HAUTE AUTORITÉ DE SANTÉ

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**TRANSPARENCY COMMITTEE**

OPINION

21 July 2010

Examination of the dossier for the medicinal product included on the list for a period of 5 years by the order of 4 October 2004 (Official Gazette of 28 October 2004)

**BONDRONAT 6 mg concentrate for solution for infusion**
**B/1 (CIP code: 363 485.7)**

**Applicant: ROCHE**

ibandronic acid
ATC code: M05BA06

Medicine requiring special monitoring during treatment.
List I

Date of Marketing Authorisation: October the 31th 2003 (centralised procedure)

Reason for request: Renewal of inclusion on the list of medicines refundable by National Health Insurance.

Medical, Economic and Public Health Assessment Division

## 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Ibandronic acid

### 1.2. Indications

- "Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
- Treatment of tumour-induced hypercalcaemia with or without metastases. (not reimbursable)"

Note:
To recap, the actual benefit of BONDRONAT 6 mg had been described as insufficient in the indication hypercalcaemia of malignancy as the 6 mg dosage is not appropriate for this indication as stated in the SPC. In the clinical studies, the high dosage of 6 mg had not been shown to provide any additional benefit in terms of efficacy relative to the 4 and 2 mg dosages.

### 1.3. Dosage

See SPC.

Since its inclusion on the list of medicines refundable in 2004, the time infusion has been reduced from 1 h to at least 15 min solely in patients with normal renal function or mild renal impairment on the basis of a phase II tolerance study and a pharmacokinetics study (marketing authorisation revision of 06.03.2007).

## 2 UPDATE OF AVAILABLE DATA SINCE THE PREVIOUS OPINION (June 2nd 2004)

### 2.1. Efficacy

A Cochrane meta-analysis published in 2005[1] aimed to evaluate the effect of bisphosphonates on skeletal events, bone pain, quality of life, and survival in women with breast cancer of any stage. Only 9 of the 21 included studies related to the population of the indication (breast cancer with bone metastases). Consequently, the results of this meta-analysis will not be taken into account.

### 2.2. Adverse effects

A phase II, open, randomised study (unpublished) compared the tolerance of BONDRONAT 6 mg administered in a 15 min infusion (n = 102) with that of BONDRONAT 6 mg administered in a 1 h infusion (n = 28) in 130 breast cancer patients with bone metastases over a period of 6 months. No differences in renal function parameters were observed.

1 Pavlakis et al. Bisphosphonates for breast cancer. Cochrane Database of systematic reviews 2005. Issue 3

The adverse effects reported in the two groups were comparable. The 15 min duration of infusion was not investigated in the cancer patients with creatinine clearance < 50 ml/min.

Pharmacovigilance data

Analysis of the world pharmacovigilance data for ibandronic acid (all forms and all indications together - osteoporosis and oncology) covering the period from January 1st 2004 to December 31th 2008 showed 6438 reported cases; 2193 cases were serious and 305 of these were fatal. The most often adverse effects reported were: "musculoskeletal disorders", in particular arthralgia, myalgia, and bone pain, "general disorders and administration site conditions", and gastrointestinal disorders.

Ibandronic acid, in common with all bisphosphonates, has been the subject of three tolerance re-assessments by the EMA:

- osteonecrosis of the jaw (ONJ)
- stress fracture
- atrial fibrillation

Osteonecrosis of the jaw[2] (mandibular and/or maxillary):

Following the first re-assessment of the bisphosphonates class in respect of ONJ by the EMEA in 2005, the SPC of all medicinal products of this class, was revised to include warnings and precautions for use in respect of the risk of ONJ in cases of infection or dental extraction.

Despite the changes to the bisphosphonates SPCs of, ONJ cases 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[3].

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[4]: "in patients who are to be treated with bisphosphonates for osteoporosis or Paget's disease, it is recommended that an initial oral and dental assessment, followed by any necessary dental treatment, be carried out. An annual oral and dental check-up is recommended. On the basis of the current available data, use of bisphosphonates in osteoporosis cannot be considered a contraindication for the placement of a dental implant."

The frequency of spontaneous reporting of ONJ in cancer patients treated with ibandronic acid was 4.39 per 100,000 patients. No additional change was made to the SPC, in which the risk of ONJ was already mentioned.

2 Osteonecrosis of the jaw is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a healthcare professional in a patient who is receiving or has received bisphosphonates and has not had radiation therapy to the craniofacial region.

3 EMA. CHMP Assessment report on bisphosphonates and osteonecrosis of the jaw. 24/09/2009.

4 AFSSAPS. Letter to healthcare professionals. Recommendations on the oral and dental care of patients treated with bisphosphonates. 18/12/2007

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 fracture; this may be associated with an excessive increase in bone metabolism after long-term treatment with alendronic acid. Because of the mechanism mentioned, a "class effect" could not be ruled out. The EMA consequently carried out a re-assessment of the class as a whole in 2008[5].
The EMA pharmacovigilance working group concluded that:

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

For BONDRONAT, monitoring of the stress fracture cases was recommended with the addition of a specific analysis in the PSURs but the SPC was not modified.

Atrial fibrillation (AF):
In June 2008, the EMA pharmacovigilance working group re-assessed the benefit/risk ratio for bisphosphonates in respect of the risk of AF[6.] This class re-assessment 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 benefit/risk ratio remained favourable for the entire class;
- the risk of developing AF seemed higher with certain bisphosphonates, for biochemical reasons;
- the data obtained from the clinical studies indicated an increased risk with zoledronic acid and the data from the extension phases indicated an increased risk with alendronic acid and pamidronic acid.

All in all, no increase in the risk of AF has been identified for ibandronic acid.

## 3 USAGE DATA

This medicinal product does not appear in the available prescription panels (EPPM IMS DOREMA). The table below shows the number of packs sold in retail market and in hospital according to GERS.

Total number of boxes of BONDRONAT sold in the community and in hospital.

| | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|
| ° In retail market | 93 | 972 | 3672 | 3617 | 2661 |
| ° In hospital | 20 | 410 | 1074 | 882 | 790 |

5 MHRA. Bisphosphonates and stress fractures. January 2009.
6 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:

Treatment of tumour-induced hypercalcaemia
Given that the 6 mg dosage is not appropriate for this indication as stated in the SPC, and in the absence of data provided by the company, the actual benefit of BONDRONAT 6 mg concentrate for solution for infusion in this indication remains insufficient.

Prevention of bone complications in patients with breast cancer and bone metastases
Bone complications of malignant origin are serious disorders which can be life-threatening.
In the light of the new tolerance data, the transparency Committee considers that the efficacy/adverse effects ratio of the medicinal product BONDRONAT, like that of all medicinal products of the bisphosphonates class, is moderate.
This medicinal product is a first-line therapy.
There are treatment alternatives.
The actual benefit of BONDRONAT 6 mg concentrate for solution for infusion in this indication remains substantial in the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

4.2. Transparency Committee recommendations

The transparency Committee recommends maintaining inclusion on the list of medicines refundable by National Health Insurance in the refundable indication: “Prevention of bone complications in patients with breast cancer and bone metastases”.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%