

EMA/465528/2024

European Medicines Agency decision

P/0376/2024

of 25 October 2024

on the acceptance of a modification of an agreed paediatric investigation plan for posaconazole (Noxafil), (EMA-000468-PIP02-12-M09) 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 726/2004¹,

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 Agency²,

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, the decision P/0196/2022 issued on 9 June 2022 and the decision P/0200/2023 issued on 5 June 2023,

Having regard to the application submitted by MSD Europe Belgium SRL on 3 June 2024 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 6 September 2024, 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, 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, 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 MSD Europe Belgium SRL, Boulevard du Souverain 25, 1170 – Brussels, Belgium.

EMA/PDCO/278973/2024 Corr. ¹
Amsterdam, 6 September 2024

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan EMA-000468-PIP02-12-M09

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:

MSD Europe Belgium SRL

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, MSD Europe Belgium SRL submitted to the European Medicines Agency on 3 June 2024 an application for modification of the

¹ 7 October 2024

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, the decision P/0196/2022 issued on 9 June 2022 and the decision P/0200/2023 issued on 5 June 2023.

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

The procedure started on 8 July 2024.

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 and to the deferral in the scope set out in the Annex I of this opinion.

The Paediatric Committee member of Norway 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;
- 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 <i>Deleted in procedure EMEA-000468-PIP02-12-M04</i>

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 <i>Deleted (procedure EMEA-000468-PIP02-12-M03)</i> 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 <i>Deleted (procedure EMEA-000468-PIP02-12-M03)</i> 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 2025
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
 - Invented name(s): Noxafil
 - Authorised pharmaceutical form(s): Gastro-resistant tablet, concentrate for solution for infusion
 - Authorised route(s) of administration: Oral use, intravenous use
 - Authorised via centralised procedure

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

Noxafil gastro-resistant tablets are indicated for use in the treatment of the following fungal infections in paediatric patients (from 2 years of age weighing more than 40 kg for gastro-resistant tablets; from 2 years of age for concentrate for solution for infusion and for gastro resistant powder and solvent for oral suspension):

- 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.
- 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): Gastro-resistant tablet, concentrate for solution for infusion, gastro resistant powder and solvent for oral suspension
 - 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 adult 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

Noxafil is also indicated for prophylaxis of invasive fungal infections in the following paediatric patients (from 2 years of age weighing more than 40 kg for gastro-resistant tablets; from 2 years of age for concentrate for solution for infusion and for gastro resistant powder and solvent for oral suspension):

- 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): Gastro-resistant tablet, concentrate for solution for infusion, gastro resistant powder and solvent for oral suspension

- Authorised route(s) of administration: Oral use, intravenous use
- Authorised via centralised procedure