European Medicines Agency

London, 19 February 2009
EMEA/CHMP/188952/2009

ASSESSMENT REPORT
FOR

Fosavance

International Nonproprietary Name:
alendronate sodium / colecalciferol

Procedure No. EMEA/H/C/000619/II/0010

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Introduction

Fosavance is a combination of alendronate and colecalciferol (vitamin D3) developed for treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency. It is presented as a fixed combination tablet containing 70 mg alendronic acid (as alendronate sodium trihydrate) and 70 or 140 micrograms (2800 IU or 5600 IU) colecalciferol, which is intended as a once weekly treatment.

Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected.

The combination of alendronate/colecalciferol ensures in a one tablet a week regimen a level of vitamin D supplementation, which would help to provide a background of adequate vitamin D status upon which alendronate can act.

The Pharmacovigilance Working Party (PhVWP) of the CHMP initiated a class review on bisphosphonates and atypical stress fractures in July 2008 following literature reports of stress fractures and a label change requested by the Australian authorities. A List of Questions was issued to MAHs requesting further information about published literature, pre-clinical studies, clinical trials, post-marketing reports, planned studies, possible mechanisms and proposed risk minimisation activities. The MAHs' responses were reviewed at the December 2008 meeting of the PhVWP. The CHMP recommended after having revieved the available data that information about atypical stress fractures should be added to the product information for medicinal products containing alendronic acid and proposed a wording. The CHMP agreed with the MAH of Fosavance to update the Product Information to include information on atypical stress fractures.

Clinical aspects

Background

The Australian Therapeutic Goods Administration (TGA) had conducted a mandatory label change for alendronic acid/ alendronic acid colecalciferol to include a warning about the possible risk of stress fractures in association with alendronic acid. Recent literature reports also discussed stress fractures in association with alendronic acid by *Neviaser et al 2008 and Kwek et al. 2008.*

The PhVWP initiated a class review of bisphosphonates and atypical stress fractures in July 2008. A List of Questions was issued to MAHs of bisphosphonates containing medicinal products requesting further information about published literature, pre-clinical studies, clinical trials, post-marketing reports, planned studies, possible mechanisms and proposed risk minimisation activities.

Analysis of data submitted

The majority of literature reports of stress fractures after the use of bisphosphonates were in association with alendronic acid (5 case series and 6 individual case reports). The most common site of stress fracture reported was the femur ('femoral shaft', 'subtrochanteric femur' and 'proximal femoral diaphysis) often occurring after minimal or no trauma. The duration of alendronic acid therapy in the majority of these reports ranged from 18 months to 10 years. Common characteristics were the presence of prodromal pain in the affected limb in the weeks or months prior to sustaining a complete fracture. A bilateral tendency of stress fractures was also observed. Some of the literature reports suggested that continuing alendronic acid treatment may delay or prevent healing of this fracture.

Published animal studies have demonstrated that alendronic acid may be associated with microdamage, decreased repair and impaired healing in bone.

Overall the number of reports of stress fracture was low in clinical trials with bisphosphonates and some cases were confounded by underlying disease or concomitant treatment. The MAH stated in the responses received during the class-review that the number of post-marketing reports of stress fractures in association with alendronic acid was 115 (84 of which involving the femur) and included a large number of the literature cases.

In addition there is clinical evidence that alendronic acid may increase microdamage accumulation in low bone mineral density patients following long-term treatment (*Stephan et al 2007*). *Odvina et al 2005* proposed that increased bone microdamage accumulation and the subsequent increased risk of non-spinal fractures with prolonged alendronic acid use may be related to severe suppression of bone turnover. These authors also suggest that severe suppression of bone turnover by alendronic acid may result in increased bone mineralization causing the bone to become more brittle. Other possible mechanisms for stress fractures in association with prolonged bisphosphonate use include microfractures, outdated collagen and inadequate mineralisation *(Lenart et al 2008*).

Discussion and conclusion

Osteoporosis is considered to be the main risk factor for stress fractures in the older population. Other risk factors listed in the literature include fluoride treatment, osteopenia, rheumatoid arthritis, corticosteroid and oestrogen use, radiation therapy, renal osteodystrophy, osteomalacia, Paget's disease, hyperparathyroidism, hyperthyroidism, joint arthroplasty, lumbosacral fusion, diabetes mellitus and fibrous dysplasia. Additional risk factors may include low bone mass, vitamin D deficiency, single unusually large loading events, exercise and malabsorption. Stress fractures in patients receiving bisphosphonates for malignancy may be confounded by underlying disease and concomitant treatment.

Overall, the data for alendronic acid however support an association between atypical stress fractures and long-term use of alendronic acid due to the specific and distinct fracture pattern with unicortical beak, bilaterality, prodromal pain and poor healing of fracture. A biologically plausible mechanism has also been suggested, with suppression of bone turnover leading to increased mineralisation causing bone to become more brittle.

The CHMP further highlighted the uncertainty of a class effect for the other bisphosphonates. Therefore, unnecessary and inappropriate switching of bisphosphonates should be avoided at this point in time.

Conclusions and Benefit / Risk Assessment

Overall, the inclusion of the warning on atypical stress fractures reflects the current state of knowledge of this adverse event after long-term use of alendronate and gives guidance to physician and patients to detect early signs of the condition. The benefit/risk balance of alendronate continues to be favourable.

Changes to the Product Information

The detailed changes can be found in the final approved highlighted SPC/ PL attached to this report.

Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were agreed and subsequently implemented by the MAH.

The MAH requested a number of changes to the wording initially requested by the CHMP. However, the final wording was in line with the initially requested wording, with the exception that the CHMP agreed to add that the time to onset ranged from 18 months to 10 years in the majority of cases and to include information on imaging features of stress fractures weeks to months before a femoral fracture.

In addition, the MAH took this opportunity to correct the German annexes by updating the outer Labelling section particulars to appear on the immediate packaging, method and route(s) of administration, and section 5 of the Package Leaflet.

Conclusion

On 19 February 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.