EMA/2239/2012

European Medicines Agency decision

P/0078/2012

of 27 April 2012

on the acceptance of a modification of an agreed paediatric investigation plan for apixaban (Eliquis), (EMEA-000183-PIP01-08-M02) 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.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8409
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

European Medicines Agency decision
P/0078/2012

of 27 April 2012

on the acceptance of a modification of an agreed paediatric investigation plan for apixaban (Eliquis), (EMEA-000183-PIP01-08-M02) 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/8/2009 issued on 27 January 2009 and the decision P/210/2011 issued on 2 September 2011,

Having regard to the application submitted by Bristol-Myers Squibb/Pfizer EEIG on 12 December 2011 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 9 March 2012, 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.

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.

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

Article 2

This decision is addressed to Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House Uxbridge Business Park, Sanderson Road, UB8 1DH - Uxbridge

Done at London, 27 April 2012

For the European Medicines Agency
Guido Rasi
Executive Director
(Signature on file)

EMA/PDCO/992409/2011

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

EMEA-000183-PIP01-08-M02

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8409
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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 12 December 2011 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, and the decision P/210/2011 issued on 2 September 2011.

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

The procedure started on 12 January 2012.

Scope of the modification

The conditions and some measures of the agreed paediatric investigation plan were 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 annex(es) and appendix.

London, 09 March 2012

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

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 for the film-coated tablet, the 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 for the film-coated tablet, the oral liquid for 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 pediatric patients (birth to below 18 years old) with indwelling central venous catheters (CVC).

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 for oral use, liquid for oral use.

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) Multicenter, randomized, double-blind, parallel-group, placebo-controlled, multiple-dose trial in paediatric subjects to evaluate safety and efficacy of apixaban in children with an indwelling Catheter from birth to below 18 years old.

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 for oral use, liquid for oral use.

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, 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 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

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 April 2019
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 indications:

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

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