EMA/826798/2022

European Medicines Agency decision

P/0428/2022

of 28 October 2022

on the acceptance of a modification of an agreed paediatric investigation plan for ambrisentan (Volibris), (EMEA-000434-PIP01-08-M09) 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 and the decision P/0370/2019 issued on 8 November 2019,

Having regard to the application submitted by Glaxo Group Limited on 27 May 2022 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 9 September 2022, 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 ambrisentan (Volibris), 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 Glaxo Group Limited, 980 Great West Road, TW8 9GS – Brentford, United Kingdom.

EMA/PDCO/597796/2022
Amsterdam, 9 September 2022

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

EMEA-000434-PIP01-08-M09

Scope of the application

Active substance(s):

Ambrisentan

Invented name:

Volibris

Condition(s):

Treatment of pulmonary arterial hypertension

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Glaxo Group Limited

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Glaxo Group Limited submitted to the European Medicines Agency on 27 May 2022 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 and the decision P/0370/2019 issued on 8 November 2019.

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

The procedure started on 11 July 2022.

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:

   - to agree to changes to the paediatric investigation plan 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 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 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	Number of measures	Description
Quality-related studies	2	**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	2	**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	2	**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 2 years of age to less than 8 years of age with Pulmonary Arterial Hypertension. (AMB112530)
Extrapolation, modelling and simulation studies	2	**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	0	Not applicable.
Other measures	0	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

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.

Authorised pharmaceutical form(s)

Film-coated tablet

Authorised route(s) of administration

Oral use