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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aclasta

zoledronic acid

Procedure No.: EMEA/H/C/000595/A20/0026

Note

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

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1. Background information on the procedure

Following the addition of a warning about atypical stress fractures of the proximal femoral shaft to the product information for alendronic acid containing medicinal products, the Pharmacovigilance Working Party (PhVWP) recommended to keep the issue of bisphosphonates and atypical stress fractures under close review, The PhVWP considered this issue again in April 2010 and noted that further data had emerged from both the published literature and post-marketing reports suggesting that atypical stress fractures may be a class effect.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 19 October 2010 to assess the above concerns and its impact on the benefit/risk for Aclasta, and to give its opinion on measures necessary to ensure the safe and effective use of Aclasta, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

The scope of the review was the class review of the relation between bisphosphonates and atypical stress fractures.

After reviewing all the available data submitted by the MAH to address the concerns discussed, the CHMP adopted an opinion on 14 April 2011.

2. Scientific discussion

Bisphosphonates are medicinal products that are used to treat and prevent bone disorders including hypercalcaemia and the prevention of bone problems in patients with cancer, the treatment of osteoporosis and Paget's disease. Bisphosphonate-containing medicinal products include alendronic acid, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, tiludronic acid. Bisphosphonates have been authorised in the EU via the centralised procedure and also through national procedures.

In 2008, evidence from the published literature suggesting that long-term use of alendronic acid may be associated with an increased risk of atypical stress fractures prompted a review of bisphosphonates and atypical stress fractures by the CHMP Pharmacovigilance Working Party (PhVWP). The PhVWP concluded that the data supported an association between alendronic acid and atypical stress fractures, and a warning about atypical stress fractures of the proximal femoral shaft was subsequently added to the product information (PI) for alendronic acid containing medicinal products across Europe. With regard to the other bisphosphonates, the available data did not provide evidence of a causal association, and no changes to the product information were recommended. However as a class effect could not be ruled out, the PhVWP recommended that this issue should be kept under close review.

In light of the PhVWP recommendation to keep the issue of bisphosphonates and atypical stress fractures under close review, the PhVWP considered this issue again in April 2010. The PhVWP noted that further data had emerged from both the published literature and post-marketing reports, suggesting that atypical stress fractures may be a class effect of bisphosphonates. Although the majority of case reports of atypical stress fracture had been reported in association with alendronic acid use, a number of cases have now also been reported in association with the majority of the other bisphosphonates (etidronic acid, ibandronic acid, pamidronic acid, risedronic acid and zoledronate). No cases of atypical stress fractures have been reported for clodronic acid, neridronic acid or tiludronic acid, although this may be related to the lower usage of these products compared to other bisphosphonates. It was also the view of the PhVWP that a possible class effect of bisphosphonates and atypical stress fractures is supported by the proposed pathophysiological mechanisms of this potential adverse reaction, which may apply to all bisphosphonates.

Further to the PhVWP discussions and the emerging data from both the published literature and post-marketing reports that suggest that atypical stress fractures may be a class effect of bisphosphonates, the, the European Commission initiated a procedure under Art 20 of Regulation (EC) No 726/2004 for bisphosphonate-containing products and referred the matter to the CHMP, to give its opinion on measures necessary to ensure the safe and effective use of these medicinal products and whether the Marketing Authorisations should be maintained, varied, suspended or withdrawn.

The CHMP reviewed the currently available safety data from non-clinical and histological studies, relevant clinical trials, epidemiological studies, post-marketing reports and published literature. The review of the CHMP focussed specifically on the available data mentioned above, the discussion on the definition of atypical femoral fracture, risk factors and discussion on the need for further clinical studies to be conducted.

2.1. Non-clinical aspects

Although pre-clinical studies have provided limited information on the risk of atypical fractures with bisphosphonates, some studies have demonstrated that suppression of bone turnover by bisphosphonates may increase microdamage accumulation and the accumulation of advanced glycation end-products resulting in changes in the biomechanical properties of bone (Brennan et al, 2011, Hofstaetter et al, 2010, Mashiba et al, 2000, O'Neal et al, Tang et al, 2009[1]). However not all pre-clinical studies have found adverse effects of alendronic acid on bone (Burr et al[2]).

2.2. Clinical aspects

Cases of atypical stress fractures in association with bisphosphonates have been described in the literature using a variety of terms such as pathological fractures, instability fractures, fragility fractures, stress fractures, low-energy fractures, and atypical fractures. The main reported fracture site is the femur described as proximal femoral shaft, subtrochanteric and diaphyseal fractures.

The task force of the American Society for Bone and Mineral Research (ASBMR) on atypical subtrochanteric and diaphyseal femoral fractures have defined major and minor features of atypical femoral fracture (Shane et al, 2010[3]) and recommend that for a case to be considered an atypical femoral fracture all major features need to be present, whereas the minor features have commonly been described in cases of atypical femoral fractures, but are not present in all patients.

Based on the small number of spontaneous reports of comminuted atypical femoral fracture in association with bisphosphonates, one published case report (Schneider, 2006[4]), as well as preliminary

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[1] Brennan O et al The effects of estrogen deficiency and bisphosphonate treatment on tissue mineralisation and stiffness in an ovine model of osteoporosis. J Biomech 2011; 44:386-90
Hofstaetter JG et al. The effects of high-dose, long-term alendronate treatment on microarchitecture and bone mineral density of compact and trabecular bone in the proximal femur of adult male rabbits. Arch Orthop Trauma Surg 2010; 30: 937-944
Mashiba T et al Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 2000; 15: 613-620
O'Neal JM et al One year of alendronate treatment lowers microstructural stresses associated with trabeclar microdamage initiation. Bone 2010; 47: 241-247
Tang SY et al Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. Osteoporosis Int 2009; 20: 887-894

[2] Burr DB et al Effects of one to three years treatment with alendronate on mechanical properties of the femoral shaft in a canine model: implications for subtrochanteric femoral fracture risk. J Orthop Res 2009; 27: 1288-1292

[3] Shane E et al Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010; 25: 2267-2294

[4] Schneider P. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics 2006; 61: 31-33

data presented at the October meeting of the ASBMR (Nitche et al, 2010[5]), the CHMP agreed to adopt a modified case definition that lists 'noncomminuted' as a minor feature rather than a major feature of atypical femur femoral fracture, as mentioned below. It was the view of the CHMP that a modified version of the ASBMR case definition for atypical femoral fracture as described below should be used for the purpose of this assessment.

CHMP agreed definition of atypical fracture of the femur (based on the ASBMR definition of Atypical Femoral Fracture): Major and Minor Features

Major features[b]

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

Minor features[a]

- Noncomminuted
- Localized periosteal reaction of the lateral cortexc
- Generalized increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia)

Use of pharmaceutical agents (eg, bisphosphonates, glucocortoids, proton pump inhibitors)

[a]Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.

[b]All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.

[c]Often referred to in the literature as beaking or flaring.

The possible underlying pathophysiological mechanism(s) of atypical fractures

The mechanism(s) for the development of atypical fractures in patients taking bisphosphonates is not known. However the postulated mechanisms may be applicable across the class of bisphosphonates

[5] Nitche J et al Subtrochanteric femoral stress fractures in patients on chronic bisphosphonate therapy: a case series. J Bone Miner Res 25 (Suppl 1) 2010; Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=223582c5-f5bb-4d66-bd16-d073267b2a47. Accessed 5 April 2011

although it is possible some differences may exist between individual bisphosphonates due to their different effects on farnesyl pyrophosphate synthase (FPPS) enzyme inhibition and mineral binding affinity (Russell et al, 2008[6]).

There are 2 main types of bisphosphonates: non-nitrogen containing bisphosphonates and nitrogen containing bisphosphonates (Russell et al, 2008). Non-nitrogen containing bisphosphonates (etidronic acid, clodronic acid and tiludronic acid) act by interacting with ATP in osteoclasts forming ATP analogues that induce osteoclast apoptosis. Nitrogen-containing bisphosphonates inhibit FPPS, a key enzyme in the mevalonic acid pathway in osteoclasts which prevents the production of proteins essential for their function and survival. Inhibition of this enzyme also leads to an accumulation of isopentenyl diphosphate (IPP) which is incorporated into an analogue of ATP that can induce osteoclast apoptosis.

A number of possible mechanisms of atypical fracture in association with bisphosphonate use have been postulated. The main postulated mechanism is the suppression of bone turnover leading indirectly to ageing bone and the delay or prevention of repair of naturally occurring stress fractures although the evidence is not conclusive.

The proposed mechanisms may also apply to the development of atypical fractures in association with bisphosphonates at sites other than the femur.

2.2.1. Clinical safety

The main fracture site reported in the vast majority of the cases of atypical stress fractures is the femur, described as proximal femoral shaft, subtrochanteric and diaphyseal fractures.

However a number of literature and spontaneous reports describing atypical fractures at sites other than the femur in association with alendronic acid have been received although extremely low (17 reports), compared to the high level of reports of atypical fractures in association with alendronic acid at the site of the femur (397 reports). The other stress fracture sites reported include the foot, ankle, metatarsal, tibia and fibia, most of which are typical sites of stress or osteoporotic fractures, and were often reported in association with femoral fracture or reported as multiple stress fractures. The number of post-marketing reports of atypical fracture at sites other than the femur in association with other bisphosphonates is also low.

Clinical trials

Black et al 2010 [7]reviewed fracture records and available radiographs for all hip and femur fractures from 3 large, randomised bisphosphonate trials for osteoporosis: the Fracture Intervention Trial (FIT) of alendronic acid and its extension study, the FIT Long-Term Extension (FLEX) trial, and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial. The overall incidence of subtrochanteric or diaphyseal femur fractures in these clinical trials was 2.3 per 10,000 patient years. The risk of subtrochanteric or diaphyseal fracture was not significantly increased with alendronic acid compared to placebo in the FIT trial (HR 1.03 (0.06-16.46)) and the FLEX trial (HR 1.33 (0.02-14.67)) or with zoledronate in the HORIZON-PFT trial (HR 1.50 (0.25-9)) although the confidence intervals were wide.

[6] Russell RG et al Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporosis Int 2008; 19:733-759

[7] Black DM et al Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur
N Eng J Med 2010; 362:1761-1771

This study has a number of limitations including the relatively short length of bisphosphonate treatment in the majority of patients in the FIT and the zoledronate HORIZON trials, the lack of availability of radiographs for all femur fractures and the exclusion of patients taking medicines such as corticosteroids which may increase the risk of atypical femoral fractures.

In clinical trials for other bisphosphonates for osteoporosis, Paget's disease and oncology indications the number of possible cases of atypical fractures was also low and no increased risk was identified compared with placebo. However these clinical trials are also limited by trial duration and also lack of radiograph evaluation of fracture sites.

Epidemiological studies

- Cohort studies

A study in 2 national registry databases in Denmark found that the proportion of patients exposed to alendronic acid was similar for subtrochanteric fracture (6.7%), diaphyseal femur fracture (7.1%) and hip fracture (6.7%) (Abrahamsen et al, 2009[8]). The use of alendronic acid was associated with an increased risk of both subtrochanteric/diaphyseal femur fracture (HR 1.46 CI 0.91-2.35, p=0.12) and hip fracture (HR 1.45 CI 1.21-1.74, p<0.001). The ratio between hip and subtrochanteric/diaphyseal femur fractures was the same in alendronic acid treated patients and controls (14 % and 13% subtrochanteric/diaphyseal femur fractures, respectively).

A further larger study in Denmark by the same authors found that the risk of subtrochanteric and diaphyseal fractures was 13 per 10,000 patient-years in women who were not receiving alendronic acid and 31 per 10,000 patient years in patients taking alendronic acid (adjusted hazard ratio 1.88 95% CI 1.62-2.17) (Abrahamsen et al 2010[9]). The risks of the same femur fractures in alendronic acid unexposed and exposed men were 6 and 31 per 10,000 patient-years, respectively (adjusted hazard ratio 2.47 95% CI 2.07-2.95). The risks of subtrochanteric and diaphyseal fractures were similar in patients who had received almost 9 years of treatment with alendronic acid (31.3/10,000 patient-years) and patients who only received 3 months treatment (47.3/10,000 patient-years) (P=0.22).

Another study in the same database examined the risk of femoral shaft and subtrochanteric fractures among users of different bisphosphonates and also raloxifene (Vestergaard et al, 2010[10]). An increased risk of subtrochanteric and femoral shaft fractures was seen for alendronic acid (HR 2.41, CI 1.78-3.27), etidronic acid (HR 1.96, CI 1.62-2.36) and clodronic acid (HR 20.0, CI 1.94-205) but not raloxifene (HR 1.06, CI 0.34-3.32) however this increased risk was also present before the start of alendronic acid (OR 2.36, CI 2.05-2.72), etidronic acid (OR 3.05, CI 2.59-3.58), clodronic acid (OR 10.8, CI 1.14-103), raloxifene (OR 1.90, CI 1.07-3.40) and strontium (OR 2.97, CI 1.07-8.27). The increased risk was not associated with bisphosphonate dose or duration.

The authors of the above studies suggest that subtrochanteric and diaphyseal femur fractures may be normal osteoporotic fractures and that the increased risk of these fractures in patients taking bisphosphonates may be due to the use of this drug in patients who are at the greatest risk of fracture rather than a causal relationship between this fractures and alendronic acid (Abrahamsen et al, 2009, Abrahamsen et al, 2010, Vestergaard et al, 2010). However these studies do not contain information

[8] Abrahamsen B et al Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res 2009; 24: 1095-1102

[9] Abrahamsen B et al Cumulative alendronate dose and the long term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab 2010; 95:5258-5265

[10] Vestergaard P et al Risk of femoral shaft and subtrochanteric fractures among users of bisphosphonates and raloxifene. Osteoporos Int 2010; DOI 10.1007/s00198-010-1512y

about radiographic fracture pattern and therefore do not specifically relate to atypical femoral fractures.

Atypical femur fractures identified from radiograph examination in patients receiving bisphosphonates have been described in a small study in Sweden estimating that the incidence density of stress fractures of the femoral shaft in patients receiving bisphosphonates in women over 55 years was 1/1000 per year compared to 0.02/1000 per year for patients who were not taking bisphosphonates (Schilcher et al 2009[11]). In this study 3,087 women on continuous treatment with bisphosphonates 5 were found to have atypical femoral stress fractures (identified from radiograph examination) compared with 3 cases of atypical femoral stress fractures identified in 88,869 women not receiving bisphosphonates.

Radiographic findings were also available from preliminary data in a US health maintenance organisation database, which found that the incidence of atypical femur fracture increased with duration of bisphosphonate treatment from 2/100,000 cases per year with 2 years oral bisphosphonate treatment to 78/100,000 cases per year with 8 years oral bisphosphonate treatment (Dell et al, 2010). This study screened cases of femur fracture and reviewed radiographs to identify subtrochanteric and femur shaft fracture cases with atypical features. Characteristic radiographic findings were found in 102 patients, 97 of whom were on oral bisphosphonates with an average duration of 5.5 years.

- Case control studies

A population-based, nested case-control study in Canada found that long-term oral bisphosphonate use was associated with an increased risk of subtrochanteric and femoral shaft fractures in women aged 68 years or older (Park-Wyllie et al, 2011[12]). Bisphosphonate treatment for 5 years or more significantly increased the risk of subtrochanteric or femoral shaft fracture compared with bisphosphonate use for less than 100 days (OR 2.74, CI 1.25-6.02), whereas intermediate (3 to 5 years) and short term (100 days to 3 years) bisphosphonate treatment did not significantly increase the risk of subtrochanteric or femoral shaft fracture. The risk of typical osteoporotic fractures of the intertrochanteric region or femoral neck was reduced with more than 5 years of bisphosphonate therapy (OR 0.76, CI 0.63-0.93). In women with 5 or more years of bisphosphonate use a subtrochanteric or femoral shaft fracture occurred in 0.13 % within one year and 0.22% within 2 years. In these patients 64 % of subtrochanteric or femoral shaft fractures were attributable to long-term bisphosphonates use. Although this study excluded fractures sustained with trauma, the radiographic features of these patterns could not be determined.

A number of case-control studies including radiograph examination have also been reported. A retrospective case-control study examined the x-ray pattern low-energy subtrochanteric and femoral fractures in 41 patients (Lenart et al, 2009[13]). A unique x-ray pattern (described as a simple transverse or oblique fracture with beaking of the cortex on one side and cortical thickened around the site of the fracture) was identified in 10/15 subtrochanteric fractures receiving alendronic acid and in 3/26 fractures in patients not receiving bisphosphonates. This pattern was associated with bisphosphonates use (OR 15.33, CI 3.06-76.90, P<0.001).

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[11] Schilcher J et al Incidence of stress fractures of the femoral shaft in women treated with bisphosphonates. Acta Orthopaedica 2009; 80: 413-415

[12] Park-Wyllie LY et al Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women. JAMA 2011; 305:783-789

[13] Lenart BA et al Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int 2009; 20: 1353-1362

Another case-control study examined 100 patients with low-energy femoral shaft fractures before and after bisphosphonates became available for use (Issacs et al, 2010[14]). Following the review of radiographs, insufficiency femoral fractures were found in 41 patients. These patients had all received bisphosphonates (40 patients had received alendronic acid and one patient had received risedronic acid). Insufficiency femoral fractures were not found in the 21 patients with low-energy fractures before bisphosphonates became available, however fewer radiographs were available for review during this time period. Bisphosphonate use was associated with insufficiency fracture (OR >1000) and the mean duration of bisphosphonate use was longer in patients with insufficiency fractures (7.1 years) compared to patients without this type of fracture (3.2 years).

Case-control studies report a distinct radiographic pattern and clinical features of atypical femoral fractures associated with bisphosphonate use and provide evidence of a causal relationship between atypical fractures and bisphosphonate (Lenart et al, 2009, Issacs et al, 2010). Estimates of the incidence of atypical fractures in patients suggest that the frequency of these fractures in patients receiving bisphosphonates is rare (Dell et al, 2010[15]).

Post-marketing reports

The number of cases of atypical fracture of the femur in association with alendronic acid has risen sharply since the previous PhVWP review in 2008. A total of 397 post-marketing reports (including both spontaneous reports and literature cases) of low energy subtrochanteric/femoral shaft fractures with alendronic acid were received by the innovator MAH for alendronic acid, MSD from 1/7/2008 to 31/10/2010. The number of reports received during this time period is substantially higher than the number of reports received at the time of the previous PhVWP when 84 reports of fracture of the stress/insufficiency fracture of the femur had been received from July 1993 to June 2008. The increase in the number of reports is likely to reflect the increased recognition and awareness of the risk of atypical femur fractures with alendronic acid among health professionals resulting in increased reporting of cases in the literature and to the MAH and regulatory authorities.

Post-marketing reports of possible atypical fracture of the femur have also been received in association with bisphosphonates for oncology indications. During the period of the current review (since the PhVWP review in 2008), the following number of post-marketing reports of possible cases of atypical femur fracture were received by the innovator MAHs for bisphosphonates for oncology indications: ibandronic acid (one case of femur fracture), pamidronic acid (20 cases of femur fracture) and zoledronate (45 cases of femur fracture). No post-marketing reports of possible atypical fracture of the femur have been received in association with clodronic acid. The post-marketing reports in patients with cancer have a number of potential confounding factors such as the presence of bone malignancy, high risk of pathological fracture in this patient group and concurrent medication (e.g. glucocortoids, chemotherapy and aromatase inhibitors). One post-marketing report of possible atypical femoral fracture has been received with zoledronate in a patient with Paget's disease. No post-marketing reports of possible atypical fracture of the femur have been reported in association with tiludronic acid, which is indicated for Paget's disease, or neridronic acid which is indicated for Osteogenesis Imperfecta and Paget's disease. The very low number of reports of possible atypical fracture reported in association with bisphosphonates indicated for Paget's disease and Ostegenesis Imperfecta may be related to the lower usage of bisphosphonates in these indications compared with the use of

[14] Isaacs JD et al Femoral insufficiency fractures associated with prolonged bisphosphonate therapy. Clin Orthop Relat Res 2010; 468: 3384-3392

[15] Dell R et al A retrospective analysis of all atypical femur fractures seen in a large California HMO from the years 2007 to 2009. J Bone Miner Res 25 (Suppl 1) 2010; Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=05caf316-b73e-47b8-a011-bf0766b062c0. Accessed 15 February 2011

bisphosphonates in osteoporosis although this finding may also be related to differences in the clinical effects of bisphosphonates in these populations such as the distribution of bisphosphonate uptake or dosing regimens.

Possible risk factors for atypical fracture of the femur in association with bisphosphonates

A number of possible risk factors have been proposed. These are based mainly on the patient characteristics in cases of atypical femoral fracture.

- Duration of bisphosphonate exposure

The long-term use of bisphosphonates is thought to be the main risk factor for atypical femoral fractures. Preliminary estimates found that the incidence of atypical femur fracture was almost 40 times greater with 8 years of bisphosphonate treatment compared with 2 years treatment (Dell et al, 2010). Case-control studies have also found that the mean duration of bisphosphonate use was longer in patients with atypical femoral fractures than in patients without these fractures (Issacs et al, 2010, Lenart et al, 2008). Although duration of use appears to increase the risk of atypical fractures, cases have also occurred in association with short-term use (Giusti et al, 2010[16]).

- Concomitant treatment

In the recently published systematic review of cases by Giusti et al glucocorticoids and proton pump inhibitors (PPI) were identified as important risk factors for atypical femur fracture with their use occurring in 25.5 and 38.9 % of patients, respectively (Giusti et al, 2010). A study of 20 cases of atypical fractures identified using fracture radiographs also found that glucocorticoid treatment for more than 6 months was significantly associated with atypical femur fracture (OR 5.2 CI 1.3-31.0) (Girgis et al 2010[17]). Concomitant treatment with other anti-resorptive drugs such as hormone replacement therapy and raloxifene have also been proposed as possible risk factors (Compston, 2009[18]).

- Co-morbid conditions

The study by Girgis et al also found that a history of low-energy fracture (OR 3.2: CI 2.1-17.1), active rheumatoid arthritis (OR 16.5 CI 1.4-142.3) and a low level of serum-25-hydroxyvitamin D (OR 3.5 CI 1.7-18.7) were associated with an increased risk of atypical fracture ($P<0.001$). Diabetes mellitus has also been reported as a possible risk factor (Compston, 2009). The systematic review cases by Giusti et al found that other than osteoporosis, the most prevalent co-morbid conditions in patients with atypical femur fracture were chronic obstructive pulmonary disease or asthma (14.9%), rheumatoid arthritis (10.3%) and diabetes (10.3%) (Giusti et al, 2010).

- Ethnicity and genetic factors

The study by Giusti et al also found patients who developed atypical fractures after 5 years or less of treatment were more likely to be of Asian ethnicity than patients treated for more than 5 years (60.0% and 14.5 % of patients, respectively $P<0.001$) (Giusti et al, 2010). It has also been proposed that carriers of the gene for hypophosphatasia may be at increased risk of atypical femoral fractures as patients with hypophosphatasia develop fractures similar to atypical femur fractures observed in patients taking bisphosphonates (Shane et al, 2010).

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[16] Giusti A et al Atypical fractures of the femur and bisphosphonate therapy. A systematic review of case/case series studies. Bone 2010; 47: 169-180

[17] Girgis CM et al Atypical femoral fractures and bisphosphonate use. N Eng J Med 2010; 36: 1848-1849

[18] Compston JE Bisphosphonates and atypical femoral fractures: A time for reflection. Maturitas 2009; 65: 3-4

Optimal duration of bisphosphonate treatment for osteoporosis

The optimal duration of use of bisphosphonates for osteoporosis is not known, There is currently no robust evidence regarding the value of interrupting treatment with bisphosphonates. It has been suggested that bisphosphonate treatment could be limited to 5 years initially followed by an evaluation of the need for continuing treatment on an individual patient basis and that patients who remain at high risk of fracture should continue therapy whereas a drug break could be considered in patients at lower risk of fracture (Compston, 2009[19]). The Task Force of the ASBMR on atypical subtrochanteric and diaphyseal femoral fractures also recommend that the possibility of stopping treatment with bisphosphonates may be considered after 4 to 5 years, particularly in patients at low or moderate fracture risk who are also taking glucocorticoids, PPIs, oestrogen or tamoxifen which may be possible risk factors for atypical femur fractures (Shane et al, 2010[20]).

Since the optimal duration of use of bisphosphonates for osteoporosis is not known, the CHMP agreed that advice about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis should be added to the product information for bisphosphonates for osteoporosis.

Discussion and conclusion on safety

The CHMP has reviewed the data regarding atypical fracture (both at the site of the femur and other sites) from pre-clinical studies, clinical trials, epidemiological studies, post-marketing reports and the published literature that has become available since the time of the previous PhVWP review of this issue in 2008.

For the purpose of the assessment, the CHMP agreed a modified version of the case definition of atypical femoral fracture recommended by the task force of the ASBMR on atypical subtrochanteric and diaphyseal femoral fractures (Shane et al, 2010). The CHMP adopted case definition lists noncomminuted as a minor feature rather than a major feature of atypical femur femoral fracture.

The mechanism(s) for the development of atypical fractures in patients taking bisphosphonates is not known. The main postulated mechanism is the suppression of bone turnover leading indirectly to ageing bone and the delay or prevention of repair of naturally occurring stress fractures, although the evidence is not conclusive. Other possible mechanisms have been proposed.

Although the highest number of possible atypical femoral fracture by far continue to be reported in association with alendronic acid for osteoporosis, post-marketing reports have also been reported for other bisphosphonates for osteoporosis (etidronic acid, ibandronic acid, risedronic acid and zoledronate) and also for Paget's disease (zoledronate) and oncology indications (ibandronic acid, pamidronic acid and zoledronate). The lack of reports with some bisphosphonates, clodronic acid, neridronic acid and tiludronic acid may be related to the lower exposure of the drugs compared with other bisphosphonates, and a lack of an association can not be excluded.

At the present time there is little evidence from literature and spontaneous reports to support an association between bisphosphonates and atypical fracture at sites other than the femur. The potential risk of atypical fractures at sites other than the femur should be kept under review.

The main proposed possible risk factor is long-term bisphosphonate treatment, however cases have been observed after short term use. Other possible risk factors proposed include concomitant treatment, particularly with glucocorticoids and PPIs, co-morbid conditions including diabetes and rheumatoid arthritis, and possible genetic factors.

[19] Compston JE Bisphosphonates and atypical femoral fractures: A time for reflection. Maturitas 2009; 65: 3-4

The available data suggests that atypical femoral fracture is a class effect of bisphosphonates. Therefore the CHMP agreed that a warning regarding this risk is added to the product information (PI) for all bisphosphonates and that atypical femoral fracture is added to section 4.8 (Undesirable effects) of the Summary of Product Characteristics (SmPC) accompanied by a statement that this adverse effect is a class attribution of bisphosphonates.

The MAH is requested to update their Risk Management Plan to reflect "atypical femoral fractures" as a potential risk.

In addition, given the lack of evidence regarding the optimal duration of bisphosphonate treatment for osteoporosis, and considering that duration of treatment is a risk factor for atypical femoral fractures, the CHMP also recommended that information should be added to section 4.2. of the product information for bisphosphonates authorised for osteoporosis, about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis.

2.3. Changes to the Product information

Since the PhVWP recommendation in 2008 to include a warning about the risk of atypical fracture of the proximal and mid femoral shaft in the PI for all alendronic acid products, further data has become available and the evidence now suggests that atypical fractures of the femur may be a class effect of bisphosphonates.

The CHMP therefore agreed that a warning should be added to the product information for all bisphosphonates. The proposed wording for section 4.4 of the SmPC (Special warnings and precautions for use) is based on wording implemented for alendronic acid in 2008 which has been updated to reflect the currently available information.

The MAH's were informed of the CHMP proposed wording for sections 4.4, 4.8 and 4.2 of the SmPC, and the corresponding package leaflet (PL) in the CHMP List of Outstanding Issues (LoOI) adopted in March 2011. The majority of the responses received from the MAHs confirmed their agreement to update the SmPC and PL in accordance with the wording provided in the LoOI. Some other MAHs agreed to update the product information to include atypical femoral fractures but with proposed changes to the wording.

In particular it was proposed by the MAHs that 'non-comminuted' should not be included in the wording of section 4.4, as reports of comminution have been described in cases of atypical femoral fracture (Schneider, 2006[21], Nitche et al, 2010[22]). Due to the small number of cases describing comminution in atypical femoral fracture, it was therefore considered appropriate to remove 'non-comminuted' from the SmPC wording. The MAH's argument to include imaging features of stress fractures was also accepted as this wording is included in the current alendronic acid SmPC wording, and the ASBMR task force report states that the radiologic presentation of atypical femoral fractures is strikingly similar to that of stress fractures. The MAH also suggested changing the wording regarding the evaluation of patients with symptoms from 'possible fracture' to 'an incomplete' fracture in order to ensure that physicians link the pain syndrome to the need to rule-out incomplete fractures of the femur before

[21] Schneider P. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics 2006; 61: 31-33

[22] Nitche J et al Subtrochanteric femoral stress fractures in patients on chronic bisphosphonate therapy: a case series. J Bone Miner Res 25 (Suppl 1) 2010; Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=223582c5-f5bb-4d66-bd16-d073267b2a47. Accessed 5 April 2011

they evolve into a completed femur fracture. This change was also considered to be acceptable, and the CHMP proposed wording for section 4.4 of the SmPC was updated to reflect all these changes.

Since it was considered appropriate to remove 'non-comminuted' from the SmPC wording, given that a small number of cases describing comminution in atypical femoral fracture have been reported, a modified case definition for atypical femoral fracture was agreed by the CHMP, listing 'non-comminuted' as a minor feature rather than a major feature of atypical femur femoral fracture.

Some other MAHs proposed additional statements to section 4.4 of the SmPC eg. that a causal relationship has not been established, that atypical femoral fractures occur in patients in patients who have not been treated with bisphosphonates, that no increased risk of atypical subtrochanteric fractures was noted in certain product-related clinical trials, changing the frequency to very rare, listing glucocorticoid as one of the risk factors, and also that updates are not necessary for those bisphosphonates such as clodronic acid and tiludronic acid, where atypical stress fractures have not been observed so far. These proposals were not considered to be acceptable by the CHMP.

The CHMP agreed on the following amendments to the SmPC and PL for all bisphosphonates:

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Section 4.8 Undesirable effects

During post-marketing experience the following reactions have been reported (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

Package Leaflet

Section 4. Possible side effects

Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.

The CHMP also agreed that for bisphosphonates indicated for osteoporosis, advice is included in 4.2 (Posology) of the SmPC, about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis.

The CHMP agreed on the following additional amendment to the SmPC for bisphosphonates indicated for osteoporosis:

Summary of Product Characteristics

Section 4.2 Posology and method of administration
The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Aclasta on an individual patient basis, particularly after 5 or more years of use.

3. Overall discussion and benefit/risk assessment

Safety

Having considered the overall submitted data, the CHMP concluded the available data suggests that atypical femoral fracture is likely to be a class effect of bisphosphonates.

At the present time there is little evidence from literature and spontaneous reports to support an association between bisphosphonates and atypical fracture at sites other than the femur. The potential risk of atypical fractures at sites other than the femur should be kept under review.

The MAH for Aclasta is requested update the Risk Management Plan to reflect "atypical femoral fractures" as a potential risk.

Taking into account all the available evidence, the CHMP agreed that a warning regarding the risk of atypical femoral fracture is added to the product information for all bisphosphonates in section 4.4 of the SmPC (Special warnings and precautions for use), and that atypical femoral fracture is added to section 4.8 (Undesirable effects) of the SmPC accompanied by a statement that this adverse effect is a class attribution of bisphosphonates.

Given the lack of evidence regarding the optimal duration of bisphosphonate treatment for osteoporosis, the CHMP also supports the view that advice should be added to the product information for bisphosphonates authorised for osteoporosis, about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis. The CHMP also agreed that this advice regarding the duration of bisphosphonate therapy for osteoporosis is included in section 4.2 of the SmPC.

Benefit/risk balance
The findings of this review do not change the overall balance of risks and benefits of Aclasta in its authorised indications, which remain favourable.

4. Overall conclusion

The CHMP recommended the amendment to the terms of the marketing authorisation for Aclasta for which the revised summary of product characteristics, annex II and package leaflet are set out respectively in annexes I, II and IIIB of the opinion.

The scientific conclusions and the grounds for the amendment of the SPC, Annex II, and package leaflet are set out in Annex IV of the opinion.

5. Communication plan

As part of this referral procedure, the CHMP agreed the wording of a Key Message document intended to inform healthcare professionals, professional and patient groups of the risk of atypical femoral fractures with the use of bisphosphonates, primarily in patients receiving long-term treatment for osteoporosis.

The National Competent Authorities will disseminate the Key Message document on 18 April 2011 to all healthcare professionals, professional and patient groups via national mechanisms (bulletins, websites) by the National Competent Authorities, as agreed in the parallel Article 31 referral procedure.

6. Conclusion and grounds for the recommendation

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Aclasta initiated by the European Commission.

- The Committee considered all the available data submitted (pre-clinical, clinical, epidemiological studies, post-marketing reports, published literature) in relation to the risk of atypical femoral fractures with biphosphonates.

- On the basis of the available evidence, mainly from epidemiological studies and post-marketing reports, the Committee concluded that use of bisphosphonates may be associated with the risk of atypical femoral fractures. The CHMP also concluded that main risk factor associated with these fractures appears to be long-term bisphosphonate treatment.

- The Committee concluded that the Product Information of all bisphopshonates should include a warning in section 4.4 on the risk of atypical fractures of the femur and this adverse reaction should also be listed in section 4.8 of the SPCs. The Committee also concluded that information should be added to section 4.2. of the product information for bisphosphonates authorised for osteoporosis, about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis.

The CHMP has recommended the variation of the Marketing Authorisations for Aclasta (see Annex A), for which the Summary of Product Characteristics and Package Leaflets are set out in Annex I and IIIB and subject to the conditions set out in Annex II of this Opinion.