EMA/215013/2019

European Medicines Agency decision

P/0126/2019

of 17 April 2019

on the acceptance of a modification of an agreed paediatric investigation plan for rivaroxaban (Xarelto), (EMEA-000430-PIP01-08-M11) 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[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/223/2009 issued on 4 November 2009, the decision P/95/2010 issued on 2 June 2010, the decision P/171/2011 issued on 8 July 2011, the decision P/0134/2012 issued on 6 July 2012, the decision P/0163/2013 issued on 29 July 2013, the decision P/0084/2014 issued on 4 April 2014, the decision P/0090/2015 issued on 8 May 2015, the decision P/0268/2015 issued on 27 November 2015, the decision P/0126/2016 issued on 20 May 2016 and the decision P/0194/2017 issued on 3 July 2017,

Having regard to the application submitted by Bayer AG on 22 November 2018 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 1 March 2019, 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 rivaroxaban (Xarelto), oral suspension, film-coated tablet, 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 Bayer AG, Berlin, D-13342 - Berlin, Germany.

EMA/PDCO/852768/2018 Corr
London, 1 March 2019

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

EMEA-000430-PIP01-08-M11

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):

Oral suspension

Film-coated tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Bayer AG

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, Bayer Pharma AG submitted to the European Medicines Agency on 22 November 2018 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, the decision P/95/2010 issued on 2 June 2010, the decision P/171/2011 issued on 8 July 2011, the decision P/0134/2012 issued on 6 July 2012, the decision P/0163/2013 issued on 29 July 2013, the decision P/0084/2014 issued on 4 April 2014, the decision P/0090/2015 issued on 8 May 2015, the decision P/0268/2015 issued on 27 November 2015, the decision P/0126/2016 issued on 20 May 2016 and the decision P/0194/2017 issued on 3 July 2017.

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

The procedure started on 3 January 2019.

Scope of the modification

Some 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

1.2. 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 oral suspension 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)

Oral suspension for oral use

Film-coated tablet oral use

2.1.4. Measures

Area	Number of measures	Description
Quality related studies	1	**Study 1** Development of age-appropriate liquid formulation for oral use
Non-clinical studies	2	**Study 2** Toxicology study in juvenile rats with a treatment duration of three weeks **Study 3** Toxicology study in juvenile rats with a treatment duration of

		thirteen weeks
Clinical studies	6	**Study 4** Relative bioavailability and food effect of oral suspension in healthy adults **Study 5** Multicentre, open-label, non-controlled, single dose study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of rivaroxaban in children from 6 months to less than 18 years of age who have been treated for venous thromboembolism **Study 6** Multicentre, single-arm, multiple dose study to evaluate safety and PK/PD of rivaroxaban film-coated tablets and oral suspension in paediatric patients from 6 years to less than 18 years of age who have been pre-treated with either low molecular weight heparin, fondaparinux and/or vitamin K antagonist for venous thromboembolism **Study 7** Multicentre, single-arm, multiple dose study to evaluate safety and PK/PD of rivaroxaban oral suspension in paediatric patients from 6 months to less than 6 years of age who have been pre-treated with either low molecular weight heparin, fondaparinux and/or vitamin K antagonist for venous thromboembolism **Study 8** Multicentre, open-label, active-controlled, randomized, multiple dose study to evaluate safety and efficacy of rivaroxaban oral suspension and film-coated tablets in paediatric patients from birth to less than 18 years of age who have acute venous thromboembolism **Study 9** (Study deleted during procedure EMEA-000430-PIP01-08-M10) **Study 10** (study added during procedure EMEA-000430-PIP01-08-M10) Multicenter, open label study to evaluate safety and PK/PD of rivaroxaban oral suspension in paediatric subjects from birth to less than 6 months of age and who have been pretreated with anticoagulant therapy for venous or arterial thrombosis

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety or efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	By October 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 thromboembolic events

   Authorised indications:

   - Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery;
   - Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age 75 years and above, diabetes mellitus, prior stroke or transient ischaemic attack.
   - Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.
   - Co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

2. Treatment of thromboembolic events

   Authorised indications:

   - Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) in adults.

Authorised pharmaceutical form(s):

Film-coated tablet

Authorised route(s) of administration:

Oral use