EMA/756036/2012

European Medicines Agency decision

P/0289/2012

of 7 December 2012

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for posaconazole (Noxafil) (EMEA-000468-PIP02-12) 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 application submitted by Merck Sharp & Dohme (Europe), Inc. on 10 April 2012 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 9 November 2012, in accordance with Article 18 of Regulation (EC) No 1901/2006, and Article 21 of said Regulation and Article 13 of said Regulation,

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 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 agreeing 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 posaconazole (Noxafil), oral suspension, tablet, age-appropriate oral powder for suspension formulation, solution for infusion, oral use, intravenous 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 posaconazole (Noxafil), oral suspension, tablet, age-appropriate oral powder for suspension formulation, solution for infusion, oral use, intravenous 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 posaconazole (Noxafil), oral suspension, tablet, age-appropriate oral powder for suspension formulation, solution for infusion, oral use, intravenous 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 Merck Sharp & Dohme (Europe), Inc., Clos du Lynx 5, 1200 – Brussels, Belgium.

Done at London, 7 December 2012

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

EMA/PDCO/549104/2012

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver

EMEA-000468-PIP02-12

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

Tablet

Age-appropriate oral powder for suspension formulation

Solution for infusion

Route(s) of administration:

Oral use

Intravenous use

Name/corporate name of the PIP applicant:

Merck Sharp & Dohme (Europe), Inc.

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Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Merck Sharp & Dohme (Europe), Inc. submitted for agreement to the European Medicines Agency on 10 April 2012 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 15 May 2012.

Supplementary information was provided by the applicant on 6 August 2012. The applicant proposed modifications to the paediatric investigation plan.

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 European Medicines Agency, together with its annexes and appendix.

London, 9 November 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 invasive fungal infections

The waiver applies to:

- all subsets of the paediatric population from birth to less than 3 months of age;
- for tablet, oral use, for oral suspension, oral use, age-appropriate oral powder for suspension formulation, oral use, and for solution for infusion, intravenous 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

Not applicable.

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

Tablet

Age-appropriate oral powder for suspension formulation

Solution for infusion

2.1.4. Studies

Area	Number of studies	Description
Quality	3	1. Development of an age-appropriate oral powder for suspension formulation 2. Analytical studies with the age appropriate oral powder for suspension formulation after extrusion through feeding tubes to demonstrate dose accuracy and recovery using age relevant feeding tubes and rinse volumes. 3. 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	4	4. Three-month oral toxicity and toxicokinetic study in neonatal and juvenile rats with a six-week recovery period (SN 07193) 5. Intravenous (IV) toxicity and toxicokinetic study in neonatal and juvenile Beagle dogs with a 5-month recovery (TT 12-9018) 6. 12-week oral (gavage) toxicity and toxicokinetic study of posaconazole (SCH 56592) in neonatal and juvenile rats. (SN 09005) 7. Nine-month oral (gavage) neurotoxicity study of SCH 56592 with a three-month post-dose period in juvenile beagle dogs. (SN 07194)
Clinical	3	8. 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) 9. Comparative, double-blind, randomized trial of posaconazole versus fluconazole for the prevention of invasive fungal infections among high risk paediatric subjects aged 2 to less than 18 years. (P05206/PN095) 10. 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)

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

Tablet

Age-appropriate oral powder for suspension formulation

Solution for infusion

2.2.4 Studies

Area	Number of studies	Description
Quality	3	Same as for condition “Prevention of invasive fungal infections”.
Non-clinical	4	Same as for condition “Prevention of invasive fungal infections”.
Clinical	5	Same as study 8 in the condition “Prevention of invasive fungal infection” (P03579/PN032) Same as study 10 in the condition “Prevention of invasive fungal infection” (P07748/PN097) 11. 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) 12. Open-label, uncontrolled study to evaluate safety and efficacy of posaconazole for the treatment of invasive aspergillosis in paediatric patients 3 months of age and older. (20149/PN104) 13. 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)

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 February 2018
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 infection

   Authorised indications:

   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.
   - 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 infection

   Authorised indications:

   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;
   - 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.

Authorised pharmaceutical formulation(s):

Oral suspension

Authorised route(s) of administration:

Oral use