablet

Authorised route(s) of administration:

Oral use