12 October 2017
EMA/848543/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

XGEVA

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/002173/II/56

Note

Variations assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Declarations

X The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

Assessment Timetable / Steps taken for the assessment

Timetable	Planned dates	Actual dates
Start of procedure:	14 August 2017	14 August 2017
CHMP Rapporteur Assessment Report	12 September 2017	12 September 2017
PRAC Rapporteur Assessment Report	15 September 2017	12 September 2017
PRAC members comments	20 September 2017	20 September 2017
Updated PRAC Rapporteur Assessment Report	21 September 2017	27 September 2017
PRAC Outcome	28 September 2017	28 September 2017
CHMP members comments	2 October 2017	2 October 2017
Updated CHMP Rapporteur Assessment Report	5 October 2017	5 October 2017
Opinion	12 October 2017	12 October 2017

Table of contents

1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 27 July 2017 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.4 and 4.8 of the SmPC in relation to Multiple Vertebral Fractures (MVF) following treatment discontinuation of Xgeva following a cumulative safety review from 2 clinical trials 20060359 (ongoing randomized, placebo-controlled, blinded study of denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence) and 20040113 (a completed phase 2 study comparing denosumab and intravenous (IV) bisphosphonate treatment, collected data on bone turnover markers during the 32-week post-treatment follow-up period) and post-marketing experience. A minor change is also proposed for section 5.1 of the SmPC to provide some further information to prescribers regarding the reversibility of the inhibition of bone turnover following cessation of treatment. The Package Leaflet is updated accordingly. The RMP version 26.0 has also been submitted. A Direct Healthcare Professional Communication is also proposed.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

1.2. Rationale for the proposed change

Denosumab with osteoporosis indication (Prolia)

The MAH has previously submitted variation EMEA/H/C/001120/II/0062 regarding multiple new vertebral fractures (MVF) following treatment discontinuation with Prolia. This was based on a post-hoc analysis of osteoporosis-related fracture data in subjects who discontinued investigational product in either the Prolia phase 3 pivotal fracture study (Study 20030216) or its study extension (Study 20060289). Some publications at that time described patients sustaining MVF following Prolia discontinuation (Anastasilakis et al, 2017; Popp et al, 2016; Gonzalez-Rodriquez et al, 2016; Anastasilakis and Makras, 2016).

The PRAC did not agree with the MAH analyses and interpretation of the data in the above named variation. In Prolia pivotal study 20030216, the rate of off-treatment new vertebral fractures was identical in the subjects who discontinued placebo and in the subjects that discontinued denosumab and there were no imbalances in patients who had two, three or four vertebral off-treatment fractures. The scientific value of stimulated non-study reports of fractures occurring after treatment was considered low. The fact that ad hoc analyses with serious methodological concerns have been published does not change the fact that the data did not indicate an increased risk of multiple vertebral fractures after treatment discontinuation when assessed objectively. Recommendations and warnings proposed by the MAH were not accepted.

Xgeva (denosumab with oncology indications)
XGEVA has the same active substance as Prolia and the concomitant medical conditions in the XGEVA patient population may overlap with that of Prolia (i.e., postmenopausal women). During routine data review of an XGEVA clinical study, Study 20060359 (DCARE), MAH identified 2 subjects with post-treatment non-pathologic fractures involving multiple vertebrae. Therefore, a signal evaluation of MVF with discontinuation of XGEVA treatment was undertaken and is described in this variation. It is unknown at this time whether these subjects with vertebral fractures received denosumab or placebo.

The Prolia studies included measurement of bone mineral density by dual-energy X-ray absorptiometry, fracture incidence, measurement of bone turnover markers, and bone histology/histomorphometry. None of these measurements were regularly performed during XGEVA studies; thus, the signal evaluation of MVF with discontinuation of XGEVA treatment was qualitatively different from that of MVF with discontinuation of Prolia.

2. Overall conclusion and impact on the benefit/risk balance

A signal evaluation of multiple vertebral fractures (MVF) after discontinuation of XGEVA treatment has been carried out by the MAH. However, as stated in the previous Prolia variation, no specific biologically plausible mechanism for an adverse event of two or more vertebral fractures exists, that would be different from single vertebral fracture. Both single and multiple vertebral fractures can occur in the target population for Xgeva treatment (such as patients with breast cancer and multiple myeloma) both without treatment and during treatment. Further, if the intended effect of a medicinal product is not achieved in a patient who is **not** treated with the product, this is normally not considered as a signal.

As of 27 September 2016, the cumulative exposure for XGEVA in clinical studies was 9092 subjects and the cumulative estimated postmarketing exposure was 622 437 patient-years.

In a review by the MAH, one study case of MVF was found in an 85-year-old woman with multiple myeloma who had previously received Xgeva in Study 20090482. In addition, the MAH has identified 3 patients with MVF approximately 1 year following the last dose of investigational product in Study 20060359 in women with breast cancer.

No confirmed MVF cases more than 30 days following XGEVA treatment discontinuation were identified among the 12 post-marketing cases of vertebral fracture retrieved from MAHs safety database that were confirmed to involve XGEVA treatment,. No reports in the literature were identified describing vertebral fracture risk following XGEVA treatment discontinuation.

In summary, four patients with documented multiple vertebral fractures after last dose of Xgeva were described. In relation to cumulative exposure to Xgeva, this is likely lower than expected in this population at risk for vertebral fractures. Data for denosumab does not indicate an increased risk of multiple vertebral fractures after Prolia treatment discontinuation as discussed in a previous variation for Prolia and the data from Xgeva treated patients presented now does not support an association. The proposed changes to the SmPC with new warnings and recommendations and the RMP by the MAH are not acceptable. A Direct Healthcare Professional Communication (DHPC) is not appropriate.
The benefit-risk balance of Xgeva, including stopping the treatment with the product, remains unchanged.

Scientific Summary for the EPAR

Please refer to Scientific Discussion Xgeva-H-C-2173-II-0056

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.4 and 4.8 of the SmPC in relation to Multiple Vertebral Fractures (MVF) following treatment discontinuation of Xgeva following a cumulative safety review from 2 clinical trials 20060359 (ongoing randomized, placebo-controlled, blinded study of denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence) and 20040113 (a completed phase 2 study comparing denosumab and intravenous (IV) bisphosphonate treatment, collected data on bone turnover markers during the 32-week post-treatment follow-up period) and post-marketing experience. A minor change is also proposed for section 5.1 of the SmPC to provide some further information to prescribers regarding the reversibility of the inhibition of bone turnover following cessation of treatment. The Package Leaflet is updated accordingly. The RMP version 26.0 has also been submitted. A Direct Healthcare Professional Communication is also proposed.

X is not recommended for approval.

Grounds for refusal:

Whereas:

- A signal evaluation of multiple vertebral fractures (MVF) after discontinuation of treatment with Xgeva (denosumab) has been carried out by the MAH. However, no specific biologically plausible mechanism for an adverse event of two or more vertebral fractures exists, that would be different from single vertebral fracture. Both single and multiple vertebral fractures can occur in the target population for Xgeva treatment (such as patients with breast cancer and multiple myeloma) both without treatment and during treatment. Further, if the intended effect of a medicinal product is not achieved in a patient who is **not** treated with the product, this is normally not considered as a signal. Four patients with documented multiple vertebral fractures after last dose of investigational product in clinical studies were described. No confirmed MVF cases more than 30 days following XGEVA treatment discontinuation were identified among the 12 post marketing cases of vertebral fractures retrieved from the MAH's safety database that were confirmed to involve XGEVA treatment. In relation to cumulative exposure to Xgeva in clinical studies (9092 subjects) and post-marketing (622 437 patient-years), this is likely lower than expected in this population at risk for vertebral fractures. Furthermore, data for denosumab used in another indication did not indicate an increased risk of multiple vertebral fractures after Prolia treatment discontinuation as discussed in a previous variation for Prolia; similarly, the data from Xgeva-treated patients presented now does not support such an association,

the CHMP has recommended the refusal of the variation to the terms of the marketing authorisation.

4. Scientific discussion

4.1. Clinical safety aspects

4.1.1. Methods – analysis of data submitted

Clinical Data Review

A review of data in the XGEVA clinical study database was performed for 2 studies, Study 20060359 and Study 20040113. Study 20060359 is an ongoing randomized, placebo-controlled, blinded study (denosumab 120 mg Q4W for 6 months, followed by denosumab 120 mg every 3 months for up to 4.5 years) of denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence. In the XGEVA clinical development program, Study 20060359 is the only XGEVA clinical study to systematically collect centrally-reviewed imaging (yearly skeletal scintigraphy and CT/MRI imaging) and clinical fracture data during a post-treatment follow-up period (up to 5 years of follow-up after completion of treatment). Upon documented disease recurrence in the bone, all scheduled imaging ceases, although subjects could undergo additional imaging if clinically indicated (eg, for back pain). Once the primary analysis cutoff date is reached (currently projected for third quarter 2017), no further protocol-scheduled imaging or clinical fracture data collection will be conducted on any subjects. Levels of bone turnover markers are being measured in Study 20060359 as an exploratory endpoint.

For Study 20060359, all reported fractures involving the spine were reviewed manually, excluding the following:

- pathologic vertebral fracture with documentation of concurrent bone metastasis
- single vertebral level compression fracture
- fractures in subjects still on study treatment or within 30 days of their last dose of blinded investigational product (ie, within the dosing interval for XGEVA) at the onset or time of diagnosis of the fracture event

Study 20040113, a completed phase 2 study comparing denosumab and intravenous (IV) bisphosphonate treatment, collected data on bone turnover markers during the 32-week post-treatment follow-up period. Data from Study 20040113 were reviewed to evaluate changes in bone turnover markers following denosumab treatment discontinuation. Urinary N-telopeptide (uNTx) was measured at baseline, week 13, and week 25 (end of treatment period), as well as at weeks 33, 45, and 57 in the follow-up period (8, 20, and 32 weeks following treatment discontinuation). Subjects were allowed to receive IV bisphosphonate treatment during the 32-week follow-up period following discontinuation of investigational product. Radiologic evaluation of the spine was not conducted during the post-treatment follow-up period and only serious adverse events were to be reported during the post-treatment follow-up period.

Aggregate review of the MAH's Global Safety Database

A cumulative search of the Amgen Global Safety Database (AGSD) for serious clinical study and postmarketing cases of MVF following denosumab treatment discontinuation was initially conducted on 09 February 2016 as part of a comprehensive evaluation of post-treatment MVF with any denosumab treatment (Prolia or XGEVA). An updated search was conducted on 15 January 2017 to identify relevant cases of MVF following discontinuation of treatment with XGEVA and received by Amgen from 10 February 2016 to 15 January 2017.

A medical review of all identified cases from both searches of the AGSD was conducted, including a review of treatment duration, prior fracture history, confounding concomitant medications, location and number of vertebral fractures, treatment with alternative antiresorptive therapy, and severity of any trauma precipitating the fracture.

Literature Review and Epidemiology Assessment

A literature review was conducted in February 2016 to identify publications with mention of MVF following discontinuation of denosumab treatment. On 01 March 2017, an updated search of MEDLINE and Embase databases was conducted using the search strategy "denosumab and vertebral fracture" for the period of 01 February 2016 to 01 March 2017. Citations from both literature reviews with reports of vertebral fracture occurring post-treatment with denosumab were further reviewed.

PubMed searches were conducted to identify literature on MVF incidence rates in patients with osteoporosis, multiple myeloma, or solid tumors. Source articles for general population statistics were also reviewed.

4.1.2. Results

Clinical Study Data

Study 20060359

Within the XGEVA clinical development program, MVF following blinded investigational product discontinuation had been seen in 2 subjects (index cases) who had participated in the ongoing, blinded Study 20060359. Both subjects developed MVF approximately 1 year following completion of the blinded treatment. During the safety signal evaluation, a third subject in Study 20060359 was identified with MVF occurring more than 30 days after discontinuing blinded investigational product. Unblinding of Study 20060359 is currently projected to occur during the fourth quarter of 2017, and therefore it is unknown at this time whether these subjects received denosumab or placebo.

Of the 3 subjects who experienced MVF following discontinuation of investigation product in Study 20060359; 2 were post-surgically menopausal and 1 had a history of osteoporosis; all 3 had a history of nonvertebral fractures (upper or lower appendages). In each subject, the MVF events occurred approximately 1 year following the last dose of investigational product. None of the MVF events was reported as serious adverse events and none required surgery. None of the 3 subjects received a bone-targeted agent following discontinuation of blinded investigational product.

Study 20040113

In Study 20040113, levels of the bone turnover marker uNTx were measured and adjusted by urinary creatinine levels (uNTx/Cr). In the 120 mg Q4W cohort, the median reduction in uNTx/Cr was approximately 80% by week 13. At Week 57, 32 weeks following the last dose of denosumab, the median uNTx/Cr level had increased to 23.5% over baseline. Similar results (reduction in levels at weeks 13 and 25; increase to baseline or above by week 57) were seen for levels of other bone turnover markers (serum C-telopeptide, bone-specific alkaline phosphatase, procollagen 1 N-terminal peptide, tartrate-resistant acid phosphatase 5b). These results support the reversibility of XGEVA's inhibition of bone turnover.

Only serious adverse event data were collected during the off-treatment follow-up period of Study 20040113, and no serious adverse events of vertebral fracture were reported during this period.

Aggregate Review of Amgen Global Safety Database

During the initial review of the AGSD for cases of MVF following discontinuation of XGEVA, the only cases identified were pathologic fractures due to metastatic disease progression; no cases of MVF following XGEVA discontinuation were identified. The follow-up review in January 2017 identified 24 case reports (10 from clinical studies and 14 postmarketing reports). Two of the postmarketing cases were determined to involve Prolia and not XGEVA. The other 22 cases were further evaluated.

Clinical Study Cases

Among the 10 serious adverse event reports of MVF from blinded clinical studies, 2 fracture events were identified with on set > 30 days after the last dose of investigational product and thus were considered off-treatment. One of these events, in a postmenopausal woman who participated in Study 20060359, involved a single (ie, not MVF) lumbar compression fracture. The other event was reported in an woman who had received denosumab 120 mg Q4W in Study 20090482, a study comparing XGEVA with zoledronic acid for prevention of SREs in subjects with multiple myeloma. The subject developed thoracic vertebral fractures approximately 19 months following her final dose of denosumab. The subject had a history of thoracic vertebral fracture and concomitant medications including dexamethasone. The investigator considered the event not related to either the investigational product or the study conduct.

Post-marketing cases

Among the 12 postmarketing cases of vertebral fracture retrieved from AGSD that were confirmed to involve XGEVA treatment, none was identified that confirmed MVF more than 30 days following XGEVA treatment discontinuation.

Literature Review and Epidemiology

Literature Review

No reports in literature were identified describing vertebral fracture risk following XGEVA treatment discontinuation.

Six articles (case reports or case series) were identified that described 24 women who developed vertebral fractures following their last doses of Prolia (Anastasilakis et al, 2017; Lamy et al, 2017; Anastasilakis et al, 2016; Aubry-Rozier et al, 2016; Polyzos and Terpos, 2016; Popp et al, 2016). All 24 women were postmenopausal with osteopenia or osteoporosis.

Epidemiology

The events of MVF following investigational product discontinuation occurred in 3 women with breast cancer participating in Study 20060359 and 1 woman with multiple myeloma participating in Study 20090482. Both populations have a higher incidence of non-pathologic vertebral fractures. The estimated prevalence for osteoporosis and low bone mass in the United States were 10.3% and 43.9%, respectively, in 2010 (Wright et al, 2014). In women, osteoporosis prevalence increased from 6.8% at ages 50 to 59 years to 34.9% at age 80 years and older. In a recent cohort study, from 2009 to 2011 the age-adjusted incidence of vertebral fractures per 100 000 person-years was 1092 in women and 798 in men (Amin et al, 2014). In women with breast cancer, both chemotherapy and chemotherapy-induced menopause increase the risk of osteoporosis (Rivkees and Crawford, 1988; Saarto et al, 1997). The incidence of non-metastatic vertebral fractures was significantly higher in women with breast cancer than in controls and in women treated with aromatase inhibitors (AI) compared with those not on AI therapy (Pedersini et al, 2017; Kanis et al, 1999). Finally, osteopenia is found in up to 90% of patients

with multiple myeloma, with lytic lesions in approximately 80% of patients (Hameed et al, 2014; Berenson et al, 1996).

Patient Exposure

As of 27 September 2016, the cumulative exposure for XGEVA in clinical studies was 9092 subjects and the cumulative estimated postmarketing exposure was 622 437 patient-years.

4.1.3. MAH Discussion

XGEVA has not been associated with reports of MVF following treatment discontinuation until early 2017, when several reports were received from subjects in an ongoing blinded study of women with breast cancer at high risk of occurrence (Study 20060359) or an ongoing study of subjects with multiple myeloma (Study 20090482) who experienced MVF approximately 1 year after the final dose of blinded investigational product. The characteristics and medical history among these subjects were similar to those of subjects who had contributed to the assessment supporting MVF as an identified risk for Prolia; ie, postmenopausal women with a history of fractures, osteopenia, osteoporosis, or who had risk factors for low bone density.

The off-treatment effects on bone turnover and remodeling following XGEVA treatment discontinuation are not as well characterized as for Prolia. Nonetheless, Study 20040113 supports the reversibility of XGEVA's effect on bone turnover, showing an increase in bone turnover markers to above baseline levels.

While few MVF events have been identified following discontinuation of XGEVA treatment, these types of events may be medically important and there are interventions that may be undertaken (eg, dietary, exercise, pharmacologic) to mitigate the risk of osteoporotic vertebral fractures. Amgen has taken the step of modifying its CDS to alert health care professionals and patients to this risk.

Rapporteurs comment: The conclusions of the MAH are not endorsed, please see overall conclusions of this AR.

4.1.4. Direct Healthcare Professional Communication

A DHPC is proposed by the MAH and a draft of such communication has been submitted. This is not endorsed.

4.2. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Safety concerns

Important identified risks	hypocalcemia, osteonecrosis of the jaw, hypersensitivity reactions, atypical femoral fracture, musculoskeletal pain, hypercalcemia following treatment discontinuation in patients with growing skeletons, multiple vertebral fractures following discontinuation of XGEVA treatment
Important potential risks	infection, cardiovascular events, malignancy, osteonecrosis outside the jaw including external auditory canal, immunogenicity, cataracts in men with prostate cancer undergoing androgen deprivation therapy, thyroid function disorder, delay in diagnosis of primary malignancy in giant cell tumor of bone
Missing information	risks during pregnancy and lactation, pediatric patients, patients with multiple myeloma, patients with hepatic impairment, and patients with prior IV bisphosphonate treatment, safety with long-term treatment and with long-term follow--up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone, off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

Considering the data in the safety specification, the proposed new safety concern is not endorsed.

Pharmacovigilance plan

No changes in on-going and planned studies in the post-authorisation pharmacovigilance development plan are proposed, which is endorsed.

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

The currently existing risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Elements for a public summary of the RMP

The MAH proposes the following addition:

Risk of broken bones in the spine after stopping treatment with XGEVA (multiple vertebral fractures following discontinuation of XGEVA treatment).	After treatment with XGEVA is stopped, there may be an increased risk of having broken bones in your spine especially in people who have had a fracture or who have had osteoporosis (a condition in which bones become thin and fragile).	Do not stop taking XGEVA without first talking with your doctor.

In line with the conclusions of this report, the addition is not accepted.

Overall conclusion on the RMP

For the reasons expressed in the conclusions of this report, the changes to the RMP are not acceptable.

4.3. Changes to the Product Information

MAH proposes the following language in Section 4.4, Special Warnings and Precautions for Use:

> Multiple vertebral fractures following treatment discontinuation
> Multiple vertebral fractures, not due to bone metastases, may occur following discontinuation of treatment with XGEVA, particularly in patients with risk factors such as osteoporosis or prior fractures.
>
> Patients should be advised not to interrupt XGEVA therapy without their physician's advice. When XGEVA treatment is discontinued, evaluate the individual patient's risk.

MAH proposes the following text in SmPC Section 4.8, Adverse Reactions:

Table 1: Adverse reactions reported in patients with advanced malignancies involving bone or with giant cell tumour of bone

MedDRA system organ class	Frequency category	Adverse reactions
Immune system disorder	Rare	Drug hypersensitivity[1]
	Rare	Anaphylactic reaction[1]
Metabolism and nutrition disorders	Common	Hypocalcaemia[1, 2]
	Common	Hypophosphataemia
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Tooth extraction
Skin and subcutaneous tissues disorders	Common	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[1]
	Common	Osteonecrosis of the jaw[1]
	Rare ~~Not Known~~	Atypical femoral fracture[1] ~~Osteonecrosis of the external auditory canal[3,4]~~
	Rare	Multiple vertebral fractures following treatment discontinuation[1,3]
	Not known	Osteonecrosis of the external auditory canal[3,4]

Description of selected adverse reactions

Multiple vertebral fractures
In the clinical trial programme, rare events of multiple vertebral fractures (not due to bone metastases) have occurred, approximately 1 year following the final dose, in women with risk factors such as osteoporosis or prior (non-vertebral or vertebral) fractures (see section 4.4).

MAH proposes the following text in SmPC Section 5.1 Pharmacodynamic properties:

Pharmacodynamic effects
In phase II clinical studies of patients with advanced malignancies involving bone, subcutaneous (SC) dosing of XGEVA administered either every 4 weeks or every 12 weeks resulted in a rapid reduction in markers of bone resorption (uNTx/Cr, serum CTx), with median reductions of approximately 80% for uNTx/Cr occurring within 1 week regardless of prior bisphosphonate therapy or baseline uNTx/Cr level. The inhibition of bone turnover was reversible, with median uNTx/Cr levels returning to approximate baseline levels by 32 weeks after the last dose of XGEVA. In the phase III clinical trials, median reductions of approximately 80% were maintained in uNTx/Cr after 3 months of treatment in 2,075 XGEVA-treated advanced cancer patients' naïve to IV-bisphosphonate.

MAH proposes the following text in the PL:

Risk of broken bones in the spine after stopping treatment with XGEVA
Do not stop taking XGEVA without first talking with your doctor. After treatment with XGEVA is stopped, there may be an increased risk of having broken bones in your spine especially in people who have had a fracture or who have had osteoporosis (a condition in which bones become thin and fragile).

Rare side effects (may affect up to 1 in 1,000 people)
- allergic reactions (e.g. wheezing or difficulty breathing; swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin). In rare cases allergic reactions may be severe,
- new or unusual pain in your hip, groin or thigh (this may be an early indication of a possible fracture of the thigh bone),
- broken bones in your spine after stopping treatment with XGEVA.

Overall conclusion on the SmPC and PIL

For the reasons expressed in the conclusions of this report, the changes above are not acceptable.