HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

21 July 2010

CLASTOBAN 300/5 ml, ampoule
B/5 (CIP code: 354 232-2)

Applicant: BAYER SANTE

clodronate disodium tetrahydrate
ATC code: M05BA02

Injectable form: Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation: 10 July 1989 for the 300 mg/5 ml (national)

Reason for request: Review of actual benefit in accordance with article R. 163-21 of the Social Security Code.

Medical, Economic and Public Health Assessment Division

CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Clodronate disodium tetrahydrate

1.2. Indications

"Initial treatment of severe hypercalcaemia of malignant origin. Treatment must be given alongside optimal rehydration. The duration of treatment is limited to the time needed for blood calcium to normalise."

1.3. Dosage

see SPC

2 UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION (4 October 2006)

2.1. Efficacy

The company has not supplied any new efficacy data.

2.2. Adverse effects

Clodronic 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[1] (mandibular and/or maxillary):
Following the first re-assessment of the class of bisphosphonates in respect of ONJ by the EMA in 2005, the SPCs of most bisphosphonates were revised 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 EMA consequently undertook a second re-assessment in December 2007, the conclusions of which were published in September 2009[2].
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.

[1] 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 professional, in a patient who was receiving or had been exposed to bisphosphonates and had not had radiation therapy to the craniofacial region.
[2] EMA. CHMP Assessment report on bisphosphonates and osteonecrosis of the jaw. 24/09/2009.

For clodronic acid more specifically, analysis of the available literature and clinical trials identified 25 reported cases between 2006 and 2008. In two-thirds of cases, patients had been treated with other bisphosphonates and 10 out of 25 patients had had dental surgery.
Special warnings and precautions for use were added to the SPC in 2009 for the 300 mg (injectable) and 400 mg (oral) dosages and in 2010 for the 800 mg dosage (oral).

"Osteonecrosis of the jaw, generally associated with a dental extraction and/or local infection (including osteomyelitis) has been reported in cancer patients receiving treatment with bisphosphonates administered in the majority of cases intravenously. A large number of these patients had also been undergoing chemotherapy and treatment with corticoids. Osteonecrosis of the jaw has also been reported in patients treated for osteoporosis who were taking oral bisphosphonates.
A dental examination and appropriate preventive dental care must be considered before treatment with bisphosphonates in patients with concomitant risk factors (for example: cancer, chemotherapy, radiotherapy, corticoids, poor oral and dental hygiene).
Such patients must, where possible, avoid invasive dental procedures during treatment. Dental surgery can aggravate the condition of patients developing osteonecrosis of the jaw during treatment with bisphosphonates. For patients requiring dental procedures, there are no available data suggesting that stopping bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.
The exact course of action to be followed for each patient is guided by the clinical judgement of the treating doctor, based on an individual benefit/risk ratio."

The transparency Committee draws attention to the recommendations on the oral and dental care of patients treated with bisphosphonates[3]: "patients who are to be treated with bisphosphonates for malignant disease must always undergo a dental and radiological assessment. Thereafter, oral/dental follow-up every four months is recommended. It is also recommended to avoid all traumatising dental procedures (extraction, surgical parodontal treatment) during treatment with bisphosphonates and to proscribe the use of implants in such patients."

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 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[4].
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 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.

There are no reported cases in the literature of stress fracture with clodronic acid. In clinical studies, a small number of stress fractures were seen with both clodronic acid and placebo.

[3] AFSSAPS. Letter to healthcare professionals. Recommendations on the oral and dental care of patients treated with bisphosphonates. 18/12/2007
[4] MHRA. Bisphosphonates and stress fractures. January 2009.

These cases occurred in patients treated for osteoporosis (off-label). Further data are necessary in order to draw any conclusions. Surveillance of stress fracture cases was recommended as well as inclusion of a specific analysis in the PSUR[5], but with no changes made to the SPC.

Atrial fibrillation (AF):
In June 2008, the EMA pharmacovigilance working group re-evaluated the benefits/risk ratio of bisphosphonates in respect of the risk of AF[6]. 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 cases of AF have been identified with clodronic acid.

Other adverse effects (renal impairment):

In 2007, a fatal case of acute renal failure that developed after 22 months of treatment with CLASTOBAN was reported in a patient co-treated with thalidomide for multiple myeloma. Between 1 March and 31 October 2009, 3 fatal cases of renal failure were reported in patients treated with oral CLASTOBAN (breast cancer with bone metastases, multiple myeloma, renal cell carcinoma) plus 1 case with the injectable dosage form.
The “Undesirable effects” section of the SPC has been revised for all dosages. “Rare: Renal impairment (elevations in serum creatinine and proteinuria) and serious kidney lesions, particularly after rapid intravenous infusion of high doses of clodronate. Isolated cases of renal impairment and rare cases with a fatal outcome have been reported, particularly with concomitant use of NSAIDs.”

For the injectable form, special warnings and special precautions for use were also added to take account of this risk:
- “Serious kidney damage has been reported after rapid intravenous administration of doses higher than recommended.
- Renal function and blood calcium must be regularly monitored before and during treatment.”

[5] Periodic Pharmacovigilence Report
[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

3 USAGE DATA

These products do not appear in the available prescription panels (EPPM IMS DOREMA). The table below shows the number of packs sold in retail pharmacies and hospitals according to GERS [French association for the study and performance of statistics].

Total number of units (ampoules, capsules or tablets) of CLASTOBAN sold in hospitals

	UN 2005	UN 2006	UN 2007	UN 2008	UN 2009	UN 03/2010 CM12
CLASTOBAN 300 mg inj.	3475	2625	2890	2050	2080	2160
Oral forms CLASTOBAN 400 mg and 800 mg	192,360	229,860	262,380	274,920	247,080	234,900
Total CLASTOBAN	195,835	232,485	265,270	276,970	249,160	237,060

Total number of packs of CLASTOBAN sold in pharmacies

	UN 2005	UN 2006	UN 2007	UN 2008	UN 2009	UN 03/2010 CM12
CLASTOBAN 400 mg	35,731	26,168	21,013	16,692	13,189	12,634
CLASTOBAN 800 mg	17,079	28,558	42,902	50,879	51,717	51,891
Total CLASTOBAN	52,810	54,726	63,915	67,571	64,906	64,525

4 TRANSPARENCY COMMITTEE CONCLUSIONS

The clinical conditions relating to this product are serious and can be life-threatening.

In the light of the new tolerance data, the Transparency Committee considers that the efficacy/
adverse effects ratio of CLASTOBAN 300 mg/5 ml, like that of all products of the bisphosphonates class, is moderate.

This product is a first-line medicinal product for use in symptomatic treatment.

Alternative medicinal products exist.

The transparency Committee considers that the actual benefit provided by this product remains substantial.