European Medicines Agency

Doc. Ref. EMEA/32088/2009
P/8/2009

EUROPEAN MEDICINES AGENCY DECISION

of 27 January 2009

on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver for apixaban (EMEA-000183-PIP01-08) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended

(ONLY THE ENGLISH TEXT IS AUTHENTIC)

DISCLAIMER: This Decision does not entitle to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006, as amended.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 70
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

EUROPEAN MEDICINES AGENCY DECISION

of 27 January 2009

on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver for apixaban (EMEA-000183-PIP01-08) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended

THE EUROPEAN MEDICINES AGENCY,

Having regard to the Treaty establishing the European Community,

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 as amended 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 application submitted by Bristol-Myers Squibb International Corporation on 6 March 2008 under Article 16(1) of Regulation (EC) No 1901/2006 as amended also requesting a waiver under Article 13 of said Regulation and a deferral under Article 20 of said Regulation,

Having regard to the Opinion of the Paediatric Committee of the European Medicines Agency, issued on 12 December 2008, in accordance with Article 18 of Regulation (EC) No 1901/2006 as amended, and Article 13 of said Regulation and Article 21 of said Regulation**,**

Having regard to Article 25 of Regulation (EC) No 1901/2006 as amended,

WHEREAS:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver,

(2) It is therefore appropriate to adopt a Decision granting a Paediatric Investigation Plan.

(3) It is therefore appropriate to adopt a Decision granting a deferral.

(4) It is therefore appropriate to adopt a Decision granting a 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

A Paediatric Investigation Plan for apixaban, film-coated table, oral liquid , oral use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A deferral for apixaban, film-coated table, oral liquid , oral use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted .

Article 3

A waiver for apixaban, film-coated table, oral liquid , oral use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 4

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, 27 January 2009

For the European Medicines Agency
Thomas Lönngren
Executive Director

(Signature on file)

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

EMEA/PDCO/626317/2008
EMEA-000183-PIP01-08

OPINION OF THE PAEDIATRIC COMMITTEE ON THE AGREEMENT OF A PAEDIATRIC INVESTIGATION PLAN AND A DEFERRAL AND A WAIVER

Scope of the application

Active substance:
Apixaban

Condition(s):
Venous embolism and thrombosis
Arterial embolism and thrombosis

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

Basis for opinion

Pursuant to Article 16.1 of Regulation (EC) No 1901/2006 as amended, Bristol-Myers Squibb International Corporation submitted for agreement to the EMEA on 6 March 2008 a paediatric investigation plan for the above mentioned medicinal product.

The procedure started on 10 April 2008.

Supplementary information was provided by the applicant on 2 October 2008.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 40
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree the paediatric investigation plan in accordance with Article 18 of said Regulation,
- to grant a deferral in accordance with Article 21 of said Regulation,
- to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The Icelandic and the Norwegian Paediatric Committee members agree with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the agreed 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 Agency, together with its annex(es) and appendix(ces).

London, 12 December 2008

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature on file)

ANNEX I

THE MEASURES AND TIMELINES OF THE AGREED PAEDIATRIC INVESTIGATION PLAN AND THE SUBSET(S) OF THE PAEDIATRIC POPULATION AND CONDITION(S) COVERED BY THE WAIVER

A. CONDITION(S)

Venous embolism and thrombosis
Arterial embolism and thrombosis

B. WAIVER

- **Condition**

1) 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.

2) 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.

C. PAEDIATRIC INVESTIGATION PLAN

- **Condition to be investigated**

1) Venous embolism and thrombosis
2) Arterial embolism and thrombosis

- **Proposed PIP indication**

1) Prevention of VTE in pediatric patients (birth to below 18 years old) with indwelling central venous catheters (CVC).
2) Prevention of TE in pediatric patients (birth to below 18 years old) with cardiac disease.

- **Subset(s) of the paediatric population concerned by the paediatric development**

1) From birth to less than 18 years
2) From birth to less than 18 years

- **Formulation(s)**

film-coated tablet for oral use, liquid for oral use.

- **Studies**

Area	Number of studies	Description
Quality	1	Development of an age appropriate formulation of Apixaban
Non-clinical	2	Range-finding Juvenile toxicity study in rats, post natal day 4-21 Definitive Juvenile toxicity study in rats, post natal day 4-90
Clinical	4	Bioequivalence of Apixaban Oral Solution and Tablet Formulations in Healthy Adult Subjects Multiple-Dose, Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Tolerability of Apixaban in Paediatric Subjects with an Indwelling Central Venous Catheter 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. 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

Measures to address long term follow-up of potential safety issues in relation to paediatric use:	**No**
Date of completion of the paediatric investigation plan:	**By December 2018**
Deferral for initiation of some or all studies contained in the paediatric investigation plan:	**Yes**
Deferral for completion of some or all studies contained in the paediatric investigation plan:	**Yes**