EMA/424850/2011

European Medicines Agency decision

P/158/2011

of 4 July 2011

on the acceptance of a modification of an agreed paediatric investigation plan for denosumab (XGEVA, previously Amgiva and Prolia) (EMEA-000145-PIP01-07-M03) 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 European Medicines Agency's decision P/89/2008 issued on 14 October 2008, the decision P/148/2009 issued on 15 July 2009, and the decision P/14/2010 issued on 4 February 2010,

Having regard to the application submitted by Amgen Europe B.V. on 7 March 2011 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 20 May 2011, 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 and 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, 4 July 2011

For the European Medicines Agency
Andreas Pott
Acting Executive Director
(Signature on file)

EMA/PDCO/326763/2011

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

EMEA-000145-PIP01-07-M03

Scope of the application

Active substance(s):

Denosumab

Invented name:

XGEVA (previously Amgiva)

Prolia

Condition(s):

Bone loss associated with sex hormone ablative therapy

Bone metastases

Rheumatoid arthritis

Juvenile idiopathic arthritis

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 7 March 2011 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 and the decision P/14/2010 issued on 4 February 2010.

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

The procedure started on 23 March 2011.

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

2. The measures and timelines of the paediatric investigation plan 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, 20 May 2011

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: 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: Rheumatoid arthritis

The waiver applies to:

- children from birth to less than 18 years;
- 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: Juvenile idiopathic arthritis

The waiver applies to:

- children from birth to less than 4 years;
- 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: 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).

2. Paediatric Investigation Plan

2.1. Condition: Bone metastases

2.1.1. Indication(s) targeted by the PIP

Prevention of skeletal-related events in paediatric patients with bone metastases.

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

All subsets of the paediatric population from birth 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) by the completion of the proposed dose range finding study (Study 7) in paediatrics
Non-clinical	6	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 Study 5: Effect of RANKL inhibition in in vivo bone metastasis models of human NB-19 paediatric neuroblastoma in mice Study 6: Effect of RANKL inhibition in in vivo bone metastasis models of human IMR-32 paediatric neuroblastoma in mice
Clinical	2	Study 7: Pharmacokinetic, pharmacodynamic and safety open label dose finding study in paediatric patients with solid tumours and bone metastases aged from birth to less than 18 years of age Study 8 Open-label, single arm, non-randomised, single dose efficacy and safety study in paediatric patients with solid tumours and bone metastases aged from birth to less than 18 years of age

2.2. Condition: Juvenile idiopathic arthritis

2.2.1. 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

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

Children from 4 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	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) by the completion of the proposed dose range finding study (Study 7) in paediatrics
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 9: Pharmacokinetic, pharmacodynamic and safety study in patients in children from 12 years to less than 18 years of age with polyarticular juvenile idiopathic arthritis Study 10: Pharmacokinetic, pharmacodynamic and safety study in children from 4 years to less than 12 years of age with polyarticular juvenile idiopathic arthritis

Area	Number of studies	Description
		Study 11: 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 12: 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

2.3. Condition: Giant cell tumour of bone

2.3.1. Indication(s) targeted by the PIP

Treatment of giant cell tumour of bone in children.

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

Adolescents from 12 to less than 18 years of age.

2.3.3. Pharmaceutical form(s)

Solution for injection.

2.3.4. 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) by the completion of the proposed dose range finding study (Study 7) in paediatrics
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:

Area	Number of studies	Description
		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 13: 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

Measures to address long term follow-up of potential 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.

EMEA Number	**(Invented) name**	**Strength**	**Pharma-ceutical Form**	**Route of Administration**	**Packa-ging**	**Content (concen-tration)**	**Package size**
EMEA/H/C/002173/0000/001	XGEVA	120 mg	Solution for injection	Subcutaneous use	vial (glass)	1.7 ml	1 vial
EMEA/H/C/002173/0000/002	XGEVA	120 mg	Solution for injection	Subcutaneous use	vial (glass)	1.7 ml	4 vials

EU Number	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of Administration**	**Packaging**	**Package size**
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