EMADOC-1700519818-1791595

European Medicines Agency decision

EMA/PE/0000182170

of 5 December 2024

on the acceptance of a modification of an agreed paediatric investigation plan for regorafenib (Stivarga) 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/0258/2012 issued on 31 October 2012, the decision P/0270/2014 issued on 27 October 2014, the decision P/0190/2016 issued on 15 July 2016, the decision P/0091/2017 issued on 11 April 2017, the decision P/0158/2019 issued on 17 April 2019, the decision P/0141/2020 issued on 17 April 2020 and the decision P/0495/2021 issued on 3 December 2021,

Having regard to the application submitted by Bayer AG on 14 June 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 an opinion on the acceptance of changes to the agreed paediatric investigation plan and to the deferral.

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

[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 regorafenib (Stivarga), including changes to the deferral, 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 Bayer AG, Muellerstrasse 178, 13353 – Berlin, Germany.

EMADOC-1700519818-1622500
Amsterdam, 18 October 2024

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

EMA/PE/0000182170

Scope of the application

Active substance(s):

Regorafenib

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of all conditions contained in the category of malignant neoplasms (except haematopoietic and lymphoid tissue)

Pharmaceutical form(s):

Film-coated tablet

Granules

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Bayer AG

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Bayer AG submitted to the European Medicines Agency on 14 June 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/0258/2012 issued on 31 October 2012, the decision P/0270/2014 issued on 27 October 2014, the decision P/0190/2016 issued on 15 July 2016, the decision P/0091/2017 issued on 11 April 2017, the decision P/0158/2019 issued on 17 April 2019, the decision P/0141/2020 issued on 17 April 2020 and the decision P/0495/2021 issued on 3 December 2021.

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

The procedure started on 19 August 2024.

Scope of the modification

Some timelines 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 and to the deferral 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 all conditions contained in the category of malignant neoplasms (except haematopoietic and lymphoid tissue)

The waiver applies to:

- the paediatric population from birth to less than 6 months of age;
- film-coated tablet, granules, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric Investigation Plan

2.1. Condition

Treatment of all conditions contained in the category of malignant neoplasms (except haematopoietic and lymphoid tissue)

2.1.1. Indication(s) targeted by the PIP

Treatment of paediatric patients with a solid malignant tumour(s) integrated with anti-cancer therapy

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

From 6 months to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Film-coated tablet

Granules

2.1.4. Measures

Area	Description
Quality-related studies	**Study 1** Development of granules for oral use as age-appropriate formulation
Non-clinical studies	**Study 2** Juvenile toxicity study **Study 3** Pharmacology testing of regorafenib in paediatric tumour models including biomarker exploration and combination testing

Clinical studies	**Study 4** Physiologically-based pharmacokinetic model to predict pharmacokinetics in the paediatric population from 6 months to less than 18 years of age **Study 5** Multi-centre, open-label, dose-escalating, cohort-expanding trial to evaluate pharmacokinetics, pharmacodynamics, tolerability, safety and tumour activity of regorafenib in the paediatric population with a solid malignant tumour refractory to standard therapy *Study 6* *Deleted in procedure EMEA-001178-PIP01-11-M03.* **Study 7** Multi-centre, randomised, controlled, open label trial to evaluate the activity, safety and efficacy of regorafenib in combination with vincristine and irinotecan (VI) compared to VI alone in the paediatric population from 6 months to less than 18 years with a first and subsequent relapses of rhabdomyosarcoma.

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 December 2027
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s)

1. Treatment of all conditions contained in the category of malignant neoplasms (except haematopoietic and lymphoid tissue)

Authorised indication(s):

- Stivarga is indicated for the treatment of adult patients metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.
  - Authorised pharmaceutical form(s): Film-coated tablet
  - Authorised route(s) of administration: Oral use
  - Authorised via centralised procedure

2. Treatment of colon carcinoma

Authorised indication(s):

- Stivarga is indicated for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.
  - Authorised pharmaceutical form(s): Film-coated tablet
  - Authorised route(s) of administration: Oral use
  - Authorised via centralised procedure

3. Treatment of hepatocellular carcinoma

Authorised indication(s):

- Stivarga is indicated hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.
  - Authorised pharmaceutical form(s): Film-coated tablet
  - Authorised route(s) of administration: Oral use
  - Authorised via centralised procedure