EMA/554940/2011

European Medicines Agency decision

P/210/2011

of 2 September 2011

on the acceptance of a modification of an agreed paediatric investigation plan for apixaban (Eliquis), (EMEA-000183-PIP01-08-M01) 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 apixaban (Eliquis), (EMEA-000183-PIP01-08-M01) 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,

Having regard to the application submitted by Bristol-Myers Squibb International Corporation on 27 May 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 15 July 2011, 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.

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

[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, 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 International Corporation, Parc de l'Alliance, Avenue de Finlande 8, 1420 - Braine-l'Alleud, Belgium.

Done at London, 2 September 2011

For the European Medicines Agency
Andreas Pott
Acting Executive Director
(Signature on file)

EMA/PDCO/430169/2011

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

EMEA-000183-PIP01-08-M01

Scope of the application

Active substance(s):

Apixaban

Invented name:

Eliquis

Condition(s):

Venous embolism and thrombosis

Arterial embolism and thrombosis

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 International Corporation

Information about the authorised medicinal product:

See Annex II

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Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Bristol-Myers Squibb International Corporation submitted to the European Medicines Agency on 27 May 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.

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

The procedure started on 15 June 2011.

Scope of the modification

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 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, 15 July 2011

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: Venous embolism and thrombosis

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: Arterial embolism and thrombosis

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: Venous embolism and thrombosis

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) Bioequivalence of Apixaban Oral Solution and Tablet Formulations in Healthy Adult Subjects Study 4) Multiple-Dose, Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Tolerability of Apixaban in Paediatric Subjects with an Indwelling Central Venous Catheter 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: Arterial embolism and thrombosis

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) Bioequivalence of Apixaban Oral Solution and Tablet Formulations in Healthy Adult Subjects Study 4) Multiple-Dose, Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Tolerability of Apixaban in Paediatric Subjects with an Indwelling Central Venous Catheter 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 December 2018
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.

EMEA Number	(Invented) name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Package size
EMEA/H/C/002148/0000/001	Eliquis	2.5 mg	Film-coated tablet	Oral use	blister (PVC/PVDC/alu)	10 tablets
EMEA/H/C/002148/0000/002	Eliquis	2.5 mg	Film-coated tablet	Oral use	blister (PVC/PVDC/alu)	20 tablets
EMEA/H/C/002148/0000/003	Eliquis	2.5 mg	Film-coated tablet	Oral use	blister (PVC/PVDC/alu)	60 tablets
EMEA/H/C/002148/0000/004	Eliquis	2.5 mg	Film-coated tablet	Oral use	blister (PVC/PVDC/alu)	60 x 1 tablet (unit dose)
EMEA/H/C/002148/0000/005	Eliquis	2.5 mg	Film-coated tablet	Oral use	blister (PVC/PVDC/alu)	100 x 1 tablet (unit dose)