



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/382958/2015

## European Medicines Agency decision

P/0141/2015

of 10 July 2015

on the acceptance of a modification of an agreed paediatric investigation plan for posaconazole (Noxafil) (EMA-000468-PIP02-12-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.**



# European Medicines Agency decision

P/0141/2015

of 10 July 2015

on the acceptance of a modification of an agreed paediatric investigation plan for posaconazole (Noxafil) (EMA-000468-PIP02-12-M02) 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<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/0289/2012 issued on 7 December 2012, and the decision P/0328/2014 issued on 22 December 2014,

Having regard to the application submitted by Merck Sharp & Dohme (Europe), Inc. on 2 March 2015 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 22 May 2015, 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.

---

<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 posaconazole (Noxafil), oral suspension, gastro-resistant tablet, powder for oral suspension/modified-release granules for oral suspension, concentrate for solution for infusion, oral use, intravenous 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 Merck Sharp & Dohme (Europe), Inc., Clos du Lynx 5, 1200 - Brussels, Belgium.

Done at London, 10 July 2015

For the European Medicines Agency  
Jordi Llinares Garcia  
Head of Division (ad interim)  
Human Medicines Research and Development Support  
(Signature on file)



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/PDCO/156089/2015

London, 22 May 2015

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

EMA-000468-PIP02-12-M02

### Scope of the application

**Active substance(s):**

Posaconazole

**Invented name:**

Noxafil

**Condition(s):**

Prevention of invasive fungal infections

Treatment of invasive fungal infections

**Authorised indication(s):**

See Annex II

**Pharmaceutical form(s):**

Oral suspension

Gastro-resistant tablet

Powder for oral suspension/modified-release granules for oral suspension

Concentrate for solution for infusion

**Route(s) of administration:**

Oral use

Intravenous use

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

Merck Sharp & Dohme (Europe), Inc.

**Information about the authorised medicinal product:**

See Annex II



## **Basis for opinion**

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Merck Sharp & Dohme (Europe), Inc. submitted to the European Medicines Agency on 2 March 2015 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/0289/2012 issued on 7 December 2012, and the decision P/0328/2014 issued on 22 December 2014.

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

The procedure started on 24 March 2015.

## **Scope of the modification**

Some measures and 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 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

Prevention of invasive fungal infections

The waiver applies to:

- all subsets of the paediatric population from birth to less than 3 months of age;
- for gastro-resistant tablet, oral use, for oral suspension, oral use, for powder for oral suspension/modified-release granules for oral suspension, oral use, and for concentrate for solution for infusion, intravenous use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

The waiver applies to:

- all subsets of the paediatric population from 3 months to less than 18 years of age;
- for oral suspension, oral use;
- on the grounds that the specific medicinal product is not efficacious in the subsets of the paediatric population.

The waiver applies to:

- all subsets of the paediatric population from 3 months to less than 12 years of age and adolescents with a body weight less than 50 kg;
- for gastro-resistant tablet, oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

## 1.2. Condition

Treatment of invasive fungal infections

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- for oral suspension, oral use;
- on the grounds that the specific medicinal product is not efficacious in all subsets of the paediatric population.

The waiver applies to:

- all subsets of the paediatric population from birth to less than 12 years of age and adolescents with a body weight less than 50 kg;
- for gastro-resistant tablet, oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

## 2. Paediatric Investigation Plan

### 2.1. Condition

Prevention of invasive fungal infections

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

For prophylaxis of invasive fungal infections in the following paediatric patients:

- patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

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

From 3 months of age to less than 18 years of age

#### 2.1.3. Pharmaceutical form(s)

Oral suspension

Gastro-resistant tablet

Powder for oral suspension/modified-release granules for oral suspension

Concentrate for solution for infusion

#### 2.1.4. Measures

| Area                    | Number of measures | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Quality-related studies | 3                  | <b>Study 1</b><br>Development of an age-appropriate powder for oral suspension/modified-release granules for oral suspension formulation<br><b>Study 2</b><br>Analytical studies with the age appropriate powder for oral suspension/modified-release granules for oral suspension formulation after extrusion through feeding tubes to demonstrate dose accuracy and recovery using age relevant feeding tubes and rinse volumes<br><b>Study 3</b><br>Analytical studies demonstrating dosing accuracy and dose recovery after extrusion through feeding tubes using smaller age-appropriate devices (dose volumes lower than 1 mL), to ensure accurate administration of posaconazole (POS) oral suspension in children below 2 years of age |

|                                                 |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-clinical studies                            | 4 | <p><b>Study 4</b></p> <p>Three-month oral toxicity and toxicokinetic study in neonatal and juvenile rats with a six-week recovery period (SN 07193)</p> <p><b>Study 5</b></p> <p>Intravenous (IV) toxicity and toxicokinetic study in neonatal and juvenile Beagle dogs with a 5-month recovery (TT 12-9018)</p> <p><b>Study 6</b></p> <p>12-week oral (gavage) toxicity and toxicokinetic study of posaconazole (SCH 56592) in neonatal and juvenile rats. (SN 09005)</p> <p><b>Study 7</b></p> <p>Nine-month oral (gavage) neurotoxicity study of SCH 56592 with a three-month post-dose period in juvenile beagle dogs. (SN 07194)</p> |
| Clinical studies                                | 2 | <p><b>Study 8</b></p> <p>Open-label, uncontrolled, sequential dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics (PK) of posaconazole oral suspension in immunocompromised children with neutropenia aged 3 months to less than 18 years. (P03579/PN032)</p> <p><b>Study 9</b></p> <p>Open-label, uncontrolled, sequential dose-escalation study to evaluate the safety, tolerability, and PK of posaconazole intravenous (IV) solution in immunocompromised paediatric subjects with neutropenia aged 3 months to less than 18 years. (P07748/PN097)</p>                                                   |
| Extrapolation, modelling and simulation studies | 2 | <p><b>Study 10</b></p> <p>Extrapolation study to support extrapolation of efficacy in prophylaxis of invasive fungal infections</p> <p><b>Study 11</b></p> <p>Modelling and simulation study for dose determination</p>                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Other studies                                   |   | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Other measures                                  |   | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

## 2.2 Condition

Treatment of invasive fungal infections

### 2.2.1 Indication(s) targeted by the PIP

Treatment of invasive aspergillosis

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

From birth to less than 18 years of age

### **2.2.3 Pharmaceutical form(s)**

Oral suspension

Gastro-resistant tablet

Powder for oral suspension/modified-release granules for oral suspension

Concentrate for solution for infusion

### **2.2.4 Measures**

| <b>Area</b>                                     | <b>Number of measures</b> | <b>Description</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Quality-related studies                         | 3                         | Same as for condition "Prevention of invasive fungal infections".                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Non-clinical studies                            | 4                         | Same as for condition "Prevention of invasive fungal infections".                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Clinical studies                                | 5                         | <p>Same as study 8 in the condition "Prevention of invasive fungal infection" (P03579/PN032).</p> <p>Same as study 9 in the condition "Prevention of invasive fungal infection" (P07748/PN097).</p> <p><b>Study 12</b></p> <p>Randomized double-blind study to evaluate the efficacy and safety of posaconazole versus voriconazole for treatment of invasive aspergillosis in adolescents (and adults). (P06200/PN069)</p> <p><b>Study 13</b></p> <p>Open-label, uncontrolled study to evaluate the safety and efficacy of posaconazole for the treatment of invasive aspergillosis in paediatric patients 3 months of age and older. (20149/PN104)</p> <p><b>Study 14</b></p> <p>Open-label, uncontrolled study to evaluate the safety, tolerability, and PK of posaconazole solution for infusion in neonates and infants less than 3 months of age (P20144/PN103)</p> |
| Extrapolation, modelling and simulation studies |                           | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Other studies                                   |                           | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                |  |                 |
|----------------|--|-----------------|
| Other measures |  | Not applicable. |
|----------------|--|-----------------|

### 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 September 2020 |
| 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. Treatment of invasive fungal infections

Authorised indication(s):

- Noxafil is indicated for use in the treatment of the following fungal infections in adults:
- invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;
- oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor (for oral suspension only);
- refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

### 2. Prevention of invasive fungal infections

Authorised indication(s):

- Noxafil is also indicated for prophylaxis of invasive fungal infections in the following patients:
- patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- haematopoietic-stem-cell-transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft-versus-host disease and who are at high risk of developing invasive fungal infections.

## Authorised pharmaceutical form(s)

Oral suspension

Gastro-resistant tablet

Concentrate for solution for infusion

## Authorised route(s) of administration

Oral use

Intravenous use