EMA/611454/2012

European Medicines Agency decision

P/0211/2012

of 28 September 2012

on the acceptance of a modification of an agreed paediatric investigation plan for denosumab (Xgeva (previously Amgiva), Prolia) (EMEA-000145-PIP01-07-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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on the acceptance of a modification of an agreed paediatric investigation plan for denosumab (Xgeva (previously Amgiva), Prolia) (EMEA-000145-PIP01-07-M05) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

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, and the decision P/0007/2012 issued on 24 January 2012,

Having regard to the application submitted by Amgen Europe B.V. on 25 May 2012 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 17 August 2012, 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 denosumab (Xgeva (previously Amgiva), Prolia), solution for injection, subcutaneous 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 Amgen Europe B.V., Minervum 7061,4817-ZK Breda - The Netherlands.

Done at London, 28 September 2012

For the European Medicines Agency
Guido Rasi
Executive Director
(Signature on file)

EMA/PDCO/356234/2012

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

EMEA-000145-PIP01-07-M05

Scope of the application

Active substance(s):

Denosumab

Invented name:

Xgeva (previously Amgiva)

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 rheumatoid arthritis

Treatment of juvenile idiopathic arthritis

Treatment of giant cell tumour of bone

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 25 May 2012 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 and the decision P/0007/2012 issued on 24 January 2012.

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

The procedure started on 19 June 2012.

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.

   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 annex(es) and appendix.

London, 17 August 2012

On behalf of the Paediatric Committee
Dr Daniel Brasseur, 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

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 for 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: Treatment of rheumatoid arthritis

The waiver applies to:

- children from birth to less than 18 years;
- for solution for injection for 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 juvenile idiopathic arthritis

The waiver applies to:

- children from birth to less than 4 years;
- for solution for injection for subcutaneous use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

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 for 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: 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 for subcutaneous use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

2. Paediatric Investigation Plan

2.1. Condition: Treatment of juvenile idiopathic arthritis

2.1.1. Indication(s) targeted by the PIP

Treatment of polyarticular juvenile idiopathic arthritis - inhibition of progression of structural damage in paediatric patients who are treated with concomitant disease modifying anti-rheumatic drugs.

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

Children from 4 to less than 18 years of age.

2.1.3. Pharmaceutical form(s)

Solution for injection

2.1.4. Studies

Area	Number of studies	Description
Quality	1	The applicant must assess the need for an adapted presentation of denosumab product for use in paediatric patients (e.g need for smaller vial, adapted syringe, dilutions etc)
Non-clinical	4	**Study 1:** The effects of OPG-Fc, RANK-Fc or alendronate on tooth eruption and bone density, geometry, and strength in neonatal rats **Study 2:** Long bone geometry in 1- and 2-month old transgenic rats overexpressing the soluble RANKL inhibitor OPG during growth and development **Study 3:** 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:** Evaluation of the dose-dependent effects of OPG-Fc on tooth eruption, bone growth and bone strengths in neonatal rats
Clinical	4	**Study 5:** Pharmacokinetic, pharmacodynamic and safety study in patients in children from 12 years to less than 18 years of age with polyarticular juvenile idiopathic arthritis

Area	Number of studies	Description
		Study 6: Pharmacokinetic, pharmacodynamic and safety study in children from 4 years to less than 12 years of age with polyarticular juvenile idiopathic arthritis **Study 7:** Randomised, placebo-controlled efficacy and safety study in patients from 12 to less than 18 years of age with polyarticular juvenile idiopathic arthritis (RF+), evaluating inhibition of progression of structural damage by denosumab in combination with disease modifying anti-rheumatic drugs (DMARDs) **Study 8:** Randomised, placebo-controlled efficacy and safety study in patients from 4 to less than 12 years of age with polyarticular juvenile idiopathic arthritis (RF+) evaluating inhibition of progression of structural damage by denosumab in combination with DMARDs

2.2. Condition: Treatment of giant cell tumour of bone

2.2.1. Indication(s) targeted by the PIP

Treatment of giant cell tumour of bone in children.

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

Adolescents from 12 to less than 18 years of age.

2.2.3. Pharmaceutical form(s)

Solution for injection.

2.2.4. Studies

Area	Number of studies	Description
Quality	0	N.A.
Non-clinical	4	**Study 1:** The effects of OPG-Fc, RANK-Fc or alendronate on tooth eruption and bone density, geometry, and strength in neonatal rats **Study 2:** Long bone geometry in 1- and 2-month old transgenic rats overexpressing the soluble RANKL inhibitor OPG during growth and development

Area	Number of studies	Description
		Study 3: 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:** Evaluation of the dose-dependent effects of OPG-Fc on tooth eruption, bone growth and bone strengths in neonatal rats
Clinical	1	**Study 9:** Open label safety study in patients from 12 to less than 18 years of age with giant cell tumour of bone (as part of the safety study in adults)

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 2034
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 osteoporosis in postmenopausal women at increased risk of fractures.

   Authorised indications:

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

2. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

   Authorised indications:

   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.

3. Prevention of skeletal related events in adults with bone metastases

   Authorised indications:

   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.

EU Number	**Invented name**	**Strength**	**Pharmaceutical form**	**Route of administration**	**Packaging**	**Content (concentration)**	**Package size**
EU/1/11/703/001	Xgeva	120 mg	Solution for injection	Subcutaneous use	vial (glass)	1.7 ml	1 vial
EU/1/11/703/002	Xgeva	120 mg	Solution for injection	Subcutaneous use	vial (glass)	1.7 ml	4 vials
EU/1/11/703/003	Xgeva	120 mg	Solution for injection	Subcutaneous use	vial (glass)	1.7 ml	3 vials
EU/1/10/618/001	Prolia	60 mg/ml	Solution for injection	Subcutaneous use	pre-filled syringe (glass)		1 pre-filled syringe (blistered)
EU/1/10/618/002	Prolia	60 mg/ml	Solution for injection	Subcutaneous use	pre-filled syringe (glass)		1 pre-filled syringe (unblistered)
EU/1/10/618/003	Prolia	60 mg/ml	Solution for injection	Subcutaneous use	pre-filled syringe (glass)		1 pre-filled syringe with automatic needle guard (blistered)
EU/1/10/618/004	Prolia	60 mg/ml	Solution for injection	Subcutaneous use	vial (glass)		1 vial