EMA/112114/2019

European Medicines Agency decision

P/0065/2019

of 22 March 2019

on the acceptance of a modification of an agreed paediatric investigation plan for dabrafenib (mesilate) (Tafinlar), (EMEA-001147-PIP01-11-M06) 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 Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0024/2012 issued on 27 January 2012, the decision P/0239/2013 issued on 24 September 2013, the decision P/0332/2014 issued on 22 December 2014, the decision P/0022/2016 issued on 29 January 2016 and the decision P/0260/2017 issued on 4 September 2017,

Having regard to the application submitted by Novartis Europharm Limited on 26 October 2018 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 1 February 2019, 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 waiver.

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

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for dabrafenib (mesilate) (Tafinlar), capsule, hard, dispersible tablet, oral use, including changes to the waiver, 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 Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, D04 A9N6 – Dublin, Ireland.

EMA/PDCO/782079/2018
London, 1 February 2019

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

EMEA-001147-PIP01-11-M06

Scope of the application

Active substance(s):

Dabrafenib (mesilate)

Invented name:

Tafinlar

Condition(s):

Treatment of melanoma

Treatment of solid malignant tumours (excluding melanoma)

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Capsule, hard

Dispersible tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Novartis Europharm Limited

Information about the authorised medicinal product:

See Annex II

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Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Novartis Europharm Limited submitted to the European Medicines Agency on 26 October 2018 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/0024/2012 issued on 27 January 2012, the decision P/0239/2013 issued on 24 September 2013, the decision P/0332/2014 issued on 22 December 2014, the decision P/0022/2016 issued on 29 January 2016 and the decision P/0260/2017 issued on 4 September 2017.

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

The procedure started on 4 December 2018.

Scope of the modification

Some measures of the Paediatric Investigation Plan have been modified. A waiver for a new paediatric subset has been added.

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 waiver in the scope set out in the Annex I of this opinion.

   The Norwegian Paediatric Committee member 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 melanoma

The waiver applies to:

- the paediatric population from birth to less than 12 years;
- capsules, hard, dispersible tablet, oral use;
- on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

1.2. Condition

Treatment of solid malignant tumours (excluding melanoma)

The waiver applies to:

- the paediatric population from birth to less than 1 year of age;
- capsules, hard, dispersible tablet, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe in the specified paediatric subsets.

2. Paediatric Investigation Plan

2.1. Condition

Treatment of melanoma

2.1.1. Indication(s) targeted by the PIP

Treatment of adolescent patients with melanoma containing BRAF V600 activating mutations

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

From 12 to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Capsule, hard

Dispersible tablet

2.1.4. Measures

Area	Number of studies	Description
Quality-related studies	1	**Study 1** Development of an age-appropriate dispersible tablet formulation.
Non-clinical studies	3	**Study 2** Dose range / tolerability juvenile rat toxicity study to evaluate toxicokinetics and clinical observations in rats given dabrafenib or vehicle control. **Study 3** Definitive juvenile rat toxicity study to evaluate toxicokinetics, clinical observations, laboratory parameters and histopathology of major organs in rats given dabrafenib (at doses determined in study 2) or vehicle control. **Study 8** Juvenile rat renal toxicity study.
Clinical studies	3	**Study 4** Open-label, single agent, uncontrolled dose escalation trial to determine the safety, tolerability, pharmacokinetics and maximum tolerated dose of dabrafenib in children from 1 to less than 18 years of age with advanced BRAF V600-mutant solid tumours. **Study 6** Open-label, randomised, single dose 3-way cross-over relative bioavailability study in normal adult healthy volunteers. **Study 7** Measure to demonstrate that the pharmacokinetics, pharmacodynamics and efficacy of dabrafenib in adolescent patients (aged from 12 to less than 18 years of age) with BRAF V600-mutant melanoma are similar to that in adults with BRAF V600-mutant melanoma, using a modelling and simulation approach for the purpose of extrapolation.

2.2. Condition

Treatment of solid malignant tumours (excluding melanoma)

2.2.1. Indication(s) targeted by the PIP

Treatment of paediatric patients with solid malignant tumours containing BRAF V600 activating mutations

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

From 1 to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Capsule, hard

Dispersible tablet

2.2.4. Measures

Area	Number of studies	Description
Quality-related studies	1	**Study 1** As for condition "Treatment of melanoma".
Non-clinical studies	3	**Study 2** As for condition "Treatment of melanoma". **Study 3** As for condition "Treatment of melanoma". **Study 8** As for condition "Treatment of melanoma".
Clinical studies	4	**Study 4** As for condition "Treatment of melanoma". **Study 5** Open-label, randomised controlled parallel-group trial to determine the safety and efficacy of dabrafenib in combination with trametinib in children from 1 to less than 18 years of age with advanced BRAF V600-mutant Low Grade Glioma, with progression following optimal surgical treatment or for which systemic anticancer treatment is indicated. **Study 6** As for condition "Treatment of melanoma". **Study 9** Open-label single arm cohort to determine the safety and efficacy of dabrafenib with trametinib in children from 1 to less than 18 years of age with BRAF V600 mutant relapsed or refractory High Grade Glioma (HGG).

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By June 2022
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 melanoma

Authorised indication(s):

- Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

2. Treatment of solid malignant tumours (excluding melanoma)

- Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

Authorised pharmaceutical form(s)

Capsules, hard

Authorised route(s) of administration

Oral use