EMA/275963/2019

European Medicines Agency decision

P/0209/2019

of 12 June 2019

on the acceptance of a modification of an agreed paediatric investigation plan for lenvatinib (LENVIMA, Kisplyx), (EMEA-001119-PIP02-12-M05) 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, the decision P/0107/2017 issued on 11 April 2017 and the decision P/0389/2018 issued on 7 December 2018,

Having regard to the application submitted by Eisai Europe Ltd on 9 January 2019 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 26 April 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.

(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 lenvatinib (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/115434/2019 Corr
Amsterdam, 26 April 2019

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

EMEA-001119-PIP02-12-M05

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

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 9 January 2019 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, the decision P/0107/2017 issued on 11 April 2017 and the decision P/0389/2018 issued on 7 December 2018.

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

The procedure started on 26 February 2019.

Scope of the modification

Some measures 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. Condition

Treatment of follicular thyroid cancer, treatment of papillary thyroid cancer 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 cancer and treatment of papillary thyroid cancer

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 cancer and treatment of papillary thyroid cancer
Non-clinical studies	3	**Study 2** As for conditions treatment of follicular thyroid cancer and treatment of papillary thyroid cancer **Study 3** As for conditions treatment of follicular thyroid cancer and treatment of papillary thyroid cancer **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 cancer and treatment of papillary thyroid cancer

		Study 6 (deleted in procedure EMEA-001119-PIP02-12-M05) **Study 8** (added in procedure EMEA-001119-PIP02-12-M05) 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 refractory or 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