The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 July 2010

Review of the dossier of the proprietary products included on the list of reimbursable medicines for a period of 5 years from 8 March 2006 (Official Gazette, 3 August 2007)

CLASTOBAN 400 mg, capsule
B/60 (CIP code: 333 317-9)

CLASTOBAN 800 mg, film-coated tablets
B/60 (CIP code: 362 066-0)

Applicant: BAYER SANTE

clodronate disodium tetrahydrate
ATC code: M05BA02

Date of Marketing Authorisation: 10 July 1989 for the 400 mg and 2 July 2003 for the 800 mg (national procedure)

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

Medical, Economic and Public Health Assessment Division
### CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. **Active ingredient**  
Clodronate disodium tetrahydrate

1.2. **Indications**  
- Palliative treatment of osteolysis of malignant origin with or without hypercalcaemia, as adjuvant to specific treatment of the tumour.  
- Treatment of malignant hypercalcaemia in place of the injectable form. If hypercalcaemia is present, treatment must be given alongside optimal rehydration.

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.

For clodronic acid more specifically, analysis of the available literature and clinical studies 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.

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\(^1\) 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.
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: "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.

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 reported 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. 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

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3 AFSSAPS. Letter to healthcare professionals. Recommendations on the oral and dental care of patients treated with bisphosphonates. 18/12/2007
recommended as well as inclusion of a specific analysis in the PSUR\textsuperscript{5}, but with no changes made to the SPC.

**Atrial fibrillation (AF):**

In June 2008, the EMA pharmacovigilance working group re-evaluated the benefit/risk ratio of bisphosphonates in respect of the risk of AF\textsuperscript{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 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 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 levels) 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.”

\textsuperscript{5} Periodic Safety Update Report
\textsuperscript{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 proprietary 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

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

Total number of packs of CLASTOBAN sold in retail pharmacies

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

Reassessment of actual benefit:

The clinical conditions relating to these proprietary products are serious and can be life-threatening.

In the light of the available tolerance data, the transparency Committee considers that the efficacy/adverse effects ratio of the proprietary products CLASTOBAN 400 and 800 mg tablets, like that of all products of the bisphosphonates class, is moderate.

The role of oral bisphosphonates, including CLASTOBAN 400 and 800 mg tablets, is limited in the treatment of malignant hypercalcaemia.

Alternative medicinal products exist.

The transparency Committee considers that the actual benefit of CLASTOBAN remains substantial in all its indications.
Transparency Committee recommendations

The transparency Committee recommends maintaining inclusion on the list of medicines refundable by National Health Insurance in the indications and at the dosage in the Marketing Authorisation:

Packaging: appropriate for the prescription conditions.

Reimbursement rate: 65%