EMA/485479/2024

European Medicines Agency decision

P/0384/2024

of 25 October 2024

on the refusal of a modification of an agreed paediatric investigation plan for ambrisentan (Volibris), (EMEA-000434-PIP01-08-M10) 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/224/2009 issued on 4 November 2009, the decision P/0062/2013 issued on 26 March 2013, the decision P/0267/2014 issued on 16 October 2014, the decision P/0322/2016 issued on 2 December 2016, the decision P/0077/2019 issued on 22 March 2019, the decision P/0370/2019 issued on 8 November 2019, and the decision P/0428/2022 issued on 28 October 2022,

Having regard to the application submitted by GlaxoSmithKline (Ireland) Limited on 24 April 2024 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 18 October 2024, 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 following a re-examination procedure of the Paediatric Committee's opinion according to Article 25(3) of Regulation (EC) No 1901/2006, an opinion on the refusal of changes to the agreed paediatric investigation plan and to the deferral and to the waiver.

(2) It is therefore appropriate to adopt a decision on the refusal of changes to the agreed paediatric investigation plan, including changes to the deferral and to the waiver.

[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 ambrisentan (Volibris), film-coated tablet, oral use, including changes to the deferral and to the waiver, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, are hereby refused.

Article 2

This decision is addressed to GlaxoSmithKline (Ireland) Limited, 12 River Walk, Citywest Business, Campus, D24 YK11 – Dublin, Ireland.

EMA/PDCO/454328/2024
Amsterdam, 18 October 2024

Final opinion of the Paediatric Committee on the refusal of a modification of an agreed Paediatric Investigation Plan

EMEA-000434-PIP01-08-M10

Scope of the application

Active substance(s):

Ambrisentan

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of pulmonary arterial hypertension

Pharmaceutical form(s):

Film-coated tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

GlaxoSmithKline (Ireland) Limited

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 24 April 2024 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/224/2009 issued on 4 November 2009, the decision P/0062/2013 issued on 26 March 2013, the decision P/0267/2014 issued on 16 October 2014, the decision P/0322/2016 issued on 2 December 2016, the decision P/0077/2019 issued on 22 March 2019, the decision P/0370/2019 issued on 8 November 2019, and the decision P/0428/2022 issued on 28 October 2022.

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

An Opinion was adopted by the Paediatric Committee on 26 July 2024 for the above mentioned product. GlaxoSmithKline (Ireland) received the Paediatric Committee Opinion on 5 August 2024.

On 3 September 2024, GlaxoSmithKline (Ireland) submitted to the European Medicines Agency a written request including detailed grounds for a re-examination of the Opinion.

The re-examination procedure started on 19 September 2024.

A meeting with the Paediatric Committee took place on 17 October 2024.

Final Opinion

1. The Paediatric Committee, having assessed the detailed grounds for re-examination, in accordance with Article 25(3) of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   to maintain its opinion and

   - to refuse the changes regarding the measures proposed by the applicant regarding the paediatric investigation plan and the timelines of the deferraland and to amend the scope of the waiver in the scope set out in the Annex I of 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 agreed paediatric investigation plan and the subset(s) of the paediatric population and condition(s)) covered by the waiver remain unchanged and are set out in the Annex I.

3. The scientific conclusions and the grounds for refusal are set out in the summary report appended to this opinion.

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 pulmonary arterial hypertension

The waiver applies to:

- children less than one year of age;
- film-coated tablet, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric investigation plan

2.1. Condition

Treatment of pulmonary arterial hypertension

2.1.1. Indication(s) targeted by the PIP

Treatment of idiopathic (IPAH) and familial (FPAH) pulmonary hypertension; treatment of associated pulmonary hypertension (APAH)

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

From 1 year to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Film-coated tablet

2.1.4. Measures

Area	Description
Quality-related studies	**Study 1:** Development of film coated tablets 2.5 mg for oral use. **Study 2:** Development of film-coated tablets 1.25 mg for oral use.
Non-clinical studies	**Study 3:** 2-week juvenile animal study to determine tolerability and toxicokinetics of ambrisentan. **Study 4:** 8-week juvenile animal study to determine oral toxicology and toxicokinetic of ambrisentan including an 8 weeks recovery period.
Clinical studies	**Study 5:** 24 weeks randomized, open label, multi-centre, comparative trial to evaluate safety, efficacy and population PK of ambrisentan low and high dose for the treatment of children from 8 years of age to less than 18 years of age with Pulmonary Arterial Hypertension (AMB112529).

	Study 6: (deleted in procedure EMEA-000434-PIP01-08-M09) **Study 7:** 24 weeks randomized, open label, multi-centre, comparative trial to evaluate safety, efficacy and PK of ambrisentan low and high dose for the treatment of children from 1 year of age to less than 8 years of age with Pulmonary Arterial Hypertension. (AMB112530)
Extrapolation, modelling and simulation studies	**Study 8:** (added in procedure EMEA-000434-PIP01-08-M05): Pharmacokinetic (PK) and exposure-response (ER) modelling and simulation study to support ambrisentan dose recommendation for treatment of paediatric PAH. **Study 9:** (added in procedure EMEA-000434-PIP01-08-M05): Extrapolation study to evaluate the efficacy of ambrisentan in paediatric PAH based on the change in 6-minute walk distance (6MWD) observed in study AMB112529.
Other studies	Not applicable.
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:	Yes
Date of completion of the paediatric investigation plan:	By April 2021
Deferral for one or more measures 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):

- Volibris is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.
- Volibris is indicated for treatment of PAH in adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment. Efficacy has been shown in IPAH, familial, corrected congenital and in PAH associated with connective tissue disease.
  - Invented name(s): Volibris
  - Authorised pharmaceutical form(s): Film-coated tablet
  - Authorised route(s) of administration: Oral use
  - Authorised via centralised procedure.