HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

11 April 2012

XGEVA 120 mg, solution for injection
1 glass vial of 120 mg/1.7 ml (CIP code: 217 253-8)
4 glass vials of 120 mg/1.7 ml (CIP code: 580 874-1)

Applicant: AMGEN SAS

Denosumab

List I
Prescription restricted to ONCOLOGY specialists and departments
Prescription restricted to MEDICAL ONCOLOGY specialists and departments
Prescription restricted to RHEUMATOLOGY specialists and departments

ATC code: M05BX04 (other medicinal products acting on mineralisation)

Date of Marketing Authorisation (centralised procedure): 13th July 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Denosumab

1.2. Background

Denosumab is human monoclonal IgG2 antibody which targets the RANK/RANKL system. It inhibits the formation, function and survival of osteoclasts thus reducing the osseous resorption in the cortical and trabecular bone.
This is a new therapeutic class to prevent skeletal related events caused by bone metastases.

1.3. Indication

"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."

1.4. Dosage

"The recommended dose of XGEVA is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm.
Supplementation of at least 500 mg calcium and 400 IU vitamin D is required in all patients, unless hypercalcaemia is present.

Patients with renal impairment
No dose adjustment is required in patients with renal impairment. Experience in patients on dialysis or with severe renal impairment (creatinine clearance < 30 ml/min) is limited.

Patients with hepatic impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment.

Elderly patients (age ≥ 65)
No dose adjustment is required in elderly patients.

Paediatric population
XGEVA is not recommended in paediatric patients (age < 18) as the safety and efficacy of XGEVA in these patients have not been established. Inhibition of RANK/RANK-ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption. These changes were partially reversible upon cessation of RANKL inhibition.

<u>Method of administration</u>
For subcutaneous use.
XGEVA should be administered under the responsibility of a healthcare professional."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

M : Musculoskeletal system
M05 : Medicinal products for treatment of bone diseases
M05B : Medicinal products affecting bone structure and mineralisation
M05BX : Other medicinal products affecting bone structure and mineralisation
M05BAX04 : Denosumab

2.2. Medicines in the same therapeutic category

There are no other drugs in the same class (monoclonal antibodies) with the same indication.

2.3. Medicines with a similar therapeutic aim

These are bisphosphonates which have an indication in the prevention of skeletal-related events caused by bone metastases.

Proprietary medicinal product	INN	Indications	AB / IAB
ZOMETA 4 mg/5 ml concentrate for solution for infusion	Zoledronic acid	Prevention of skeletal-related events (pathological fractures, spinal compression, radiation or bone surgery, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone. Treatment of adult patients with tumour-induced hypercalcaemia (TIH).	Substantial AB / IAB III in terms of efficacy in the management of bone metastases from prostate cancer in relation to normal practice.
PAMIDRONATE DISODIUM ACTAVIS and HOSPIRA, **3 mg/ml – 6 mg/ml – 9 mg/ml** concentrate for solution for infusion	Pamidronate disodium	The treatment of tumour-induced hypercalcaemia. The prevention of skeletal-related events (pathological fractures, spinal compression, radiation or bone surgery, hypercalcaemia) in patients with breast cancer with bone metastases, or multiple myeloma with bone lesions, in addition to specific treatment of the tumour	Substantial AB / IAB V in relation to Aredia
BONDRONAT 2 mg – 6mg concentrate for solution for infusion	Ibandronic acid	Prevention of skeletal-related events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.	Substantial AB / IAB V in relation to Zometa

3 ANALYSIS OF AVAILABLE DATA

The therapeutic benefit of denosumab in the prevention of skeletal-related events associated with the presence of metastases in adult patients was evaluated in three phase III studies:

- Study 20050136 performed in patients with breast cancer and bone metastases,
- Study 20050103 performed in patients with prostate cancer and bone metastases,
- Study 20050244 performed in patients with solid tumours and bone metastases (apart from breast or prostate cancer) or multiple myeloma with bone involvement.

The experimental design of the three studies was similar. They were randomised, double blind versus zoledronic acid studies.
The patients received one of the two following treatments:

- Denosumab 120 mg SC and placebo IV every 4 weeks
- Zoledronic acid 4mg IV and placebo SC every 4 weeks

The dosage of zoledronic acid was adjusted if creatinine clearance was ≤ 60 ml/min and was stopped in the case of renal function deterioration.
Supplementation of calcium ≥ 500 mg and vitamin D ≥ 400 IU was recommended in all patients, unless hypercalcaemia was present

A pooled analysis under the protocol of these three studies comparing denosumab with zoledronic acid was provided.

Methodology
Non-inferiority was established if the observed hazard-ratio was ≤ 0.90 in order to maintain at least 50% of the clinical benefit of zoledronic acid compared with a placebo, estimated from previous studies. Once the non-inferiority was established, a superiority test was planned. The duration of double blind treatment was determined by the occurrence of the first skeletal-related event in 745 patients to ensure statistical power of 97%.

Primary efficacy endpoint: occurrence of the first skeletal-related event, composite endpoint consisting of:

- pathological fractures,
- spinal compression,
- bone radiotherapy,
- bone surgery.

Principal secondary efficacy endpoint: the occurrence of the first and subsequent skeletal-related events (multiple events).

3.1. Efficacy

3.1.1. Study 20050136: in advanced breast cancer with bone metastases[1]

Main inclusion criteria

- patients with histologically or cytologically confirmed breast cancer
- presence of at least one radiologically confirmed bone metastasis
- ECOG status (performance index) ≤ 2
- creatinine clearance ≥ 30 ml/min

Main exclusion criteria:

- on-going or previous treatment with IV or oral bisphosphonate with an indication in bone metastases
- life expectancy < 6 months
- presence or history of osteonecrosis or osteomyelitis of the jaw
- dental or oral surgery which is non-healed or required

Patient characteristics

Amongst the patients included in this study, 1026 were randomised in the denosumab group and 1020 in the zoledronic acid group.

The characteristics of the patients were comparable on inclusion. The median age was 57.0 years in the denosumab group vs. 56.0 years in the zoledronic acid group. The median time between initial diagnosis of the cancer and diagnosis of the first bone metastasis was 32.8 months vs. 35.4 months. Visceral metastases were present in 552 (54%) vs. 525 (51%) patients. Before randomisation, 81% of patients were treated with chemotherapy and three or more metastatic bone lesions were observed in 24% of patients in each of the two groups. The percentage of patients with a skeletal-related event due to bone metastasis (fracture, spinal compression, bone surgery or radiotherapy) before inclusion in the study was similar between the two groups (37%).

Results

The study was performed over 34 months to achieve the required number of events. Adjustment of the initial dose was required in 131 (12.9%) patients treated with zoledronic acid and administration of at least one dose of zoledronic acid had to be suspended in 56 patients (5.5%) due to renal insufficiency.

Denosumab was not inferior to zoledronic acid in preventing the first skeletal-related event (HR: 0.82 [0.71; 0.95]. The superiority of denosumab in comparison to zoledronic acid in this criterion was demonstrated. The median time to onset of the first skeletal-related event was 26.4 months with zoledronic acid and not achieved with denosumab. A “first skeletal-related event” was observed in 315/1026 patients (30.7%) in the denosumab group vs. 372/1020 patients (36.5%) in the zoledronic acid which is an absolute reduction of 5.8% over a 34-month follow-up period. The risk of developing “first and subsequent skeletal-related events” was lower in the denosumab group than in the zoledronic acid group (HR: 0.77 [0.66-0.89]) (table 1). In total 474 skeletal-related events were reported in the denosumab group and 608 in the zoledronic acid.

The overall survival (HR: 0.95 [0.81-1.11]) and the time to disease progression (HR: 1.00 [0.89-1.11]) were similar in the two groups.

[1] Stopeck AT et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010 10; 28: 5132-9.

Table 1: Results on the efficacy criteria (ITT population)

Criteria	Denosumab *vs.* Zoledronic acid	p
Primary efficacy endpoint		
Hazard Ratio of the first skeletal-related event (non-inferiority test)	0.82 [0.71; 0.95]	<0.0001
Secondary endpoints		
Hazard Ratio of the first skeletal-related event (superiority test)	0.82 [0.71; 0.95]	0.01
Hazard Ratio of the first and subsequent skeletal-related events (superiority test)	0.77 [0.66-0.89]	0.0006

3.1.2. Study 20050103: in castrate-resistant prostate cancer with bone metastases[2]

Main inclusion criteria

- histologically confirmed hormone-resistant prostate cancer
- presence or history of at least one radiologically confirmed bone metastasis
- ECOG status ≤ 2
- creatinine clearance ≥ 30 ml/min

Main exclusion criteria:

- on-going or previous treatment with IV or oral bisphosphonate with an indication in bone metastases
- bone radiotherapy or surgery planned
- presence or history of osteonecrosis or osteomyelitis of the jaw
- life expectancy ≤ 6 months
- dental or oral surgery which is non-healed
- dental procedure scheduled

Patient characteristics

Amongst the patients included in this study, 950 were randomised in the denosumab group and 951 in the zoledronic acid group. The characteristics of the patients were comparable on inclusion. Median age was 71 years in both groups. The median time between initial diagnosis of the cancer and diagnosis of the first bone metastasis was similar in both groups (24.5 months). Gleason score was greater than 8 in 394 (41.5%) patients in the denosumab group vs. 408 (42.9%) patients in the zoledronic acid group. Visceral metastases were present in 161 (17%) vs. 181 (19%) patients. Three or more metastatic bone lesions were identified in 318 (33.5%) patients in the denosumab group vs. 328 (34.5%) patients in the zoledronic group. The percentage of patients having already had a skeletal related event due to bone metastasis (fracture, spinal compression, bone surgery or radiotherapy) before inclusion in the study was similar between the two groups (24%).

[2] Fizazi K et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377: 813-22.

Results

The study was performed over 41 months to achieve the required number of events. In the zoledronic acid group, a dosage adjustment due to altered renal function at inclusion was performed in 213 (22%) patients. In 143 (15%) patients in the group treated with zoledronic acid, infusions were not performed due to elevated plasma creatinine.

Denosumab was not inferior to zoledronic acid in preventing the first skeletal-related event (HR: 0.82 [0.71; 0.95]. The superiority of denosumab in comparison to zoledronic acid in this criterion was demonstrated. The median time of onset of the first skeletal related event was 20.7 months with denosumab vs. 17.1 months with zoledronic acid. A "first skeletal-related event" was observed in 341/950 patients (35.9%) in the denosumab group vs. 386/951 patients (40.6%) in the zoledronic acid which is an absolute reduction of 4.7% over a 41-month follow-up period. The risk of developing "first and subsequent skeletal-related events" was lower in the denosumab group than in the zoledronic acid group (HR: 0.82 [0.71-0.94]) (table 2). In total 494 skeletal-related events were reported in the denosumab group and 584 in the zoledronic acid group.
The overall survival (HR: 1.03 [0.91-1.17]) and the time to disease progression (HR: 1.06 [0.95-1.18]) were similar in the two groups.

Table 2: Results on the efficacy criteria (ITT population)

Criteria	Denosumab *vs.* Zoledronic acid	p
Primary efficacy endpoint		
Hazard Ratio of the first skeletal-related event (non-inferiority test)	0.82 [0.71; 0.95]	0.0002
Secondary endpoints		
Hazard Ratio of the first skeletal-related event (superiority test)	0.82 [0.71; 0.95]	0.008
Hazard Ratio of the first and subsequent skeletal-related events (superiority test)	0.82 [0.71-0.94]	0,004

3.1.3. Study 20050244: in advanced solid tumours (apart from breast or prostate cancer) or multiple myeloma with bone metastases.[3]

Main inclusion criteria

- adult patients with histologically or cytologically confirmed cancer including solid tumours, multiple myelomas and lymphomas.
- presence or history of at least one bone metastasis
- ECOG status less than or equal to 2
- creatinine clearance ≥ 30 ml/min

[3] Henry DH et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011 Mar 20; 29 (9): 1125-32.

Main exclusion criteria:

- on-going or previous treatment with IV or oral bisphosphonate with an indication in the treatment of bone metastases
- cerebral metastases
- bone radiotherapy or surgery planned
- life expectancy < 6 months
- presence or history of osteonecrosis or osteomyelitis of the jaw

Patient characteristics

Amongst the patients included in this study, 886 were randomised in the denosumab group and 890 in the zoledronic acid group. The characteristics of the patients were comparable on inclusion. The proportion of men was 588/886 (66%) in the denosumab group vs. 552/890 (62%) in the zoledronic acid group. The median age was 60 years vs. 61 years. The primary cancer was non-small cell lung cancer in 350 (39%) patients in the denosumab group vs. 352 (40%) patients in the zoledronic acid group, and multiple myeloma in 87 (10%) vs. 93 (10%) patients. The median time between initial diagnosis of cancer and diagnosis of the first bone metastasis was 2.1 months in the denosumab group vs. 2.9 months in the zoledronic acid group. Chemotherapy had been performed in 84% of patients, a similar level in both groups. Visceral metastases were present in 474 (54%) vs. 448 (50%) patients. Three or more metastatic bone lesions were identified in 137 (15.5%) vs. 144 (16.2%) patients. The proportion of patients having experienced a skeletal related event due to bone metastasis (fracture, spinal compression, bone surgery or radiotherapy) before inclusion in the study was similar between the two groups (50%).

Results

The study was performed over 34 months to achieve the required number of events. In the zoledronic acid group, a dosage adjustment due to altered renal function at inclusion was performed in 152 (17.3%) patients. In 78 (8.9%) patients in the group treated with zoledronic acid, infusions were not performed due to elevated plasma creatinine.

Denosumab was not inferior to zoledronic acid in preventing the first skeletal related event without superiority being demonstrated: HR was 0.84 [0.72; 1.00] (p=0.0011) in the per protocol population (PP) and 0.84 [0.71; 0.98] (p=0.0007) in the ITT population. The median time of onset of the first skeletal related event was 20.6 months with denosumab vs. 16.3 months with zoledronic acid. A "first skeletal-related event" was observed in 278/886 patients (31.4%) in the denosumab group vs. 323/890 patients (36.3%) in the zoledronic acid group. The risk of developing "first and subsequent skeletal-related events" was similar in both groups (HR: 0.90 [0.77-1.04]). In total 392 skeletal-related events were reported in the denosumab group and 436 in the zoledronic acid. The overall survival (HR: 0.95 [0.83-1.08]) and the time to disease progression (HR: 1.00 [0.89-1.12]) were similar in the two groups.

A post-hoc analysis suggested increased mortality in patients with a multiple myeloma treated with denosumab (23/87) in relation with zoledronic acid (13/93).[4]

3.1.4. Pooled analysis of the three phase III studies

Grouping of the efficacy data in 5723 patients from the three phase III studies was performed: 2862 in the denosumab group and 2861 in the zoledronic acid group. No treatment-efficacy interaction/study on the time until a first skeletal-related event and the time to onset of the first and subsequent skeletal-related events was demonstrated.

In conclusion, denosumab was superior to zoledronic acid in delaying the onset of the first skeletal related event (HR: 0.83 [0.76 – 0.90]). The median time of onset of the first skeletal related event was 27.7 months in the denosumab group vs. 19.4 months in the zoledronic acid group. The risk of developing "first and subsequent skeletal-related events" was lower in the denosumab group than in the zoledronic acid group (HR: 0.82 [0.75-0.89]).

[4] The prevention of skeletal-related events in patients suffering from multiple myeloma is not a therapeutic indication of XGEVA according to the wording of the European MA.

Denosumab was more effective than zoledronic acid in preventing the risk of pathological fracture and use of bone radiotherapy. The risks of spinal compression and bone surgery, which are less common events, were not significantly different between the two groups (figure 1).
[*Left column : Type of skeletal related event, Pathological fracture, Bone radiotherapy, Spinal compression, Bone surgery, Any type of skeletal related event.*
Hazard ratio = Hazard ratio
3rd column: Zoledronic acid
4th column: Denosumab
Bottom: Hazard ratio, in favour of denosumab, in favour of zoledronic acid]

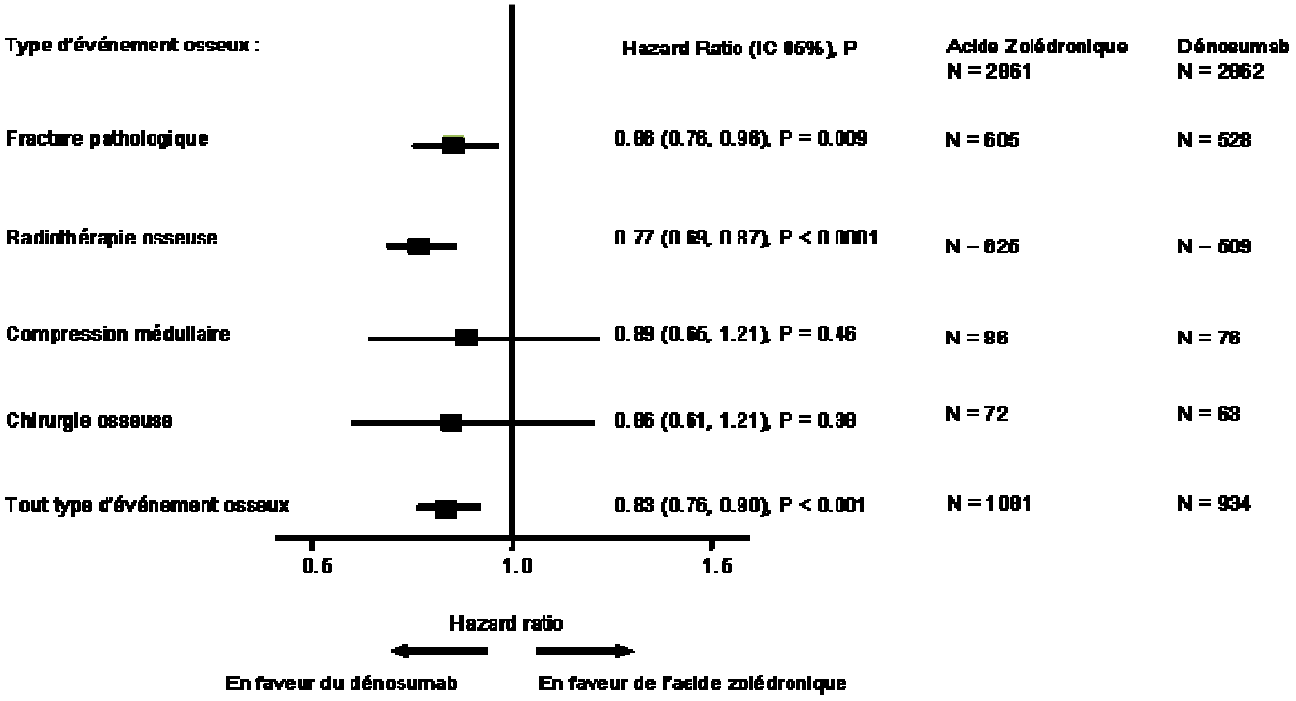

Figure 1: Specific effects of denosumab vs. zoledronic acid on each of the risks included in the "skeletal related event" criterion.

The Transparency Committee highlighted that performing a pooled analysis of the data verifies the homogeneity of the level of effect of denosumab between the three trials, verifies the homogeneity of the effect of denosumab on the different events which make up the primary efficacy endpoint and estimates the level of effect on the population of the three trials.
However, the Committee highlights the fact that three independent trials were performed. Three distinct hypothetical-deductive steps were followed to test the refutation of the three distinct hypotheses. Only two studies demonstrated the superiority of denosumab in comparison to zoledronic acid. A study of pooled data using a frequentist approach cannot conclude on the superiority of denosumab compared to zoledronic acid in each of the studied populations, particularly in the study 20050244 population where only the non-inferiority was demonstrated.

3.2. Adverse effects

3.2.1. Data from the phase III clinical studies

As part of the 3 phase III studies, 2841 patients were given denosumab as a supportive treatment of a tumour condition and 2836 patients were given zoledronic acid. Exposure to denosumab exceeded 2 years in 540 patients (19%), very rarely 3 years (0.4%).

The number of patients having had an adverse event considered to be linked to the use of the medicinal product was 827 (29.1%) in the denosumab group vs. 940 (33.1%) in the zoledronic acid group. These adverse effects were serious in 147 (5.2%) patients in the denosumab group vs. 108 (3.8%) patients in the zoledronic acid group. They resulted in death in 16 (0.6%) patients having received denosumab vs. 10 (0.4%) patients having received zoledronic acid. Discontinuation of treatment was motivated by an adverse event in 12.4% of patients in the denosumab group vs. 13.1% of patients in the zoledronic acid group.

Hypocalcaemia (9.6% versus 5.0%) and dyspnoea (20.6% versus 17.9%) were more often reported with denosumab than with zoledronic acid. In contrast, there was less fever (14.4% versus 19.8%), anaemia (27.1% versus 30.3%), bone pains (19.9% versus 22.5%), constipation (27.1% versus 30.3%), joint pains (20.1% versus 22.3%) and shivering (1.9% versus 4.1%) in the denosumab group than in the zoledronic acid group.

Osteonecrosis of the jaw: the patients at high risk of developing this complication were not included in these phase III studies. The incidence of osteonecrosis of the jaw was 52/2841 (1.8%) in patients treated with denosumab and 37/2836 (1.3%) in those treated with zoledronic acid. This difference was not statistically significant. The incidence of severe cases of grade ≥ 3 was similar at 0.4% in each arm.

Table 13: Incidence of osteonecrosis of the jaw

	Denosumab	Zoledronic acid
Study 20050136 (breast cancer)	20/1020 (2.0%)	14/1013 (1.4%)
Study 20050103 (prostate cancer)	22/943 (2.3%)	12/945 (0.8%)
Study 20050244 (other tumours and multiple myelomas)	10/878 (1.1%)	11/878 (1.3%)
Analysis of pooled data	52/2841 (1.8%)	37/2836 (1.3%)

Infections: the incidences in both groups were similar apart from staphylococcal infections which were more common with denosumab than with zoledronic acid (0.5% vs. 0.2%).

Renal toxicity: there were less renal adverse events with denosumab than with zoledronic acid.
In patients with a creatinine clearance > 60 ml/min, 7.6% of patients had a nephrotoxicity event vs. 9.0% with zoledronic acid. The proportions of renal impairment occurring on treatment were 2.1% vs. 2.7%.
In patients with a creatinine clearance ≤ 60 ml/min, 16.9% of patients experienced a nephrotoxicity event with denosumab vs. 24.7% with zoledronic acid. The proportions of renal impairment occurring on treatment were 5.2% vs. 8.1%.
Severe renal impairment defined by a creatinine clearance ≤ 30 ml/min was a non-inclusion criterion in the three phase III studies in order to meet the ambivalence clause.[5] The tolerance data on denosumab in this population is limited.

3.2.2. Risk management plan

The European risk management plan, in addition to routine pharmacovigilance, is planning the implementation of a specific questionnaire for the identified risks which are hypocalcaemia, osteonecrosis of the jaw and infections. In addition, post-marketing registry of osteonecrosis of the jaw is planned in the USA, Scandinavia (study 20101363) and in several European countries including France (study 20101102). Finally, screening for anti-denosumab antibodies will be available to physicians who request it.

[5] The use of zoledronic acid is not recommended in patients with severe renal impairment.

3.3. Conclusion

Denosumab was evaluated in three randomised, phase III studies performed double blind vs. zoledronic acid in breast cancer, prostate cancer and multiple myeloma or other solid tumours respectively. The primary efficacy endpoint “skeletal-related event” is a composite criterion including “the occurrence of a pathological fracture, spinal compression or requirement of bone surgery or radiotherapy". Non-inferiority must firstly be established then in the case of non-inferiority of denosumab in comparison to zoledronic acid, the superiority was tested.

To be included in the three studies, the patients had to have at least one bone metastasis. The non-inclusion criteria were mainly linked to the safety of use of treatments (oral or dental disease and renal function). The patients had to have a life expectancy of > 6 months and a performance index < 3.

In the study of 2046 patients with breast cancer over 34 months, denosumab was superior to zoledronic acid in preventing the first skeletal-related event (HR 0.82 [0.71-0.95]). The median time of onset of the first skeletal related event was 26.4 months in the zoledronic acid group and was not achieved in the denosumab group.

In the study of 1901 patients with prostate cancer, denosumab was superior to zoledronic acid in preventing the first skeletal-related event (HR 0.82 [0.71-0.95]). The median time to onset of the first skeletal-related event was 17.1 months in the zoledronic acid group and 20.7 months in the denosumab group.

In the study on 1776 patients with a solid tumour other than mammary or prostatic or having a multiple myeloma, denosumab was not inferior to zoledronic acid in preventing the first skeletal-related event (HR 0.84 [0.71-0.98]). The median time to onset of a skeletal-related event was 16.3 months in the zoledronic acid group and 20.6 months in the denosumab group.

In these three studies, the overall survival and duration of disease progression were similar between the denosumab group and zoledronic acid. A post-hoc analysis suggested increased mortality in patients with a multiple myeloma treated with denosumab (23/87) in relation with zoledronic acid (13/93). Consequently, the prevention of skeletal-related events in patients suffering from a multiple myeloma is not part of the therapeutic indication of the proprietary medicinal product.

Adverse events were reported in 29.1% of patients in the denosumab group and 33.1% in the zoledronic acid group. They led to discontinuation of the medicinal product in 12.4% and 13.1% of the patients respectively. The adverse events more commonly reported with denosumab than with zoledronic acid are: hypocalcaemia, dyspnoea, osteonecrosis of the jaw, and hypersensitivity reaction.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Skeletal related events (pathological fracture, bone radiotherapy, spinal compression or bone surgery) in patients with solid tumours with bone metastases are common, particularly in the advanced stages of breast and prostate cancer. These complications can severely affect the patients' quality of life. They can be life-threatening, in particular spinal compressions. The bone radiotherapy and surgery can be associated with an increased risk of morbidity and mortality.

XGEVA is a treatment for the prevention of skeletal related events in patients with a solid tumour and bone metastases.

The efficacy/adverse effects ratio is high.

This is a first-line treatment.

> Public health benefit
> The public health burden of patients included in this indication (patients suffering from solid tumours with bone metastases) can be considered as substantial.
> In these patients, delaying the complications linked to the presence of bone metastases and reducing the pain linked to osteolysis is a public health requirement within the framework of the established priorities (Public Health Law,[6] Cancer Plan 2009-2013).
> In light of the data from the clinical trials, it is anticipated that XGEVA proprietary medicinal product will have a low impact in terms of morbidity in comparison to existing treatments, in particular ZOMETA.
> XGEVA proprietary medicinal product should therefore be able to provide an additional response to the identified public health need.
> Consequently, there is a public health benefit for this proprietary medicinal product in this indication. This benefit is low.

Alternative medicinal products exist.

The actual benefit of XGEVA is substantial.

4.2. Improvement in actual benefit

XGEVA provides a minor improvement in actual benefit (level IV) in comparison to zoledronic acid, in terms of efficacy on the skeletal-related events from the metastases in patients with breast cancer or prostate cancer with bone metastases.
XGEVA does not provide an improvement in actual benefit (level V) in comparison to zoledronic acid in the prevention of skeletal-related events in patients with other types of solid tumours with bone metastases.

[6] Public Health Law 2004: Law No. 2004-806 of 9 August 2004 on public health policy: *objective 49 [rapport_DREES_indicateurs - July 2005]*

4.3. Therapeutic use

Reference therapeutic strategy:

Management of bone metastases is based on specific treatments for the primary tumour (cytotoxic, targeted treatments), local treatments with surgery and/or radiotherapy (in the case of bone pain not controlled by analgesics or bone metastases at high risk of fracturing or risk of spinal compression) and the medicinal products acting specifically on mineralisation (bisphosphonates).

Bisphosphonates are indicated in cases of bone metastases confirmed radiologically to:

- treat malignant hypercalcaemia and/or pain
- prevent skeletal-related events from the metastases (fractures, spinal compressions, need to resort to bone surgery or bone radiotherapy).

The most commonly used bisphosphonates in practice in this situation are zoledronic acid and pamidronate disodium administered in an IV infusion. The infusion duration of around 15 minutes which is required to administer zoledronic acid is preferable to pamidronate disodium which must be administered over at least 2 hours. Calcium and vitamin D supplementation must be associated with bisphosphonates. There is currently no recommended treatment duration.

In case of severe renal impairment, zoledronic acid and pamidronate disodium are not recommended, and ibandronic acid administered at appropriate doses should be chosen.

Place of denosumab 120 (XGEVA) in the therapeutic strategy:

XGEVA is an alternative to bisphosphonates but with demonstration of a higher efficacy level on the skeletal related events caused by metastases from breast and prostate cancers.

4.4. Target population

In 2010, the incidence of solid tumours was 357,500 new cases, of which 71,500 were prostate cancers, 52,500 breast cancers and 37,000 lung cancers.[7]

Prostate cancer

Metastasis occurs in around 20% of prostate cancers[8] i.e. 14,300 cases. The proportion of patients with bone localisation from all the patients at metastatic stage is estimated to be between 63 and 79% (Louis Harris 2007 data).

The incidence of patients with prostate cancer and under the indication is estimated to be between 9000 and 11500 patients.

Breast cancer

Metastasis from the outset occurs in 5% to 15% of cases, i.e. 5250 new cases and metastasis after local progression represents 28% of cases i.e. 14,700 cases.[9,10]

The proportion of patients with bone localisation from all the patients at metastatic stage is estimated to be between 41 and 57% (Louis Harris 2007 data).

The incidence of patients with breast cancer and under the indication is estimated to be between 8000 and 11,400 patients.

Other solid tumours, in particular lung cancer

The incidence of patients with a solid tumour, apart from breast or prostate cancer, and within the indication is estimated at around 13,000 patients, 8000 of which are lung cancers (Louis Harris 2007 data).

In conclusion, the target population of XGEVA is between 30,000 and 36,000 patients.

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[7] *La situation du cancer en France en 2010* [InCA www.e-cancer.fr]

[8] Bauvin E, Soulie M, Menegoz F, Mace-Lesec'h J, Buemi A, Velten M, Villers A, Grosclaude P. Medical and nonmedical determinants of prostate cancer management: a population-based study. Eur J Cancer. 2003 Nov; 39 (16): 2364-71.

[9] FNCLCC survey

[10] FRANCIM

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100 %