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

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Decision Cover Letter

Decision of the licensing authority to:

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

MHRA-100775-PIP01-22-M01

Scope of the Application

Active Substance(s)

(4R,5R)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-4- hydroxy-1,1-dioxido-1-benzothiepin-5-yl] phenoxy] methyl] phenyl] methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride; Maralixibat chloride

Condition(s)

Treatment of Alagille Syndrome (ALGS)

Pharmaceutical Form(s)

Oral solution; Tablet

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

Mirum Pharmaceuticals

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Mirum Pharmaceuticals submitted to the licensing authority on 23/11/2022 13:54 GMT an application for a

The procedure started on 06/12/2022 08:19 GMT

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-100775-PIP01-22-M01

Of 15/12/2022 14:54 GMT

On the adopted decision for (4R,5R)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-4- hydroxy-1,1-dioxido-1-benzothiepin-5-yl] phenoxy] methyl] phenyl] methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride; Maralixibat chloride (MHRA-100775-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 for (4R,5R)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-4- hydroxy-1,1-dioxido-1-benzothiepin-5-yl] phenoxy] methyl] phenyl] methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride; Maralixibat chloride, Oral solution; Tablet , ORAL USE .

This decision is addressed to Mirum Pharmaceuticals, 950 Tower Lane, Suite 1050, Foster City CA, UNITED STATES OF AMERICA, CA 94404

ANNEX I

1. Waiver

1.1 Condition:

Not applicable

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of Alagille Syndrome (ALGS)

2.2 Indication(s) targeted by the PIP:

Treatment of Alagille Syndrome (ALGS)

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

All subsets of the paediatric population from birth to less than 18 years of age

2.4 Pharmaceutical Form(s):

Oral solution Tablet

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	0	Not applicable
Non-Clinical Studies	1	Study 1 (2939-001/MRXNC-001) Juvenile toxicity study in rats.
Clinical Studies	4	Study 2 (LUM001-302) Randomised double-blind, placebo-controlled safety and efficacy study of maralixibat in children 12 months to 18 years of age with Alagille syndrome. Study 3 (LUM001-301) Randomised double-blind, placebo-controlled safety and efficacy study of maralixibat in children 12 months to 18 years of age with Alagille syndrome. Study 4 (LUM001-304) Open label with a double-blind placebo controlled randomised drug withdrawal period, safety and efficacy study maralixibat in children 12 months to 18 years of age with Alagille syndrome. Study 5 (MRX-801) Open-label, uncontrolled safety study to evaluate the safety and tolerability of maralixibat in paediatric subjects from birth to less than 12 months of age with cholestatic liver diseases due to Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC).
Extrapolation, Modeling & Simulation Studies	0	Not applicable
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:	31/12/2023
Deferral of one or more studies contained in the paediatric investigation plan:	Yes