EMA/242867/2023

European Medicines Agency decision

P/0200/2023

of 5 June 2023

on the acceptance of a modification of an agreed paediatric investigation plan for posaconazole (Noxafil), (EMEA-000468-PIP02-12-M08) 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/0200/2023

of 5 June 2023

on the acceptance of a modification of an agreed paediatric investigation plan for posaconazole (Noxafil), (EMEA-000468-PIP02-12-M08) 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[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0289/2012 issued on 7 December 2012, the decision P/0328/2014 issued on 22 December 2014, the decision P/0141/2015 issued on 10 July 2015, the decision P/0092/2017 issued on 11 April 2017, the decision P/0041/2018 issued on 16 February 2018, the decision P/0223/2019 issued on 21 June 2019, the decision P/0101/2020 issued on 18 March 2020 and the decision P/0196/2022 issued on 9 June 2022,

Having regard to the application submitted by Merck Sharp & Dohme (Europe), Inc. on 19 January 2023 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 26 May 2023, 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, following a re-examination procedure of the Paediatric Committee's opinion according to Article 25(3) of Regulation (EC) No 1901/2006, 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.

[1] OJ L 378, 27.12.2006, p.1, as amended.
[2] OJ L 136, 30.4.2004, p. 1, as amended.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for posaconazole (Noxafil), oral suspension, gastro-resistant tablet, gastro-resistant powder 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., 5 Clos du Lynx, 1200 – Brussels, Belgium.

EMA/PDCO/215390/2023
Amsterdam, 26 May 2023

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

EMEA-000468-PIP02-12-M08

Scope of the application

Active substance(s):

Posaconazole

Invented name and authorisation status:

See Annex II

Condition(s):

Prevention of invasive fungal infections

Treatment of invasive fungal infections

Pharmaceutical form(s):

Oral suspension

Gastro-resistant tablet

Gastro-resistant powder 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.

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 19 January 2023 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, the decision P/0328/2014 issued on 22 December 2014, the decision P/0141/2015 issued on 10 July 2015, the decision P/0092/2017 issued on 11 April 2017, the decision P/0041/2018 issued on 16 February 2018, the decision P/0223/2019 issued on 21 June 2019, the decision P/0101/2020 issued on 18 March 2020 and the decision P/0196/2022 issued on 9 June 2022.

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

An Opinion was adopted by the Paediatric Committee on 26 April 2023 for the above mentioned product. Merck Sharp & Dohme (Europe), Inc. received the Paediatric Committee Opinion on 5 May 2023.

On 10 May 2023 Merck Sharp & Dohme (Europe), Inc. submitted to the European Medicines Agency a written request including detailed grounds for a re-examination of the Opinion.

The re-examination procedure started on 11 May 2023.

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified.

Final Opinion

1. The Paediatric Committee, having assessed the detailed grounds for re-examination, in accordance with Article 25(3) of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

1.1. to revise its opinion and

- to agree to the changes regarding the measures and the timelines of the paediatric investigation plan in the scope set out in the Annex I of this opinion.

1.2. following re-examination, to amend the scope of the modifications of the paediatric investigation plan.

The Paediatric Committee member of Norway agrees 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.

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;
- oral suspension, oral use ; gastro-resistant tablet, oral use; gastro-resistant powder for oral suspension, oral use; 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;
- oral suspension, oral use;
- on the grounds that the specific medicinal product is likely to be ineffective 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 or equal to 40 kg;
- 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;
- 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 or equal to 40 kg;
- 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

Gastro-resistant powder for oral suspension

Concentrate for solution for infusion

2.1.4. Measures

Area	Description
Quality-related studies	**Study 1** Development of an age-appropriate gastro-resistant powder for oral suspension formulation **Study 2** Analytical studies with the age appropriate gastro-resistant powder for oral suspension formulation after extrusion through feeding tubes to demonstrate dose accuracy and recovery using age relevant feeding tubes and rinse volumes **Study 3** *Deleted in procedure EMEA-000468-PIP02-12-M04*

Non-clinical studies	**Study 4** Three-month oral toxicity and toxicokinetic study in neonatal and juvenile rats with a six-week recovery period (SN 07193) **Study 5** Intravenous (IV) toxicity and toxicokinetic study in neonatal and juvenile Beagle dogs with a 5-month recovery (TT 12-9018) **Study 6** 12-week oral (gavage) toxicity and toxicokinetic study of posaconazole (SCH 56592) in neonatal and juvenile rats. (SN 09005) **Study 7** Nine-month oral (gavage) neurotoxicity study of SCH 56592 with a three-month post-dose period in juvenile beagle dogs. (SN 07194)
Clinical studies	**Study 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 2 years to less than 18 years. (P03579/PN032) **Study 9** 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 2 years to less than 18 years. (P07748/PN097)
Extrapolation, modelling and simulation studies	**Study 10** Extrapolation study to support extrapolation of efficacy in prophylaxis of invasive fungal infections **Study 11** Modelling and simulation study for dose determination
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

Gastro-resistant powder for oral suspension

Concentrate for solution for infusion

2.2.4. Measures

Area	**Description**
Quality-related studies	Same as for condition "Prevention of invasive fungal infections"
Non-clinical studies	Same as for condition "Prevention of invasive fungal infections"
Clinical studies	Same as study 8 in the condition "Prevention of invasive fungal infection" (P03579/PN032) Same as study 9 in the condition "Prevention of invasive fungal infection" (P07748/PN097) **Study 12** *Deleted (procedure EMEA-000468-PIP02-12-M03)* **Study 13** Open-label, uncontrolled study to evaluate the safety and efficacy of posaconazole for the treatment of invasive aspergillosis in paediatric patients 2 years of age and older. (20149/PN104) **Study 14** *Deleted (procedure EMEA-000468-PIP02-12-M03)* **Study 15** *(added in procedure EMEA-000468-PIP02-12-M03)* Open-label, uncontrolled study to evaluate the safety and PK of posaconazole solution for infusion and of gastro-resistant powder for oral suspension in neonates, infants, and young children less than 2 years of age with proven or probable invasive fungal infections. (PN127)
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/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By December 2024
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Information provided by the applicant:

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.
  - Invented name(s): Noxafil
  - Authorised pharmaceutical form(s): Oral suspension, gastro-resistant tablet, concentrate for solution for infusion
  - Authorised route(s) of administration: Oral use, intravenous use
  - Authorised via centralised procedure

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.
  - Invented name(s): Noxafil
  - Authorised pharmaceutical form(s): Oral suspension, gastro-resistant tablet, concentrate for solution for infusion
  - Authorised route(s) of administration: Oral use, intravenous use
  - Authorised via centralised procedure