



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/595801/2012

## European Medicines Agency decision P/0228/2012

of 1 October 2012

on the acceptance of a modification of an agreed paediatric investigation plan for dabigatran etexilate (Pradaxa) (EMA-000081-PIP01-07-M05) 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/76/2008 issued on 14 September 2008, the decision P/246/2009 issued on 27 November 2009, the decision P/107/2010 issued on 28 June 2010, the decision P/175/2011 issued on 4 July 2011, and the decision P/0033/2012 issued on 3 February 2012,

Having regard to the application submitted by Boehringer Ingelheim International GmbH on 18 June 2012 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 7 September 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.
- (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 dabigatran etexilate (Pradaxa), capsule, hard, age-appropriate formulation, 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 Boehringer Ingelheim International GmbH, Binger Straße 173, 55216 Ingelheim am Rhein, Germany.

Done at London, 1 October 2012

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



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/PDCO/508898/2012

## Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan EMA-000081-PIP01-07-M05

### **Scope of the application**

#### **Active substance(s):**

Dabigatran etexilate

#### **Invented name:**

Pradaxa

#### **Condition(s):**

Prevention of thromboembolic events

Treatment of thromboembolic events

#### **Authorised indication(s):**

See Annex II

#### **Pharmaceutical form(s):**

Capsule, hard

Age-appropriate formulation

#### **Route(s) of administration:**

Oral use

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

Boehringer Ingelheim International GmbH

#### **Information about the authorised medicinal product:**

See Annex II



## Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 18 June 2012 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/76/2008 issued on 14 September 2008, the decision P/246/2009 issued on 27 November 2009, the decision P/107/2010 issued on 28 June 2010, the decision P/175/2011 issued on 4 July 2011, and the decision P/0033/2012 issued on 3 February 2012.

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

The procedure started on 11 July 2012.

## Scope of the modification

Some measures and timelines of the 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 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, 7 September 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 thromboembolic events

The waiver applies to:

- the paediatric population from birth to less than 18 years;
- for the hard capsule and the age-appropriate formulation, for oral use;
- on the grounds that clinical studies cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population.

# 2. Paediatric Investigation Plan

## 2.1. Condition: Treatment of thromboembolic events

### 2.1.1. Indication targeted by the PIP

Treatment of venous thromboembolic events in paediatric patients (secondary venous thrombotic event prevention).

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

Children from birth to less than 18 years.

### 2.1.3. Pharmaceutical form(s)

Capsule, hard.

Age-appropriate formulation.

### 2.1.4. Studies

| Area         | Number of studies | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Quality      | 1                 | Study 1: Development of an age-appropriate formulation.                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Non-clinical | 0                 | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Clinical     | 6                 | Study 2: Relative bioavailability study of the paediatric and adult formulations.<br><br>Study 3: Open-label trial to evaluate pharmacokinetics and safety of dabigatran etexilate in children aged 12 years to less than 18 years<br><br>Study 4: Open-label, single-dose trial to evaluate pharmacokinetics, pharmacodynamics, safety and tolerability of dabigatran etexilate in children aged 1 year to less than 12 years.<br><br>Study 6: Open-label, single-dose study to evaluate pharmacokinetics, |

|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  | <p>pharmacodynamics, tolerability and safety of dabigatran etexilate in children aged less than 1 year.</p> <p>Study 7: Open-label, randomised, active-controlled, multi-centre, non-inferiority study to evaluate efficacy and safety of dabigatran etexilate versus standard of care in children from birth to less than 18 years.</p> <p>Study 8: Open-label, single-arm, long-term study to evaluate the safety of dabigatran etexilate in children from birth to less than 18 years.</p> |
|--|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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

|                                                                                  |              |
|----------------------------------------------------------------------------------|--------------|
| Concerns on potential long term safety issues in relation to paediatric use:     | Yes          |
| Date of completion of the paediatric investigation plan:                         | By June 2018 |
| Deferral for some or all 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:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:
  - Left ventricular ejection fraction < 40 %;
  - Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2;
  - Age ≥ 75 years;
  - Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or;
  - Hypertension.

## 2. Treatment of thromboembolic events

Authorised indications:

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:
  - Previous stroke, transient ischemic attack, or systemic embolism (SEE).

| <b>EU Number</b> | <b>Invented name</b> | <b>Strength</b> | <b>Pharmaceutical form</b> | <b>Route of administration</b> | <b>Packaging</b>  | <b>Package size</b> |
|------------------|----------------------|-----------------|----------------------------|--------------------------------|-------------------|---------------------|
| EU/1/08/442/001  | Pradaxa              | 75 mg           | Capsule, hard              | Oral use                       | blister (alu/alu) | 10 x 1 capsules     |
| EU/1/08/442/002  | Pradaxa              | 75 mg           | Capsule, hard              | Oral use                       | blister (alu/alu) | 30 x 1 capsules     |
| EU/1/08/442/003  | Pradaxa              | 75 mg           | Capsule, hard              | Oral use                       | blister (alu/alu) | 60 x 1 capsules     |
| EU/1/08/442/004  | Pradaxa              | 75 mg           | Capsule, hard              | Oral use                       | bottle (PP)       | 60 capsules         |
| EU/1/08/442/005  | Pradaxa              | 110 mg          | Capsule, hard              | Oral use                       | blister (alu/alu) | 10 x 1 capsules     |
| EU/1/08/442/006  | Pradaxa              | 110 mg          | Capsule, hard              | Oral use                       | blister (alu/alu) | 30 x 1 capsules     |
| EU/1/08/442/007  | Pradaxa              | 110 mg          | Capsule, hard              | Oral use                       | blister (alu/alu) | 60 x 1 capsules     |
| EU/1/08/442/008  | Pradaxa              | 110 mg          | Capsule, hard              | Oral use                       | bottle (PP)       | 60 capsules         |
| EU/1/08/442/009  | Pradaxa              | 150 mg          | Capsule, hard              | Oral use                       | blister (alu/alu) | 10 x 1 capsules     |
| EU/1/08/442/010  | Pradaxa              | 150 mg          | Capsule, hard              | Oral use                       | blister (alu/alu) | 30 x 1 capsules     |

|                 |         |        |               |          |                             |                                                   |
|-----------------|---------|--------|---------------|----------|-----------------------------|---------------------------------------------------|
| EU/1/08/442/011 | Pradaxa | 150 mg | Capsule, hard | Oral use | blister (alu/alu)           | 60 x 1 capsules                                   |
| EU/1/08/442/012 | Pradaxa | 150 mg | Capsule, hard | Oral use | blister (alu/alu) multipack | 3 x (60 x 1) capsules                             |
| EU/1/08/442/013 | Pradaxa | 150 mg | Capsule, hard | Oral use | bottle (PP)                 | 60 capsules                                       |
| EU/1/08/442/014 | Pradaxa | 110 mg | Capsule, hard | Oral use | blister (alu/alu) multipack | 3 x (60 x 1) capsules                             |
| EU/1/08/442/015 | Pradaxa | 110 mg | Capsule, hard | Oral use | blister (alu/alu)           | 100 (2 x 50 x 1) capsules (unit dose) (multipack) |
| EU/1/08/442/016 | Pradaxa | 150 mg | Capsule, hard | Oral use | blister (alu/alu)           | 100 (2 x 50 x 1) capsules (unit dose) (multipack) |
| EU/1/08/442/017 | Pradaxa | 75 mg  | Capsule, hard | Oral use | white blister (alu/alu)     | 60 x 1 capsules (unit dose)                       |
| EU/1/08/442/018 | Pradaxa | 110mg  | Capsule, hard | Oral use | white blister (alu/alu)     | 60 x 1 capsules (unit dose)                       |
| EU/1/08/442/019 | Pradaxa | 150 mg | Capsule, hard | Oral use | white blister (alu/alu)     | 60 x 1 capsules (unit dose)                       |