MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

agree a paediatric investigation plan and grant a deferral and grant a waiver

MHRA-100558-PIP01-22

Scope of the Application

Active Substance(s)

milvexian

Condition(s)

Prevention of thromboembolism in patients with cardiovascular disease

Pharmaceutical Form(s)

Film-coated tablet; Age appropriate oral dosage form

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

Janssen-Cilag Limited

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Janssen-Cilag Limited submitted to the licensing authority on 28/06/2022 12:20 BST an application for a Paediatric Investigation Plan

The procedure started on 10/10/2022 12:29 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 agree a paediatric investigation plan and grant a deferral and grant a waiver

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-100558-PIP01-22

Of 13/02/2024 15:06 GMT

On the adopted decision for milvexian (MHRA-100558-PIP01-22) 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 a paediatric investigation plan

This decision applies to a Paediatric Investigation Plan for milvexian, Film-coated tablet; Age appropriate oral dosage form , ORAL USE .

This decision is addressed to Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, UNITED KINGDOM, HP12 4EG

ANNEX I

1. Waiver

1.1 Condition:

Prevention of thromboembolism in patients with cardiovascular disease. The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth less than 28 days of age Pharmaceutical form(s): Film-coated tablet Age appropriate oral dosage form 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):

Prevention of thromboembolism in patients with cardiovascular disease

2.2 Indication(s) targeted by the PIP:

Primary prevention of thromboembolic events in paediatric patients from 28 days to less than 18 years of age with congenital heart disease

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

The paediatric population from 28 days to less than 18 years of age

2.4 Pharmaceutical Form(s):

Film-coated tablet Age appropriate oral dosage form

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	1	Study 1 Development of an age-appropriate oral formulation.
Non-Clinical Studies	2	Study 2 In vitro assessment of coagulation assays in paediatric plasma samples spiked with milvexian. Study 3 Reproductive toxicity animal study to assess potential effects of milvexian on pregnant/lactating rabbits and postnatal development of the offspring.
Clinical Studies	2	Study 4 Open-label, single dose trial to evaluate pharmacokinetics, safety, tolerability, acceptability, and palatability of milvexian in children from 28 days to less than 18 years of age at risk of thromboembolic events. Study 5 Open label, randomised, multiple dose trial to evaluate pharmacokinetics, safety, and efficacy of milvexian compared to best standard of care in children from 28 days to less than 18 years of age with congenital heart disease at risk of thromboembolic events.
Extrapolation, Modeling & Simulation Studies	2	Study 6 Modelling and simulation study to inform the dose and treatment regimen in studies 4 and 5, and to demonstrate comparability of PK/PD relationships between adult and paediatric populations. Extrapolation Plan Studies 4, 5, 6 are

		part of an extrapolation plan covering the paediatric population from 28 days to less than 18 years of age, as agreed by the Regulatory Agency.
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:	No
Date of completion of the paediatric investigation plan:	30/06/2032
Deferral of one or more studies contained in the paediatric investigation plan:	Yes