HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 July 2010

Review of the dossier of the proprietary drug included on the list of refundable products for a period of 5 years as from 2 February 2005 (Official Gazette of 3 November 2005)

LYTOS 520 mg, film-coated tablet
B/30 (CIP code: 340 424 -1)

Applicant: ROCHE

sodium tetrahydrate clodronate
ATC code: M05BA02

List I

Date of Marketing Authorisation (national): 22 February 1996

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

sodium tetrahydrate clodronate

1.2. Indications

" - Palliative treatment of osteolytic lesions of malignant origin, with or without hypercalcaemia, in addition to specific treatment of the tumour.
- Treatment of malignant hypercalcaemia as a temporary alternative to the injected form.

Treatment must be combined with optimum rehydration in the case of patients suffering from hypercalcaemia."

1.3. Dosage:

see SPC

2 UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION (22 June 2005)

2.1. Efficacy

The pharmaceutical company has not submitted any new efficacy data.

2.2. Tolerance

Like all bisphosphonates, clodronic acid has been reviewed by the EMA for tolerance when used in three indications:

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

Osteonecrosis of the jaw[1](mandible and/or maxilla):
Following the first review of bisphosphonates in connection with ONJ by the EMA in 2005, reports of osteonecrosis of the jaw continued to be submitted. The EMA therefore launched a second review in December 2007, the findings of which were published in September 2009[2]. This analysis found that patients being treated for cancer with IV bisphosphonates were at much greater risk of ONJ (incidence ranging from 0.8 to 12%) than patients undergoing oral treatment for osteoporosis or Paget's disease (incidence ranging from 0.0004 to 0.06%). Oral administration of bisphosphonates appears to be associated with a low risk of ONJ. As the risk factors involved are numerous and as yet not fully understood, the CHMP considers that a more detailed investigation of the risk of ONJ should be conducted via the creation of a European register and clinical studies.

[1] Osteonecrosis of the jaw is defined as exposure of a bony surface of the maxillofacial region which does not heal within eight weeks, observed by a healthcare professional in a patient who is undergoing or has undergone bisphosphonate treatment and who has not had radiotherapy of the craniofacial sphere.
[2] EMA. CHMP Assessment report on bisphosphonates and osteonecrosis of the jaw. 24/09/2009.

Analysis of global pharmacovigilance data covering the period from 1 July 2005 to 28 February 2009 found 20 cases of osteonecrosis of the jaw/ONJ[3] connected to clodronic acid. Twelve of these cases were reported in France. Although cases associated with clodronic acid have been described, the SPC for LYTOS does not refer to this risk (most recent update 06/08/2004).

The transparency Committee would like to remind healthcare professionals of the guidelines for the bucco-dental management of patients undergoing treatment with bisphosphonates[4]: "it is vital that patients requiring bisphosphonate treatment for a malignant pathology have a dental and radiological examination. A bucco-dental check-up should be carried out every four months thereafter. Healthcare professionals are also advised to avoid any traumatic dental treatment (extraction, parodontal surgery) while patients are undergoing bisphosphonate treatment, and these patients must not be given dental implants."

Stress fracture (or fractures caused by bone failure)

Bisphosphonates were reassessed in the context of stress fractures as a result of the publication of articles pointing to a possible link between treatment with alendronic acid and the occurrence of stress fractures, which might be associated with an excessive increase in bone metabolism following long-term treatment with alendronic acid. The mechanism thought to be involved meant that a "class effect" could not be ruled out. The EMA therefore conducted a review of the entire class in 2008[5].

The EMA's pharmacovigilance working group concluded that:

- stress fractures of the proximal end of the femoral diaphysis were associated with long-term treatment with alendronic acid. These fractures occurred after minimal trauma or in the absence of trauma;
- the data available did not show bisphosphonates other than alendronic acid to be associated with a greater risk of stress fractures;
- although analysis of the literature showed that most reported cases involved alendronic acid, there is still some uncertainty as to the possibility of a "class effect" as little long-term data is available for the other bisphosphonates.

No reports of stress fractures in patients being treated with clodronic acid have been published. In clinical studies, a small number of stress fractures have been identified in patients being treated with either clodronic acid or placebo. Cases have been reported in patients being treated for osteoporosis (off-label use). Further data is needed before conclusions can be drawn. It has been recommended that cases of stress fracture should be monitored, with an additional specific analysis having been added to the PSURs, but the SPC has not been amended.

Atrial fibrillation (AF):

In June 2008 the EMA's pharmacovigilance working group reviewed the risk/benefit ratio of bisphosphonates in the context of the risk of AF[6]. This class review was carried out in response to the increase in the number of cases of AF compared to placebo that had been

[3] Osteonecrosis of the jaw is defined as exposure of a bony surface of the maxillofacial region which does not heal within eight weeks, observed by a healthcare professional in a patient who is undergoing or has undergone bisphosphonate treatment and who has not had radiotherapy of the craniofacial sphere.

[4] Afssaps. Letter to healthcare professionals. Guidelines for the bucco-dental management of patients undergoing bisphosphonate treatment. 18/12/2007

[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

observed among female patients taking part in the HORIZON study (zoledronic acid) and the FIT study (alendronic acid).
The working group concluded that:
- the benefit/risk ratio for the class as a whole was still favourable;
- the risk of experiencing AF appeared to be greater for some bisphosphonates for biochemical reasons;
- data obtained from clinical studies pointed to a greater risk for patients being treated with zoledronic acid, those being treated with alendronic acid in an extension phase, and those being treated with pamidronic acid.

No cases of AF have been observed with clodronic acid.

3 USAGE DATA

This proprietary drug does not appear on the prescription panels available (EPPM, IMS, DOREMA). The table below shows the number of packs sold in a primary care setting and in hospital (data from GERS, an association representing the pharmaceutical industry).

Total number of packs of LYTOS sold

	2005	2006	2007	2008	2009
° In a primary care setting	157,287	153,773	152,788	129,898	105,732
° In hospital	6,178	5,119	4,614	3,706	3,318

4 TRANSPARENCY COMMITTEE CONCLUSIONS

Reassessment of actual benefit

The medical conditions in question are serious and potentially life-threatening.

In the light of the tolerance data available, the transparency Committee is of the opinion that the efficacy/adverse effects ratio of LYTOS is moderate.

The role of oral bisphosphonates, including LYTOS 520 mg tablets, in the treatment of malignant hypercalcaemia is limited.

Alternative medicinal products exist.

The actual benefit provided by this proprietary drug remains substantial for 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 dosages in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%