EMA/107500/2018

European Medicines Agency decision

P/0098/2018

of 16 March 2018

on the acceptance of a modification of an agreed paediatric investigation plan for denosumab (Xgeva, Prolia), (EMEA-000145-PIP01-07-M09) 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/89/2008 issued on 14 October 2008, the decision P/148/2009 issued on 15 July 2009, the decision P/14/2010 issued on 4 February 2010, the decision P/158/2011 issued on 4 July 2011, the decision P/0007/2012 issued on 24 January 2012, the decision P/0211/2012 issued on 28 September 2012, the decision P/0252/2013 issued on 29 October 2013, the decision P/0006/2015 issued on 30 January 2015 and the decision P/0125/2016 issued on 20 May 2016,

Having regard to the application submitted by Amgen Europe B.V. on 6 November 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 26 January 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 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 denosumab (Xgeva, Prolia), solution for injection, subcutaneous 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 Amgen Europe B.V., Minervum 7061, 4817-ZK - Breda, The Netherlands.

EMA/PDCO/754346/2017
London, 26 January 2018

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

EMEA-000145-PIP01-07-M09

Scope of the application

Active substance(s):

Denosumab

Invented name:

Xgeva

Prolia

Condition(s):

Treatment of bone loss associated with sex hormone ablative therapy

Prevention of skeletal related events in patients with bone metastases

Treatment of giant cell tumour of bone

Treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis)

Treatment of hypercalcemia of malignancy

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Solution for injection

Route(s) of administration:

Subcutaneous use

Name/corporate name of the PIP applicant:

Amgen Europe B.V.

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, Amgen Europe B.V. submitted to the European Medicines Agency on 6 November 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/89/2008 issued on 14 October 2008, the decision P/148/2009 issued on 15 July 2009, the decision P/14/2010 issued on 4 February 2010, the decision P/158/2011 issued on 4 July 2011, the decision P/0007/2012 issued on 24 January 2012, the decision P/0211/2012 issued on 28 September 2012, the decision P/0252/2013 issued on 29 October 2013, the decision P/0006/2015 issued on 30 January 2015 and the decision P/0125/2016 issued on 20 May 2016.

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

The procedure started on 28 November 2017.

Scope of the modification

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.

   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 bone loss associated with sex hormone ablative therapy

The waiver applies to:

- children from birth to less than 18 years of age;
- for solution for injection, subcutaneous 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:

Prevention of skeletal related events in patients with bone metastases

The waiver applies to:

- children from birth to less than 18 years;
- for solution for injection, subcutaneous use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

1.3. Condition:

Treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis)

The waiver applies to:

- children from birth to less than 18 years of age;
- for solution for injection, subcutaneous use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

1.4. Condition:

Treatment of giant cell tumour of bone

The waiver applies to:

- children from birth to less than 12 years;
- for solution for injection, subcutaneous 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).

1.5. Condition:

Treatment of hypercalcemia of malignancy

The waiver applies to:

- children from birth to less than 18 years of age;
- for solution for injection, subcutaneous use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

2. Paediatric Investigation Plan

2.1. Condition:

Treatment of giant cell tumour of bone

2.1.1. Indication(s) targeted by the PIP

Treatment of giant cell tumour of bone in children

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

Adolescents from 12 to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Solution for injection

2.1.4. Measures

Area	Number of studies	Description
Quality-related studies	0	Not applicable
Non-clinical studies	4	**Study 1 (R20080340)** Evaluation of the effects of OPG-Fc, RANK-Fc or alendronate on tooth eruption and bone density, geometry, and strength in neonatal rats **Study 2 (R20090069)** Evaluation of long bone geometry in 1- and 2-month old transgenic rats overexpressing the soluble RANKL inhibitor OPG during growth and development **Study 3 (R20090070)** Evaluation of the effect of OPG-Fc or alendronate on tooth eruption and on bone density, geometry and strength in neonatal rats: A recovery study.

		Study 4 (R20090282) Evaluation of the dose-dependent effects of OPG-Fc on tooth eruption, bone growth and bone strengths in neonatal rats
Clinical studies	1	**Study 5-8** *(These studies were deleted from this PIP in modification procedures.)* **Study 9 (20062004), EudraCT No. 2008-001606-16** Open-label trial to evaluate safety of denosumab in skeletally mature adolescents (and adults) with giant cell tumour of bone.
Extrapolation, modelling and simulation studies	0	Not applicable.
Other studies	0	Not applicable.
Other measures	0	Not applicable.

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 May 2018
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of bone loss associated with sex hormone ablative therapy

   Authorised indication(s):

- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.

2. Prevention of skeletal related events in patients with bone metastases

   Authorised indication(s):

- Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

3. Treatment of giant cell tumour of bone

   Authorised indication(s):

- Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

4. Treatment of osteoporosis *(Condition covered by EMEA-000145-PIP02-12 and subsequent modifications thereof)*

   Authorised indication(s):

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Authorised pharmaceutical form(s):

Solution for injection

Authorised route(s) of administration:

Subcutaneous use