EMA/65014/2015

European Medicines Agency decision

P/0045/2015

of 6 March 2015

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) phosphorodiamidate [TH-302] (EMEA-001483-PIP01-13) 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 application submitted by Merck KGaA on 10 June 2013 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 16 January 2015, in accordance with Article 18 of Regulation (EC) No 1901/2006, and Article 21 of said Regulation and Article 13 of said Regulation,

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 agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver.

(2) It is therefore appropriate to adopt a decision agreeing a paediatric investigation plan.

(3) It is therefore appropriate to adopt a decision granting a deferral.

(4) It is therefore appropriate to adopt a decision granting a 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

A paediatric investigation plan for (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) phosphorodiamidate [TH-302], concentrate for solution for infusion, intravenous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A deferral for (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) phosphorodiamidate [TH-302], concentrate for solution for infusion, intravenous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

A waiver for (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) phosphorodiamidate [TH-302], concentrate for solution for infusion, intravenous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 4

This decision is addressed to Merck KGaA, Frankfurter Straße 250, 64293 - Darmstadt, Germany.

Done at London, 6 March 2015

For the European Medicines Agency
Jordi Llinares Garcia
Head of Division (ad interim)
Human Medicines Research and Development Support
(Signature on file)

EMA/PDCO/694562/2014

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver

EMEA-001483-PIP01-13

Scope of the application

Active substance(s):

(1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) phosphorodiamidate [TH-302]

Condition(s):

Treatment of soft tissue sarcoma

Treatment of Ewing sarcoma

Pharmaceutical form(s):

Concentrate for solution for infusion

Route(s) of administration:

Intravenous use

Name/corporate name of the PIP applicant:

Merck KGaA

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Merck KGaA submitted for agreement to the European Medicines Agency on 10 June 2013 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 17 July 2013.

Supplementary information was provided by the applicant on 27 October 2014. The applicant proposed modifications to the paediatric investigation plan.

A meeting with the Paediatric Committee took place on 15 January 2015.

Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree the paediatric investigation plan in accordance with Article 18 of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation;
   - to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

   The Icelandic and the Norwegian Paediatric Committee members agree with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the agreed 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 annex and appendix.

London, 16 January 2015

On behalf of the Paediatric Committee
Dr Dirk Mentzer, Chairman
(Signature on file)

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 soft tissue sarcoma

The waiver applies to:

- the paediatric population from birth to less than 3 months;
- to concentrate for solution for infusion, intravenous use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

1.2. Condition

Treatment of Ewing sarcoma

The waiver applies to:

- the paediatric population from birth to less than 3 months;
- to concentrate for solution for infusion, intravenous use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

2. Paediatric investigation plan

2.1. Condition

Treatment of soft tissue sarcoma

2.1.1. Indication(s) targeted by the PIP

TH-302 is used for the treatment of paediatric patients (3 months to less than 18 years) in combination with chemotherapy for first-line treatment of metastatic or unresectable, high-risk rhabdomyosarcoma, or in combination with chemotherapy for treatment of primarily disseminated, bone-involving Ewing sarcoma

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

From 3 months to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Concentrate for solution for infusion

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable.
Non-clinical studies	1	**Study 1** Pharmacology in vivo study in paediatric solid malignant tumour models.
Clinical studies	2	**Study 2** Open-label, multiple dose trial to evaluate pharmacokinetics, safety, toxicity and activity of TH-302 in children from 1 year to less than 18 years with a solid malignant tumour, with extension cohorts evaluating TH-302 compared to ifosfamide and as add-on to anti-cancer medicines. **Study 3** Open-label, randomised, controlled trial to evaluate pharmacokinetics, safety, toxicity, activity and efficacy of TH-302 as add-on to chemotherapy in children from 3 months to less than 18 years of age with a rhabdomyosarcoma or in children from 3 months to less than 18 years of age (and adults) with an Ewing sarcoma.
Extrapolation, modelling and simulation studies	0	Not applicable.
Other studies	0	Not applicable.
Other measures	1	**Study 4** Comparative analysis of patterns of response, progression and relapse of solid malignant tumours in patients treated with ifosfamide or TH-302.

2.2. Condition

Treatment of Ewing sarcoma

2.2.1. Indication(s) targeted by the PIP

TH-302 is used for the treatment of paediatric patients (3 months to less than 18 years) in combination with chemotherapy for first-line treatment of metastatic or unresectable, high-risk rhabdomyosarcoma, or in combination with chemotherapy for treatment of primarily disseminated, bone-involving Ewing sarcoma

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

From 3 months to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Concentrate for solution for infusion

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable.
Non-clinical studies	1	**Study 1** As for condition "treatment of soft tissue sarcoma".
Clinical studies	2	**Study 2** As for condition "treatment of soft tissue sarcoma". **Study 3** As for condition "treatment of soft tissue sarcoma".
Extrapolation, modelling and simulation studies	0	Not applicable.
Other studies	0	Not applicable.
Other measures	1	**Study 4** As for condition "treatment of soft tissue sarcoma".

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 2026
Deferral for one or more measures contained in the paediatric investigation plan:	Yes