European Medicines Agency

Doc. Ref. EMA/59551/2010
P/14/2010

EUROPEAN MEDICINES AGENCY DECISION

of 4 February 2010

on the acceptance of a modification of an agreed Paediatric Investigation Plan for denosumab (EMEA-000145-PIP01-07-M02) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended

(ONLY THE ENGLISH TEXT IS AUTHENTIC)

DISCLAIMER: This Decision does not entitle to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006, as amended.

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THE EUROPEAN MEDICINES AGENCY,

Having regard to the Treaty establishing the European Community,

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 as amended 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 decision P/148/2009 of the European Medicines Agency on 15 July 2009,

Having regard to the application submitted by Amgen Europe B.V. on 9 November 2009 under Article 22 of Regulation (EC) No 1901/2006 as amended proposing changes the to agreed Paediatric Investigation Plan,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 15 January 2010, in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended,

Having regard to Article 25 of Regulation (EC) No 1901/2006 as amended,

WHEREAS:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the acceptance of changes to an agreed Paediatric Investigation Plan,

(2) It is therefore appropriate to adopt a Decision on the acceptance of changes to an 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, solution for injection, subcutaneous use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, are hereby accepted.

Article 2

This decision, that supersedes previous decision of the European Medicines Agency P/148/2009, as far as the agreed changes to the Paediatric Investigation Plan for denosumab are concerned, is addressed to Amgen Europe B.V., Minervum 7061, 4817-ZK Breda, Netherlands.

Done at London, 4 February 2010

For the European Medicines Agency
Thomas Lönngren
Executive Director

(Signature on file)

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc. Ref. EMA/PDCO/7039/2010
EMEA-000145-PIP01-07-M02

OPINION OF THE PAEDIATRIC COMMITTEE ON THE ACCEPTANCE OF A MODIFICATION OF AN AGREED PAEDIATRIC INVESTIGATION PLAN

Scope of the application

Active substance(s):
Denosumab

Condition(s):
Bone loss associated with sex hormone ablative therapy
Bone metastases
Rheumatoid arthritis
Juvenile idiopathic arthritis
Giant cell tumour of bone

Pharmaceutical form(s):
Solution for injection

Route(s) of administration:
Subcutaneous use

Name/corporate name of the PIP applicant:
Amgen Europe B.V.

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Amgen Europe B.V. submitted to the Agency on 9 November 2009 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the Agency's decision P/148/2009 of 15 July 2009. The application for modification proposed changes.

The procedure started on 19 November 2009.

Scope of the modification

Some measures and/or timelines of the original Opinion have been modified. A new non clinical study was included. Two conditions were merged into one.

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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 the changes proposed by the applicant regarding the measures and the timelines of the paediatric investigation plan

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 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 Agency, together with its annex(es) and appendix.

London, 15 January 2010

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature on file)

ANNEX I

THE MEASURES AND TIMELINES OF THE AGREED PAEDIATRIC INVESTIGATION PLAN AND THE SUBSET(S) OF THE PAEDIATRIC POPULATION AND CONDITION(S) COVERED BY THE WAIVER

A. CONDITION(S) / DISEASE(S)

- Bone loss associated with sex hormone ablative therapy
- Bone metastases
- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Giant cell tumour of bone

B. WAIVER

- **Conditions**

  - Bone loss associated with sex hormone ablative therapy
  - Rheumatoid arthritis

  The waiver applies to:

  – Children from birth to less than 18 years;
  – for denosumab solution for injection for subcutaneous use;
  – on the grounds that the diseases or conditions for which the specific medicinal product is intended do not occur in the specified paediatric subset(s).

- **Condition**

  - Bone metastases

  Indication: Prevention of bone metastases in hormone-refractory prostate cancer.

  The waiver applies to:

  – Children from birth to less than 18 years;
  – for denosumab solution for injection for subcutaneous use;
  – on the grounds that the indication for which the specific medicinal product is intended does not occur in the specified paediatric subset(s)

- **Condition**

  - Juvenile idiopathic arthritis

  The waiver applies to:

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

- **Condition**

  - Giant cell tumour of bone

  The waiver applies to:

  – children from birth to less than 12 years);
  – for denosumab 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).

C. PAEDIATRIC INVESTIGATION PLAN

- **Condition to be investigated**

Bone metastases (condition 1)

- **Proposed PIP indication**

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

- **Subset(s) covered**

All subsets of the paediatric population

- **Condition to be investigated**

Juvenile idiopathic arthritis (condition 2)

- **Proposed PIP indication**

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

- **Subset(s) covered**

Children from 4 years of age to less than 18 years of age

- **Condition to be investigated**

Giant cell tumour of bone (condition 3)

- **Proposed PIP indication**

Treatment of giant cell tumour of bone in children

- **Subset(s) covered**

Adolescents (from 12 to less than 18 years of age)

- **Formulation(s)**

Denosumab 60mg/ml or 70mg/ml solution for injection for subcutaneous use

- **Studies / Measures**

Area	Number	Description
Non-clinical	6	**Related to conditions 1-2 and 3** **Non clinical study 1:** The effects of OPG-Fc, RANK-Fc or alendronate on tooth eruption and bone density, geometry, and strength in neonatal rats **Non clinical study 2:** Long bone geometry in 1- and 2-month old transgenic rats overexpressing the soluble RANKL inhibitor OPG during growth and development **Non clinical 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. **Non clinical study 4:** Evaluation of the dose-dependent effects of OPG-Fc on tooth eruption, bone growth and bone strengths in neonatal rats **Related to condition 1 only** **Non clinical study 5:** Effect of RANKL inhibition in *in vivo* bone metastasis models of human NB-19 paediatric neuroblastoma in mice **Non clinical study 6:** Effect of RANKL inhibition in *in vivo* bone metastasis models of human IMR-32 paediatric neuroblastoma in mice
Clinical	7	**Related to Condition 1:** **Clinical study 1:** 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 **Clinical study 2:** Open-label, single arm, non-randomised, single dose efficacy and safety study in paediatric patients with solid tumours and bone metastases aged from 0 to less than 18 years of age **Related to Condition 2:** **Clinical study 3:** Pharmacokinetic, pharmacodynamic and safety study in patients in children from 12 years to less than 18 years of age with polyarticular juvenile idiopathic arthritis **Clinical study 4:** Pharmacokinetic, pharmacodynamic and safety study in children from 4 years to less than 12 years of age with polyarticular juvenile idiopathic arthritis **Clinical study 5:** 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) **Clinical study 6:** 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 **Related to Condition 3** **Clinical study 7:** 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)

Measures to address long term follow-up of potential safety issues in relation to paediatric us:	**Yes**
Date of completion of the paediatric investigation plan:	**By December 2034**
Deferral for some or all studies contained in the paediatric investigation plan:	**Yes**