Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics and package leaflets presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of Bisphosphonate-containing medicinal products (see Annex I)

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.

Following a Pharmacovigilance Working Party (PhVWP) review in 2008, it was concluded that a warning about atypical stress fractures of the proximal femoral shaft would be added to the product information for alendronic acid containing medicinal products across Europe. This issue was considered again by the PhVWP in April 2010, as cases had been reported in association with other bisphosphonates, supporting the view that atypical stress fractures are a class effect of bisphosphonates.

Further to the PhVWP discussions and the emerging data from published literature and post-marketing reports that suggest that atypical stress fractures may be a class effect of bisphosphonates, the UK asked the CHMP in September 2010, to provide an opinion under Article 31 of directive 2001/83 EEC, as amended on whether the Marketing Authorisations for medicinal products containing bisphosphonates should be maintained, varied, suspended or withdrawn.

The CHMP reviewed the available data from non-clinical and histological studies, relevant clinical trials, epidemiological studies, post-marketing reports and published literature.

Non-clinical data

Although pre-clinical studies have provided limited information on the risk of atypical fractures with bisphosphonates, some of them 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]).

Definition of atypical fracture of the femur

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.

[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

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 data presented at the October meeting of the ASBMR (Nitche et al, 2010[5]), the CHMP for the purpose of its assessment agreed on a modified case definition that lists 'noncomminuted' as a minor feature rather than a major feature of atypical femur femoral fracture.

Mechanism of atypical fractures

The mechanism(s) for the development of atypical fractures in patients taking bisphosphonates is not known. However 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.

Epidemiological studies

While some epidemiology studies suggest that subtrochanteric and femoral shaft fractures may be normal osteoporotic fractures (Abrahamsen et al, 2009[6], Abrahamsen, 2010[7], Vestergaard et al, 2010[8]) other studies suggest that long-term bisphosphonate use may increase the risk of subtrochanteric and femoral shaft fractures (Park-Wyllie et al, 2011[9], Wang & Bhattacharyya, 2011[10]). However these studies do not specifically relate to atypical fracture of the femur as they do not contain information about radiographic fracture pattern.

Evidence from studies that do provide specific information about atypical femoral fractures identified from radiographs suggests that these fractures may be causally related to bisphosphonate use. Case-control studies have reported a significant association between atypical femur fracture pattern and bisphosphonate use (Lenart et al, 2009[11], Isaacs et al, 2010[12]). Other studies with radiographic evidence have also reported an increased incidence of atypical femoral fractures in patients treated with bisphosphonates compared to non-exposed patients, which may increase with duration of bisphosphonate treatment (Dell et al, 2010[13], Schilcher et al, 2009[14]).

---

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

[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

[6] **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

[7] **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

[8] **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

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

[10] **Wang Z & Bhattacharyya** T Trends in Incidence of Subtrochanteric Fragility Fractures and Bisphosphonate Use Among the US Elderly, 1996–2007. J Bone Miner Res 2011; DOI 10.1002/jbmr.233

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

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

[13] **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

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

Post-marketing reports

The number of post-marketing reports of possible atypical femur fracture suspected to be associated with bisphosphonates has increased since the 2008 PhVWP review. Although the highest number of possible atypical femoral fracture 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), suggesting that these fractures may be a class effect of bisphosphonates. The lack of reports with the remaining bisphosphonates, clodronic acid, neridronic acid and tiludronic acid may be related to the lower exposure of these medicinal products 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 lack of evidence may be due to a lack of recognition and reporting of atypical fractures at sites other than the femur with bisphosphonate use or it is possible that the unique characteristics of the femur as the major weight bearing bone in the body mean that atypical fractures only occur at this site. The potential risk of atypical fractures at sites other than the femur will be kept under review.

Risk factors

A number of possible risk factors have been proposed for atypical femoral fractures in association with bisphosphonate use. The long-term use of bisphosphonates is thought to be the main risk factor for atypical femoral fractures. However, 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. Glucocorticoids and proton pumps inhibitor (PPI) have been identified as possible important risk factors for atypical femur fracture. Concomitant treatment with other anti-resorptive drugs such as hormone replacement therapy and raloxifene have also been proposed as possible risk factors. Other than osteoporosis the most prevalent co-morbid conditions in patients with atypical femur fracture were found to be chronic obstructive pulmonary disease or asthma, rheumatoid arthritis and diabetes.

Overall conclusion

Taking into account all the available evidence, the CHMP concluded that use of biphosphonates can be associated with the risk of atypical femoral fractures and therefore recommended that the following information is included in the Product Information of all biphosphonates:

- Addition of a warning in section 4.4 of the SmPC (Special warnings and precautions for use) to reflect this risk , the main features of these fractures and the potential need for discontinuation of treatment in case a fracture is suspected.
- Addition of atypical femoral fracture to section 4.8 (Undesirable effects) of the SmPC accompanied by a statement that this adverse effect is a class attribution of all bisphosphonates.

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.

The CHMP concluded that the findings of this review do not change the overall balance of risks and benefits of individual bisphosphonates in their authorised indications.

Grounds for amendment of the summaries of product characteristics and package leaflets

Whereas

- The Committee considered the referral made under Article 31 of Directive 2001/83/EC, as amended for biphosphonates containing medicines;

- 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.

In view of the above, the CHMP has recommended the variation to the terms of the Marketing Authorisations for Bisphosphonate-containing medicinal products (see Annex I), for which the relevant sections of the Summary of Product Characteristics and Package Leaflets are set out in Annex III and subject to the conditions set out in Annex IV of this Opinion.