EMA/517330/2023

European Medicines Agency decision

P/0457/2023

of 1 December 2023

on the acceptance of a modification of an agreed paediatric investigation plan for macitentan (Opsumit), (EMEA-001032-PIP01-10-M07) 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 726/2004[1],

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 Agency[2],

Having regard to the European Medicines Agency's decision P/303/2011 issued on 21 December 2011, the decision P/0087/2012 issued on 25 May 2012, the decision P/0049/2016 issued on 18 March 2016, the decision P/0480/2021 issued on 3 December 2021 and the decision P/0012/2023 issued on 31 January 2023,

Having regard to the application submitted by Janssen-Cilag International NV on 3 July 2023 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 13 October 2023, 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.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.

[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 macitentan (Opsumit), dispersible tablet, film-coated tablet, oral use, 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 Janssen-Cilag International NV, Turnhoutseweg 30, BE-2340 – Beerse, Belgium.

EMA/PDCO/319660/2023 Corr[1]
Amsterdam, 13 October 2023

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-001032-PIP01-10-M07

Scope of the application

Active substance(s):

Macitentan

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of pulmonary arterial hypertension

Treatment of systemic sclerosis

Treatment of idiopathic pulmonary fibrosis

Pharmaceutical form(s):

Dispersible tablet

Film-coated tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Janssen-Cilag International NV

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Janssen-Cilag International NV submitted to the European Medicines Agency on 3 July 2023 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/303/2011 issued on 21 December 2011, the decision P/0087/2012 issued on 25

[1] 21 November 2023

May 2012, the decision P/0049/2016 issued on 18 March 2016, the decision P/0480/2021 issued on 3 December 2021 and the decision P/0012/2023 issued on 31 January 2023.

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

The procedure started on 14 August 2023.

Scope of the modification

Some measures 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, by a majority of 19 out of 25 votes:

   - to agree to changes to the paediatric investigation plan in the scope set out in the Annex I of this opinion.

   The divergent positions are appended to 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:

Treatment of systemic sclerosis

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- dispersible tablet, film-coated tablet, oral use;
- on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.

1.2. Condition:

Treatment of idiopathic pulmonary fibrosis

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- dispersible tablet, film-coated tablet, oral use;
- on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.

1.3. Condition:

Treatment of pulmonary arterial hypertension

The waiver applies to:

- all subsets of the paediatric population from birth to less than 1 month of age;
- dispersible tablet, film-coated tablet, oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

2. Paediatric Investigation Plan

2.1. Condition:

Treatment of pulmonary arterial hypertension

2.1.1. Indication(s) targeted by the PIP

Treatment of pulmonary arterial hypertension (PAH)

2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From 1 month to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Dispersible tablet

Film-coated tablet

2.1.4. Measures

Area	Description
Quality-related studies	**Study 1:** Development of a dispersible tablet formulation. **Study 2:** *This study was deleted during procedure EMEA-001032-PIP01-10-M02.*
Non-clinical studies	**Study 3:** 25-day dose range finding toxicity study in juvenile rats. **Study 4:** Toxicity study in juvenile rats.
Clinical studies	**Study 5:** *This study was deleted during procedure EMEA-001032-PIP01-10-M02.* **Study 6:** *This study was deleted during procedure EMEA-001032-PIP01-10-M02.* **Study 7:** *This study was deleted during procedure EMEA-001032-PIP01-10-M02.* **Study 8:** Open-label, randomised, multicentre, active controlled, parallel group study to evaluate pharmacokinetics, safety and efficacy of macitentan in children from 1 month to less than 18 years of age with pulmonary arterial hypertension. **Study 11:** *(This study was added as a result of procedure EMEA-001032-PIP01-10-M05.)* Open-label, single-arm, uncontrolled study to evaluate pharmacokinetics, and safety of macitentan in children from 1 month to less than 2 years of age with PAH. **Study 13:** *(This study was added as a result of procedure EMEA-001032-PIP01-10-M07.)* Open-label, non-comparative study to evaluate pharmacokinetics, safety and activity of macitentan in children from 3 months to less than 15 years of age with pulmonary arterial hypertension.

Extrapolation, modelling and simulation studies	**Study 9:** *(This study was added as a result of procedure EMEA-001032-PIP01-10-M04.)* Population pharmacokinetic modelling and simulation study to support extrapolation and the use of macitentan in children from 1 month to less than 18 years of age with pulmonary arterial hypertension. **Study 10:** *(This study was added as a result of procedure EMEA-001032-PIP01-10-M04.)* Pharmacodynamic similarity/comparison study.
Other studies	**Study 12:** *(This study was added as a result of procedure EMEA-001032-PIP01-10-M05.)* Combined descriptive analysis of pharmacokinetics, safety, and efficacy of macitentan in children from 1 month to less than 2 years of age with PAH treated with macitentan.
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:	No
Date of completion of the paediatric investigation plan:	By April 2024
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 pulmonary arterial hypertension

Authorised indication(s):

- As monotherapy or in combination for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

Invented name(s):

Opsumit

Authorised pharmaceutical form(s):

Film-coated tablet

Authorised route(s) of administration:

Oral use

Appendix

Divergent position statement

Divergent opinion on EMEA-001032-PIP01-10-M07 11.10.2023

The undersigned do not agree to the reduction in the number of patients <2 yrs. of age in PIP Studies 8 and 11 as this change is not scientifically justified but mainly driven by the applicants wish to terminate these studies early in order to claim the reward as detailed in the Paediatric Regulation. Especially in the light of the issues identified during the preliminary assessment of the PK data, which will likely lead to problems during the licensing process, it is considered of paramount importance to include as much patients from this age range as possible in the development program.

Dr Sabine Scherer

Dr Fernando Cabañas

Dr Johannes Taminiau

Dr Fernando de Andres Trelles

Dr Adrienn Horváth

Divergent opinion on EMEA-001032-PIP01-10-M07 12.10.2023

The undersigned, member of the PDCO, during voting procedure has been carried out on 11 October, 2023 agreed to include data from the Japanese 2 patients younger than 2 years of age (as a study 13 of the PIP) with current 9 patients younger than 2 years of age enrolled already to studies 8, 11 and 13 of the PIP.

However, I voted against requested by the applicant reduction of total number of patients younger than 2 years of age in the PIP from 10 to 9 based on the applicant's declaration (the applicant's response dated 22 September, 2023 – issue 4) – "*the Applicant will commit to keep Study 11 open to* ***recruitment until April 2024 to enable enrollment of 1 additional participant <2 years of age per protocol, which could potentially lead to the recruitment of a participant <1 year of age".***

Marek Migdal, MD, PhD