EMA/501663/2017

European Medicines Agency decision

P/0259/2017

of 4 September 2017

on the acceptance of a modification of an agreed paediatric investigation plan for trametinib (dimethyl sulfoxide) (Mekinist), (EMEA-001177-PIP01-11-M04) 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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An agency of the European Union

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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 and the decision P/0024/2016 issued on 29 January 2016,

Having regard to the application submitted by Novartis Europharm Limited on 2 May 2017 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 21 July 2017, 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.
[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, 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 Novartis Europharm Limited, Frimley Business Park, GU16 7SR - Camberley, United Kingdom.

EMA/PDCO/284116/2017 Corr
London, 21 July 2017

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

EMEA-001177-PIP01-11-M04

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, nervous system, haematopoietic and lymphoid tissue)

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

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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 2 May 2017 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 and the decision P/0024/2016 issued on 29 January 2016.

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

The procedure started on 24 May 2017.

Scope of the modification

Some measures and 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.
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 included in the category of malignant neoplasms (except melanoma, nervous system, haematopoietic and lymphoid tissue)

The waiver applies to:

- preterm and term newborn infants from birth to less than 1 month;
- for film-coated tablets, for oral use, and for powder for oral solution, for 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	4	**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 4** Double-blind, randomised, controlled, parallel-group trial to evaluate the safety and efficacy of trametinib in children from 1 month to less than 18 years of age with solid malignant tumours with known or expected RAS, RAF or MEK pathway activation. **Study 5** Relative bioavailability study in adults. **Study 7** (New measure added during procedure EMEA-001177-PIP01-11-M04) Open-label single arm cohort to determine the safety and efficacy of dabrafenib with trametinib in children from 12 months to less than 18 years of age with BRAF V600 mutant relapsed or refractory High Grade Glioma (HGG)
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, nervous system, haematopoietic and lymphoid tissue)

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	3	**Study 3** Same as for condition treatment of melanoma. **Study 4** Same as for condition treatment of melanoma. **Study 5** Same as for condition treatment of melanoma. **Study 7** Same as for condition treatment of melanoma.
Extrapolation, modelling and simulation studies	1	**Study 6** Same as for condition treatment of melanoma.
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.

2. Treatment of all conditions included in the category of malignant neoplasms (except melanoma, nervous system, 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