HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

21 July 2010

Review of the dossier of the medicinal products included on the list of reimbursable medicines for a period of 5 years from 24 May 2005 (Journal Officiel, 28 April 2005)

FOSAMAX 10 mg, tablet
B/28 (CIP code: 340 673-1)
B/84 (CIP code: 372 282-1)

FOSAMAX 70 mg, tablet
B/4 (CIP code: 359 563-7)
B/12 (CIP code: 359 566-6)

Applicant: MERCK SHARP & DOHME-CHIBRET

alendronate monosodium trihydrate
ATC code: M05BA04

List I

Dates of Marketing Authorisations:
6 June 1996 (national) - 10 mg tablet
17 June 2002 (mutual recognition procedure) - 70 mg tablet

Last revision of the Marketing Authorisation: 17 September 2009

Reason for request: Renewal of inclusion on the list of medicinal products reimbursable by National Health Insurance.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Alendronate monosodium trihydrate

1.2. Indications

FOSAMAX 10 mg, tablet
"Treatment of postmenopausal osteoporosis. FOSAMAX reduces the risk of vertebral and hip fractures.
Treatment of osteoporosis in men."

FOSAMAX 70 mg, tablet
"Treatment of postmenopausal osteoporosis. FOSAMAX reduces the risk of vertebral and hip fractures."

1.3. Dosage

See the SPC**.**

2 UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION (5 July 2006)

2.1. Efficacy

The company has supplied new clinical data in the indication post-menopausal osteoporosis[1,2,3]. These are primarily efficacy data in terms of increase in bone mineral density (surrogate endpoint). These new efficacy data are insufficient for any change to the conclusions of the last transparency Committee opinion.

2.2. Adverse effects

Analysis of pharmacovigilance data covering the period from 16 January 2005 to 15 July 2009 brought to light 17,222 cases of which 5079 were serious. The SPC has been updated to include the risk of osteonecrosis of the jaw (ONJ), stress fractures and the new adverse effects "blackouts, dizziness, asthenia, peripheral oedema and alopecia".
Alendronic acid, in common with all bisphosphonates, has been the subject of three tolerance re-assessments by the EMA:

- osteonecrosis of the jaw
- stress fracture
- atrial fibrillation

[1] Miller et al. Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. Curr. Med. Res. Opin. 2008; 24: 207-213.
[2] Reid et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-International. J. Clin. Pract. 2008; 62 (4): 575-584.
[3] Recke et al. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. Bone 2007; 40: 843-885.

Osteonecrosis of the jaw[4] (mandibular and/or maxillary):
Following the first re-assessment of the class of bisphosphonates in respect of osteonecrosis of the jaw by the EMEA in 2005, the SPC of FOSAMAX, in common with that of all medicinal products of this class, was revised (in 2006 and 2008 for the 70 mg and in 2006 and 2009 for the 10 mg dose strength) to include under "Special warnings and precautions for use" the risk of ONJ secondary to infections or dental extractions.
Despite the changes to the SPCs of bisphosphonates, cases of ONJ have continued to be reported. The EMEA consequently undertook a second re-assessment in December 2007, the conclusions of which were published in September 2009[5].
This analysis revealed that the risk of ONJ is significantly greater in patients treated with IV bisphosphonates as cancer chemotherapy (incidence 0.8-12%) than in those treated orally for osteoporosis or Paget's disease (incidence 0.0004-0.06%). The risk of ONJ with oral bisphosphonates seems low.
Since the risk factors are many and not yet fully elucidated, the CHMP would like a more in-depth assessment of the risk of ONJ through the creation of a European register and the performance of clinical studies.

The transparency Committee draws attention to the recommendations on the oral and dental care of patients treated with bisphosphonates[6]: "in patients who are to be treated with bisphosphonates for osteoporosis or Paget's disease, it is recommended to carry out an initial oral and dental assessment, followed by any necessary dental treatment. An annual oral and dental checkup is recommended. Based on the currently available data, use of bisphosphonates in osteoporosis cannot be considered a contraindication for the placement of a dental implant."

Stress fracture (or fractures due to bone weakness)
The re-assessment of bisphosphonates in respect of stress fracture was prompted by the publication of articles indicating a possible link between treatment with alendronic acid and the occurrence of stress facture; this may be associated with an excessive increase in bone metabolism after long-term treatment with alendronic acid. Because of the proposed mechanism, a "class effect" could not be ruled out. The EMA consequently carried out a re-assessment of the class as a whole in 2008[7].
The EMA pharmacovigilance working group concluded that:

- stress fractures of the proximal femoral shaft were associated with long-term treatment with alendronic acid. These fractures have occurred after minimal or no trauma;
- the available data have not demonstrated an increase in the risk of stress fractures with bisphosphonates other than alendronic acid;
- although analysis of the literature had shown that the majority of cases concerned alendronic acid, there is uncertainty about a possible "class effect", given that there are only limited long-term data for other bisphosphonates.

Changes have therefore been made to the SPC of FOSAMAX 70 mg (17/09/2009) to include cases of stress fracture and an epidemiological study has been proposed to estimate their incidence:

Special warnings "Stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (time to

[4] Osteonecrosis of the jaw is defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region.
[5] EMA. CHMP Assessment report on bisphosphonates and osteonecrosis of the jaw. 24/09/2009.
[6] AFSSAPS. Letter to healthcare professionals. Recommendations on the oral and dental care of patients treated with bisphosphonates. 18/12/2007
[7] MHRA. Bisphosphonates and stress fractures. January 2009.

onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were 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 was also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending assessment of the patient, based on an individual benefit risk assessment."

Note: The SPC of the 10 mg tablet has not been amended to take account of this risk (SPC last updated: 04/08/2009).

Atrial fibrillation (AF):
In June 2008, the EMA pharmacovigilance working group re-evaluated the benefits/risk relationship of bisphosphonates in respect of the risk of AF[8]. This re-assessment of the class was prompted by the identification of an increase in the incidence of AF relative to placebo in patients treated with zoledronic acid in the HORIZON study and in those treated with alendronic acid in the FIT study.
The working group concluded that:
- the benefits/risk relationship remained favourable for the entire class;
- the risk of developing AF seemed higher with certain bisphosphonates, for biochemical reasons;
- the data obtained from clinical studies indicated increased risk for zoledronic acid and, in the case of data from extension phases, for alendronic acid and pamidronic acid.

No change has been made to the SPC of FOSAMAX, but the company has been asked to provide additional data.

3 USAGE DATA

Prescription data:
According to the IMS-DOREMA panel, there have been 280,000 prescriptions for FOSAMAX 70 mg and 10,000 for FOSAMAX 10 mg based on the moving annual total to August 2009.

[8] EMA post-authorisation evaluation of medicines for human use. Updated overall assessment report of responses to agency request for information on bisphosphonates and the potential risk of atrial fibrillation-zoledronic acid-2008

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Re-assessment of actual benefit:
Osteoporosis is a serious disorder because of the risk of fractures. In particular, fractures of the femoral neck can be life-threatening.
FOSAMAX is a preventive treatment for osteoporotic fractures. Its efficacy has been demonstrated in the prevention of vertebral and peripheral fractures, including femoral neck fractures.
In the light of the new tolerance data, the transparency Committee considers that the efficacy/adverse effects ratio of the medicinal product FOSAMAX, like that of all products of the bisphosphonates class, is moderate.
These medicinal products are first line therapies.
Alternative medicinal products exist.
The actual medical benefit of these medicinal products remains substantial.

4.2. Transparency Committee recommendations
The transparency Committee recommends maintaining inclusion on the list of medicines refundable by National Health Insurance at the dosage of the marketing authorisation and only in the therapeutic indications qualifying for reimbursement:

FOSAMAX 10 mg:
- Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures :
  - in patients with a fracture caused by bone fragility,
  - in the absence of a fracture, in women with a substantial reduction in bone mineral density (T-score < -3) or with a T-score ≤ -2.5 associated with other risk factors for fractures, in particular age > 60 years, current or past systemic corticosteroid therapy at a dosage ≥ 7.5 mg/day prednisone equivalent, a body mass index < 19 kg/m², a history of femoral neck fracture in a first-degree relative (mother), early menopause (before the age of 40 years).

- Treatment of osteoporosis in men.

FOSAMAX 70 mg:
- Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures :
  - in patients with a fracture caused by bone fragility,
  - in the absence of a fracture, in women with a substantial reduction in bone mineral density (T-score < -3) or with a T-score ≤ -2.5 associated with other risk factors for fractures, in particular age > 60 years, current or past systemic corticosteroid therapy at a dosage ≥ 7.5 mg/day prednisone equivalent, a body mass index < 19 kg/m², a history of femoral neck fracture in a first-degree relative (mother), early menopause (before the age of 40 years).

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%