EMA/534960/2020

European Medicines Agency decision

P/0392/2020

of 23 October 2020

on the acceptance of a modification of an agreed paediatric investigation plan for trametinib (dimethyl sulfoxide) (Mekinist), (EMEA-001177-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/0044/2012 issued on 28 February 2012, the decision P/0078/2014 issued on 2 April 2014, the decision P/0024/2016 issued on 29 January 2016, the decision P/0259/2017 issued on 4 September 2017 and the decision P/0076/2019 issued on 22 March 2019,

Having regard to the application submitted by Novartis Europharm Limited on 5 June 2020 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 4 September 2020, 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.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for trametinib (dimethyl sulfoxide) (Mekinist), film-coated tablet, powder for oral solution, 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 Novartis Europharm Limited, Vista Building - Elm Park - Merrion Road, D04 A9N6 - Dublin, Ireland.

EMA/PDCO/328843/2020
Amsterdam, 4 September 2020

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

EMEA-001177-PIP01-11-M06

Scope of the application

Active substance(s):

Trametinib (dimethyl sulfoxide)

Invented name:

Mekinist

Condition(s):

Treatment of melanoma

Treatment of all conditions included in the category of malignant neoplasms (except melanoma, haematopoietic and lymphoid tissue, and glioma)

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Powder for oral solution

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

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 5 June 2020 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/0044/2012 issued on 28 February 2012, the decision P/0078/2014 issued on 2 April 2014, the decision P/0024/2016 issued on 29 January 2016, the decision P/0259/2017 issued on 4 September 2017 and the decision P/0076/2019 issued on 22 March 2019.

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

The procedure started on 6 July 2020.

Scope of the modification

Some measures of the Paediatric Investigation Plan have been modified.

Amendment of the scope of the Paediatric Investigation Plan to exclude another condition(s).

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 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;
- film-coated tablet, powder for oral solution, 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 all conditions included in the category of malignant neoplasms (except melanoma, haematopoietic and lymphoid tissue, and glioma)

The waiver applies to:

- preterm and term newborn infants from birth to less than 1 month;
- film-coated tablet, powder for oral solution, 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 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)

Film-coated tablet

Powder for oral solution

2.1.4. Measures

Area	Number of studies	Description
Quality-related studies	1	**Study 1** Development of an age-appropriate powder for oral solution formulation of trametinib.
Non-clinical studies	1	**Study 2** Juvenile rat toxicity study to evaluate toxicokinetics, clinical observations, laboratory parameters and histopathology of trametinib.
Clinical studies	2	**Study 3** Open-label, single agent, dose escalation trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of trametinib in children from 1 month to less than 18 years of age with relapsed or refractory solid malignant tumours. **Study 5** Relative bioavailability study in adults.
Extrapolation, modelling and simulation studies	1	**Study 6** Study to demonstrate that pharmacokinetics, pharmacodynamics and efficacy of trametinib 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 of efficacy.
Other studies	0	Not applicable

2.2. Condition

Treatment of all conditions included in the category of malignant neoplasms (except melanoma, haematopoietic and lymphoid tissue, and glioma)

2.2.1. Indication(s) targeted by the PIP

Treatment of paediatric patients with a solid malignant tumour with known or expected RAS, RAF or MEK pathway activation

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

From 1 month to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Film-coated tablet

Powder for oral solution

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Same as for condition treatment of melanoma.
Non-clinical studies	1	**Study 2** Same as for condition treatment of melanoma.
Clinical studies	4	**Study 3** Same as for condition treatment of melanoma. **Study 4** Study deleted during procedure EMEA-001177-PIP01-11-M06. **Study 5** Same as for condition treatment of melanoma. **Study 7** Study deleted during procedure EMEA-001177-PIP01-11-M06.
Extrapolation, modelling and simulation studies	0	Not applicable
Other studies	0	Not applicable

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 measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment melanoma

Authorised indication(s):

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

2. Treatment of all conditions included in the category of malignant neoplasms (except melanoma, haematopoietic and lymphoid tissue)

Authorised indication(s):

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

Authorised pharmaceutical form(s):

Film-coated tabled

Authorised route(s) of administration:

Oral use