

EMA/490576/2011

## European Medicines Agency decision P/171/2011

of 8 July 2011

on the acceptance of a modification of an agreed paediatric investigation plan for rivaroxaban, (Xarelto) (EMA-000430-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.**

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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<sup>1</sup>,

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<sup>2</sup>,

Having regard to the European Medicines Agency's decision P/223/2009 issued on 4 November 2009 and the decision P/95/2010 issued on 2 June 2010,

Having regard to the application submitted by Bayer Schering Pharma AG, on 7 March 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 20 May 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.

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<sup>1</sup> OJ L 378, 27.12.2006, p.1.

<sup>2</sup> OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

**Article 1**

Changes to the agreed paediatric investigation plan for rivaroxaban (Xarelto), age-appropriate liquid formulation, film-coated tablet, 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 Bayer Schering Pharma AG, Berlin, D-13342-Berlin, Germany.

Done at London, 8 July 2011

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

EMA/PDCO/334804/2011

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

EMA-000430-PIP01-08-M02

### Scope of the application

**Active substance(s):**

Rivaroxaban

**Invented name:**

Xarelto

**Condition(s):**

Prevention of thromboembolic events

Treatment of thromboembolic events

**Authorised indication(s):**

See Annex II

**Pharmaceutical form(s):**

Age-appropriate liquid formulation

Film-coated tablet

**Route(s) of administration:**

Oral use

**Name/corporate name of the PIP applicant:**

Bayer Schering Pharma AG

**Information about the authorised medicinal product:**

See Annex II

## **Basis for opinion**

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Bayer Schering Pharma AG submitted to the European Medicines Agency on 7 March 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/223/2009 issued on 4 November 2009 and the decision P/95/2010 issued on 2 June 2010.

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

The procedure started on 23 March 2011.

## **Scope of the modification**

The modification concerns details of measures of the paediatric investigation plan.

## **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 Icelandic and the Norwegian Paediatric Committee members agree 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, 20 May 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: Prevention of thromboembolic events***

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- for age-appropriate liquid formulation and film-coated tablet, 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 subset(s).

# **2. Paediatric Investigation Plan**

## ***2.1. Condition: Treatment of thromboembolic events***

### **2.1.1. Indication(s) targeted by the PIP**

Treatment (secondary prevention) of venous thromboembolism.

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

From birth to less than 18 years of age.

### **2.1.3. Pharmaceutical form(s)**

- Age-appropriate liquid formulation for oral use;
- Film-coated tablet: 1.25 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg for oral use.

### 2.1.4. Studies

| Area         | Number of studies | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Quality      | 1                 | Study 1: Age-appropriate liquid formulation for oral use.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Non-clinical | 2                 | Study 2: Toxicology study in juvenile rats with a treatment duration of three weeks.<br><br>Study 3: Toxicology study in juvenile rats with a treatment duration of thirteen weeks.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Clinical     | 5                 | Study 4: Relative bioavailability and food effect of liquid formulation in healthy adults.<br><br>Study 5: Safety, tolerability, pharmacokinetic, and pharmacodynamic study of rivaroxaban.<br><br>Study 6: Four week multinational, multicenter, open-label, active-controlled, randomized, multiple dose, prospective study to evaluate safety and PK/PD of rivaroxaban in paediatric patients from 6 years to less than 18 years of age who have been pre-treated for at least two months with either Low Molecular Weight Heparin and/or vitamin K antagonist for venous thromboembolism.<br><br>Study 7: Four week multinational, multicenter, open-label, active-controlled, randomized, multiple dose, prospective study to evaluate safety and PK/PD of rivaroxaban in paediatric patients from 6 months to less than 6 years of age who have been pre-treated for at least two months with either Low Molecular Weight Heparin and/or vitamin K antagonist for venous thromboembolism.<br><br>Study 8: Three months multinational, multicenter, open-label, active-controlled, randomized, multiple dose, prospective study to evaluate safety and efficacy of rivaroxaban in paediatric patients from birth to less than 18 years of age who have acute venous thromboembolism. |

## 3. Follow-up, completion and deferral of PIP

|                                                                                                   |                  |
|---------------------------------------------------------------------------------------------------|------------------|
| 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 October 2017. |
| 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 thromboembolic events.

Authorised indication(s):

- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

| <b>EU Number</b> | <b>Invented name<br/>Name</b> | <b>Strength</b> | <b>Pharmaceutical form</b> | <b>Route of administration</b> | <b>Packaging</b>       | <b>Package size</b> |
|------------------|-------------------------------|-----------------|----------------------------|--------------------------------|------------------------|---------------------|
| EU/1/08/472/001  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PVC/PVDC/alu) | 5 tablets           |
| EU/1/08/472/002  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PVC/PVDC/alu) | 10 tablets          |
| EU/1/08/472/003  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PVC/PVDC/alu) | 30 tablets          |
| EU/1/08/472/004  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PVC/PVDC/alu) | 100 tablets         |
| EU/1/08/472/005  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PP/alu)       | 5 tablets           |
| EU/1/08/472/006  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PP/alu)       | 10 tablets          |
| EU/1/08/472/007  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PP/alu)       | 30 tablets          |
| EU/1/08/472/008  | Xarelto                       | 10 mg           | Film-coated tablet         | Oral use                       | blister (PP/alu)       | 100 tablets         |