EMA/812163/2018

European Medicines Agency decision

P/0389/2018

of 7 December 2018

on the acceptance of a modification of an agreed paediatric investigation plan for lenvatinib (LENVIMA, Kisplyx) (EMEA-001119-PIP02-12-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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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/0125/2013 issued on 28 May 2013, the decision P/0040/2014 issued on 5 March 2014, the decision P/0282/2014 issued on 28 October 2014 and the decision P/0107/2017 issued on 11 April 2017,

Having regard to the application submitted by Eisai Europe Ltd on 10 July 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 19 October 2018, 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 envatinib (LENVIMA, Kisplyx), capsule, hard, 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 Eisai Europe Ltd, European Knowledge Centre, Mosquito Way, AL10 - 9SN Hatfield, Herts, United Kingdom.

EMA/PDCO/500063/2018
London, 18 October 2018

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

EMEA-001119-PIP02-12-M04

Scope of the application

Active substance(s):

Lenvatinib

Invented name:

LENVIMA

Kisplyx

Condition(s):

Treatment of papillary thyroid cancer

Treatment of follicular thyroid cancer

Treatment of osteosarcoma

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Capsule, hard

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Eisai Europe Ltd

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, Eisai Europe Ltd submitted to the European Medicines Agency on 10 July 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/0125/2013 issued on 28 May 2013, the decision P/0040/2014 issued on 5 March 2014, the decision P/0282/2014 issued on 28 October 2014 and the decision P/0107/2017 issued on 11 April 2017.

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

The procedure started on 21 August 2018.

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 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. Conditions

Treatment of follicular thyroid carcinoma, treatment of papillary thyroid carcinoma and treatment of osteosarcoma

The waiver applies to:

- the paediatric population from birth to less than 2 years;
- capsule, hard, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric Investigation Plan

2.1. Condition

Treatment of follicular thyroid carcinoma and treatment of papillary thyroid carcinoma

2.1.1. Indication(s) targeted by the PIP

Treatment of paediatric patients with ^{131}I-refractory follicular or papillary thyroid cancer

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

From 2 years to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Capsule, hard

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of an oral suspension prepared from the hard capsule
Non-clinical studies	2	**Study 2** Toxicity study in juvenile rats **Study 3** Toxicity study in juvenile rats

Clinical studies	1	**Study 5** Open-label, multi-centre, non-controlled trial to evaluate pharmacokinetics, pharmacodynamics, tolerability and safety of lenvatinib in children from 2 years to less than 18 years of age with a relapsed or refractory solid malignant tumour and, in patients with osteosarcoma, an extension phase to evaluate lenvatinib in combination with ifosfamide and etoposide
Extrapolation, modelling and simulation studies	1	**Study 7** (added in procedure EMEA-001119-PIP02-12-M04) Population PK analysis to establish the dose-response relationship of lenvatinib in paediatric patients with differentiated thyroid cancer (DTC) and to support extrapolation of efficacy from adult patients to paediatric patients with DTC

2.2. Condition

Treatment of osteosarcoma

2.2.1. Indication(s) targeted by the PIP

Treatment of paediatric patients with a first relapse of osteosarcoma

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

From 2 years to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Capsule, hard

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** As for conditions treatment of follicular thyroid carcinoma and treatment of papillary thyroid carcinoma
Non-clinical studies	3	**Study 2** As for conditions treatment of follicular thyroid carcinoma and treatment of papillary thyroid carcinoma

		Study 3 As for conditions treatment of follicular thyroid carcinoma and treatment of papillary thyroid carcinoma **Study 4** Pharmacology study of lenvatinib in combination with ifosfamide and etoposide in paediatric tumour models
Clinical studies	2	**Study 5** As for conditions treatment of follicular thyroid carcinoma and treatment of papillary thyroid carcinoma **Study 6** Multi-centre, randomized, controlled trial to evaluate the efficacy and safety of lenvatinib as add-on to ifosfamide and etoposide in children from 5 years to less than 18 years (and adults) with relapsed osteosarcoma

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 December 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 of papillary thyroid cancer
2. Treatment of follicular thyroid cancer

Authorised indication(s):

- LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

3. Treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney

- Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

4. Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)

- LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.

Authorised pharmaceutical form(s):

Hard capsule

Authorised route(s) of administration:

Oral use