MHRA
10 South Colonnade
Canary Wharf
London
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United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

accept change(s) to the agreed paediatric investigation plan (MHRA-100479-PIP01-22-M02) and to the deferral

MHRA-100479-PIP01-22-M03

Scope of the Application

Active Substance(s)

POSACONAZOLE

Condition(s)

Prevention of invasive fungal infections, Treatment of invasive fungal infections

Pharmaceutical Form(s)

Oral suspension Gastro-resistant tablet Gastro-resistant powder and solvent 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 (UK) Ltd

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Merck Sharp & Dohme (UK) Ltd submitted to the licensing authority on 18/09/2024 16:03 BST an application for a Modification

The procedure started on 25/10/2024 11:31 BST

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to accept change(s) to the agreed paediatric investigation plan and to the deferral

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This decision is forwarded to the applicant, together with its annex and appendix.

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Final Decision Letter

MHRA-100479-PIP01-22-M03

Of 11/11/2024 16:07 GMT

On the adopted decision for POSACONAZOLE (MHRA-100479-PIP01-22-M03) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on modification of a paediatric investigation plan (including modification of a waiver or deferral included in that paediatric investigation plan)

This decision applies to a Modification for POSACONAZOLE, Oral suspension Gastro-resistant tablet Gastro-resistant powder and solvent for oral suspension Concentrate for solution for infusion , ORAL USE; INTRAVENOUS USE .

This decision is addressed to Merck Sharp & Dohme (UK) Ltd, 120 Moorgate, London, UNITED KINGDOM, EC2M 6UR

ANNEX I

1. Waiver

1.1 Condition:

Condition 1: Prevention of invasive fungal infections. The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to 3 months of age. 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. Reason for granting waiver: on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. Paediatric Subset(s): The paediatric population from 3 months to less than 18 years of age. Pharmaceutical form(s): Oral suspension. Route(s) of administration: ORAL USE. Reason for granting waiver: on the grounds that the specific medicinal product is likely to be ineffective. Paediatric Subset(s): 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. Pharmaceutical form(s): Gastro-resistant tablet. Route(s) of administration: ORAL USE. Reason for granting waiver: on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. Condition 2: Treatment of invasive fungal infections. The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 18 years of age. Pharmaceutical form(s): Oral suspension. Route(s) of

administration: ORAL USE. Reason for granting waiver: on the grounds that the specific medicinal product is likely to be ineffective. Paediatric Subset(s): 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. Pharmaceutical form(s): Gastro-resistant tablet. Route(s) of administration: ORAL USE. Reason for granting waiver: 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(s):

Condition 1: Prevention of invasive fungal infections. Condition 2: Treatment of invasive fungal infections.

2.2 Indication(s) targeted by the PIP:

Condition 1: For prophylaxis of invasive fungal infections in the following paediatric patients: Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (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. Condition 2: Treatment of invasive aspergillosis.

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

Condition 1: The paediatric population from 3 month to less than 18 years of age. Condition 2: The paediatric population from birth to less than 18 years of age.

2.4 Pharmaceutical Form(s):

Condition 1: Oral suspension Gastro-resistant tablet Gastro-resistant powder for oral suspension Concentrate for solution for infusion Condition 2: Gastro-resistant tablet Gastro-resistant powder for oral suspension Concentrate for solution for infusion

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	For both conditions: 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 during procedure EMEA-000468-PIP02-12-M04.
Non-Clinical Studies	4	For both conditions: Study 4 (SN 07193) Three-month oral toxicity and toxicokinetic study in neonatal and juvenile rats with a six-week recovery period. Study 5 (TT 12-9018) Intravenous (IV) toxicity and toxicokinetic study in neonatal and juvenile Beagle dogs with a 5-month recovery. Study 6 (SN 09005) 12-week oral (gavage) toxicity and toxicokinetic study of Posaconazole (SCH 56592) in neonatal and juvenile rats. Study 7 (SN 07194) Nine-month oral (gavage) neurotoxicity study of SCH 56592 with a three-month post-dose period in juvenile beagle dogs. Study 12 Deleted during procedure EMEA-000468-PIP02-12-M03. Study 13 (20149/PN104) 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. Study 14 Deleted during procedure EMEA-000468-PIP02-12-M03. Study 15 (PN127) 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. Added during procedure EMEA-000468-PIP01012-M03.
Clinical Studies	4	For both conditions: Study 8 (P03579/PN032) 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. Study 9 (P07748/

		PN097) 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. For treatment of invasive fungal infections only: Study 12 Deleted during procedure EMEA-000468-PIP02-12-M03. Study 13 (20149/ PN104) 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. Study 14 Deleted during procedure EMEA-000468-PIP02-12-M03. Study 15 (PN127) 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. Added during procedure EMEA-000468-PIP01012-M03.
Extrapolation, Modeling & Simulation Studies	2	For condition prevention of invasive fungal infection only: 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	0	Not Applicable.
Other Measures	0	Not Applicable.

3. Follow-up, completion and deferral of a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	31/12/2025
Deferral of one or more studies contained in the paediatric investigation plan:	Yes