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

**gov.uk/mhra**

# Decision Cover Letter

## Decision of the licensing authority to:

accept change(s) to the agreed paediatric investigation plan (MHRA-100558-PIP01-22)

MHRA-100558-PIP01-22-M01

# Scope of the Application

## Active Substance(s)

milvexian

## Condition(s)

Prevention of thromboembolism in patients with cardiovascular diseases

## Pharmaceutical Form(s)

Film-coated tablet Age appropriate oral solid dosage form

## Route(s) of Administration

ORAL USE

## Name / Corporate name of the PIP applicant

Janssen-Cilag Ltd

## Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Janssen-Cilag Ltd submitted to the licensing authority on 28/06/2024 18:45 BST an application for a Modification

The procedure started on 30/08/2024 12:22 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

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-M01

Of 23/10/2024 18:02 BST

On the adopted decision for milvexian (MHRA-100558-PIP01-22-M01) 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 milvexian, Film-coated tablet Age appropriate oral solid dosage form , ORAL USE .

This decision is addressed to Janssen-Cilag Ltd , 50-100 Holmers Farm Way, Buckinghamshire, 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 solid 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 solid dosage form

## 2.5 Studies:

| Study Type | Number of Studies | Study Description |
|---|---|---|
| **Quality Measures** | 1 | Study 1 Development of an age-appropriate oral solid 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, to achieve comparable drug exposure between adult and paediatric |

| | | |
|---|---|---|
| | | populations and to characterise PK/ PD relationships. 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 |