HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

15 December 2010

DIDRONEL 200 mg, tablets
B/60 (CIP code: 345 098-5)

DIDRONEL 400 mg, tablets
B/14 (CIP code: 333 062-0)

Applicant : PROCTER & GAMBLE PHARMACEUTICALS

etidronate
ATC code: M05BA01

List I

Marketing Authorisations dates: 20 March 1981 (200 mg) and 27 July 1990 (400 mg)

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

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

etidronate

1.2. Indications

DIDRONEL 200 mg, tablets
"Paget's disease in adults, with or without pain, gradual or complex progression.
Malignant hypercalcaemias as a temporary alternative to treatment with injectable bisphosphonate."

DIDRONEL 400 mg, tablets
"Curative treatment of post-menopausal osteoporosis, with at least one instance of vertebral compaction.
Prevention of bone loss in patients requiring prolonged - more than 3 months' - corticosteroid therapy with a dose > 7.5 mg/day prednisone equivalent via a general administration route."

1.3. Dosage

See SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

M : Musculoskeletal system
M05 : Drugs for treatment of bone diseases
M05B : Drugs affecting bone structure and mineralisation
M05BA : Bisphosphonates
M05BA01 : etidronic acid

2.2. Postmenopausal osteoporosis

Medicines in the same therapeutic category

Bisphosphonates indicated in the treatment of postmenopausal osteoporosis which have been shown to be effective in the prevention of vertebral and peripheral fractures, including fractures of the neck of the femur:

- ACLASTA 5 mg (zoledronic acid), IV infusion once a year.
- ACTONEL (risedronic acid) 5 mg, 35 mg tablet (every day), 75 mg tablet (every week), ACTONELCOMBI tablet (35 mg risedronate + 1000 mg calcium + 880 IU vitamin D),
- FOSAMAX 10 mg (every day), 70 mg (every week) tablet and other proprietary drugs containing alendronic acid 10 mg and 70 mg, FOSAVANCE and ADROVANCE tablet (alendronic acid or alendronic acid + vitamin D combination),

Other bisphosphonate indicated in the treatment of postmenopausal osteoporosis but which has not been shown to be effective in the prevention of peripheral fractures including fractures of the neck of the femur

- BONVIVA 150 mg tablet (once a month), 2.5 mg tablet (once a day, this strength is not commercially available), 3 mg/3ml IV infusion once every three months (ibandronic acid).

Medicines with a similar therapeutic aim

Other proprietary drugs indicated for postmenopausal osteoporosis:

Drugs which have been shown to be effective in the prevention of vertebral and peripheral fractures, including fractures of the neck of the femur:

- PROTELOS (strontium ranelate) granules for oral suspension (every day)
- PROLIA (denosumab), subcutaneous injection once every six months, not included on the list of refundable proprietary drugs as of the date of this opinion.

Drugs which have not been shown to be effective in the prevention of fractures of the neck of the femur:

- FORSTEO (teriparatide), subcutanous injection every day, refundable in cases of severe osteoporosis (at least two vertebral fractures),
- PREOTACT (PTH 1-84), not refundable,
- EVISTA and OPTRUMA (raloxifene), tablet, every day.

Calcium and vitamin D are generally used for adjuvant treatment.

2.3. Corticosteroid-induced osteoporosis

These are the other bisphosphonates indicated in corticosteroid-induced osteoporosis:

- ACLASTA 5 mg (zoledronic acid), IV infusion once a year.

- ACTONEL 5mg tablet (risedronic acid): maintenance or augmentation of bone mass in postmenopausal women, requiring prolonged (more than 3 months') corticosteroid therapy with doses of at least 7.5 mg/day prednisone equivalent given by a general administration route.

- FOSAMAX 5 mg tablet (alendronic acid), not commercially available: prevention of bone loss in patients requiring prolonged - more than 3 months' - corticosteroid therapy with a dose > 7.5 mg/day prednisone equivalent given by a general administration route

Medicines with a similar therapeutic aim

- FORSTEO (teriparatide), solution for injection in a prefilled pen, indicated in the treatment of corticosteroid-induced osteoporosis in women and men at increased risk of fracture receiving long-term corticosteroid therapy given by a general administration route, refundable only in patients with at least 2 vertebral fractures.

3 UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION (4 January and 5 July 2006)

3.1. Efficacy

3.1.1. DIDRONEL 200 mg

In its opinion dated 4 January 2006, the transparency Committee did not recommend the retention of DIDRONEL 200 mg on the list of proprietary drugs refundable by National Health Insurance. The transparency Committee emphasised that, as far as the indication Paget's disease is concerned, "etidronate no longer has a role in the treatment of Paget's disease because of its low antiresorptive capacity. Other, more effective, bisphosphonates given by oral administration or injection are available. Comparative studies have shown second-generation bisphosphonates (tiludronate and risedronate) to be more effective than etidronate. Parenteral bisphosphonates (pamidronic acid and zoledronic acid) have the advantage of a faster and more persistent action than oral bisphosphonates. Furthermore, the therapeutic range of etidronate is narrow: the antiresorptive effect is close to the bone mineralisation inhibition effect. The actual benefit of this proprietary drug is insufficient."
The AB was also regarded as insufficient in the case of malignant hypercalcaemia.

DIDRONEL 200 mg is still included on the list of refundable proprietary drugs, with a reimbursement rate of 15% (Official Gazette dated 16/04/2010).

The pharmaceutical company has requested a reimbursement rate of 35% but has not provided any new clinical data.

3.1.2. DIDRONEL 400 mg

In its most recent opinion (5 July 2006), the transparency Committee concluded that DIDRONEL 400 mg still offered a significant AB. However, in the "strategic treatment" section, the Committee stated that: "etidronate (DIDRONEL® 400 mg and generics) has a minor role at present because the level of anti-fracture evidence is below that of alendronate and risedronate. Furthermore, etidronate has not been shown to be effective in non-vertebral fractures."

Since this opinion was published, new bisphosphonate proprietary drugs have been reviewed by the transparency Committee (in particular zoledronic acid IV - opinion dated 19/12/2007 and ibandronic acid IV - opinion dated 29/11/2006) and included on the list of proprietary drugs refundable in the indication 'postmenopausal osteoporosis' (PMO). Furthermore, the range of indications for which zoledronic acid and teripatide are refundable (opinions dated 21/10/2009 and 16/07/2008 respectively) has been broadened following an extension of indication to the treatment of corticosteroid-induced osteoporosis.

In the light of the change in the treatment strategy for PMO and corticosteroid-induced osteoporosis (introduction of other drugs, some of which have been shown to be effective in the prevention of both vertebral and femural neck fractures, with a lower frequency of administration (a 15-minute IV infusion once a year rather than an etidronic acid tablet once a day)), the transparency Committee decided that it would be appropriate to review the data available for DIDRONEL.

- New data for postmenopausal osteoporosis

No new studies have been conducted by the pharmaceutical company.

The only new publication on the efficacy of etidronic acid in PMO is a Cochrane systematic review of the literature published in 2008[1].
This was based on 11 clinical studies (n = 1248), two of which formed the basis of the granting of marketing authorisation for the treatment of PMO. This review of the literature showed that etidronic acid 400 mg daily is effective in the secondary prevention of vertebral fractures (RR: 0.53; 95% CI [0.32-0.87]) but ineffective in the primary prevention of vertebral fractures (RR: 3.03; 95% CI [0.32-28.44]) and non-vertebral fractures (RR: 0.98; 95% CI [0.68-1.42]), hip fractures (RR: 1.20; 95% CI [0.37-3.88]) and wrist fractures (RR: 0.87; 95% CI [0.32-2.36]).

The methodological shortcomings of the studies were highlighted: lack of clear information as to the method used to assess and classify vertebral fractures, lack of homogeneous definition of vertebral fractures, small cohort, length of follow-up varying from 1 to 4 years, imperfect randomisation, etc.).

In conclusion, unlike alendronic acid, risedronic acid and zoledronic acid, etidronic acid has not been shown to be effective in preventing femural neck fractures.

- <u>New data for corticosteroid-induced osteoporosis</u>

The pharmaceutical company presented the results of a study[2] published in 2004.
This randomised, double-blind, placebo-controlled study assessed the efficacy of etidronic acid (400 mg daily for two weeks every three months) alone or in combination with calcium (500 mg daily) in terms of the increase in bone mass density and reduction of occurrence of new fractures in asthmatic patients who had been taking oral and/or inhalational corticosteroids for at least a year.
The randomised population was made up of 352 men and postmenopausal women aged between 50 and 70 (average age 60). The analysis of the results was carried out for only 349 patients, less than 50% of the size needed to reach suitable statistical power.
The patients were stratified into three groups according to their corticosteroid consumption and randomised into four groups to receive:
- etidronic acid (N=81)
- calcium (N=85)
- etidronic acid + calcium (N=88)
- placebo (N=95)

The patients were monitored for 5 years.

The primary efficacy endpoints were change in bone mass density and occurrence of fractures.

After five years of treatment, no statistically significant difference in terms of the occurrence of new fractures was found between etidronic acid used alone or in combination with calcium and placebo. No difference between the groups was found in respect of change in bone mass density of the femur.
A significant increase in lumbar bone mass density was found for etidronic acid compared to placebo (4.1% after five years, $p<0.001$).

The pharmaceutical company also submitted the findings of:
- a Japanese study published in 2008[3] which will not be described here as the dose of etidronic acid assessed is different from that stated in the marketing authorisation;

[1]Wells et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008.
[2]Campbell et al. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. Thorax 220; 59(9): 761-768.
[3]Sato et al. Long term effect of intermittent cyclical etidronate therapy on corticosteroid-induced osteoporosis in Japanese patients with connective tissue disease: 7-Year follow up. J rheum 2008; 35(1): 142-146.

- an open-label study published in 2003[4] which, because of its open methodology, does not allow any conclusions to be drawn regarding the efficacy of etidronic acid;
- an American cost-effectiveness study published in 2003, the results of which cannot be taken into account;
- the results of two studies published in 1997 (Adachi) and 1998 (CIBLOS) which the Committee has already examined and which take lumbar bone mass density as an intermediate criterion for the primary efficacy endpoint.

In conclusion, in the light of the findings of the study conducted by Campbell et al. in 2004[2] and in the absence of data demonstrating etidronic acid to be effective in preventing non-vertebral fractures, particularly fractures of the neck of the femur, the efficacy of DIDRONEL 400 mg in reducing the occurrence of fractures in the treatment of corticosteroid-induced osteoporosis has not been demonstrated.

N.B.: marketing authorisations were granted to bisphosphonates for the treatment of corticosteroid-induced osteoporosis on the basis of extrapolation of anti-fracture efficacy data available in the context of PMO. Unlike alendronic acid, risedronic acid and zoledronic acid, etidronic acid has not been shown to be effective in preventing peripheral fractures, including fractures of the neck of the femur.

3.2. Adverse effects

Analysis of worldwide pharmacovigilance data between 2006 and 2009 found 370 spontaneous reports of adverse effects. The most relevant of these related to:
- 6 cases of osteonecrosis of the jaw (ONJ)
- 5 cases of severe digestive effects which could be caused by the consumption of NSAIDs
- 3 buccodental problems (one of which was an infection)
- 4 fractures
- 2 cases of non-Hodgkin's lymphoma.

The only one of these effects which led to a change being made to the SPC was ONJ.

Like all bisphosphonates, etidronic acid has been reviewed by the EMA for tolerance in three indications:
- osteonecrosis of the jaw
- stress fracture
- atrial fibrillation

[4]Loddenkemper et al. Calcium, vitamin D and etidronate for the prevention and treatment of corticosteroid-induced osteoporosis in patients with rheumatic diseases. Clin Exp Rheum 2003; 21 (1):19-26.

Osteonecrosis of the jaw [5](mandible and/or maxilla):

Following the first re-assessment of the class of bisphosphonates in respect of ONJ by the EMEA in 2005, the SPC of DIDRONEL, in common with that of all proprietary drugs of this class, was revised in 2007 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[6].

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[7]: "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 check-up 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[8].

The EMA 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 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 only limited long-term data are available for other bisphosphonates.

With regard to etidronic acid in particular, possible cases of stress fracture associated with etidronic acid treatment have been reported. In most cases, insufficient information is available to allow any firm conclusions to be drawn as to the nature and cause of these fractures.

[5]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 bisphosphonates and had not had radiation therapy to the craniofacial region.

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

[7]Afssaps. Letter to healthcare professionals. Recommendations on the oral and dental care of patients treated with bisphosphonates. 18/12/2007

[8] MHRA. Bisphosphonates and stress fractures. January 2009.

It has been recommended that cases of stress fracture should be monitored, with a specific analysis having been added to the PSURs, but the SPC has not been amended.

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[9]. 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 clinical studies indicated increased risk for zoledronic acid and, in the case of data from extension phases, for alendronic acid and pamidronic acid.

Overall, etidronic acid was not found to be associated with any increased risk of AF.

3.3. Conclusion

The only bisphosphonates available for the treatment of osteoporosis that have been shown to be effective in preventing both vertebral and non-vertebral fractures, including fractures of the neck of the femur, are alendronic acid, risedronic acid and zoledronic acid. Etidronic acid, the active ingredient in DIDRONEL 400 mg, has only been shown to be effective in the prevention of vertebral fractures.

[9]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 USAGE DATA

Sales in a non-hospital setting, in numbers of boxes (source: GERS):

	2005	2006	2007	2008	2009
DIDRONEL 200 mg tablets B/60	8 258	5 035	3 643	2 458	2 198
DIDRONEL 400 mg tablets B/14	250 272	147 602	85 333	45 901	36 987

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Re-assessment of actual benefit

DIDRONEL 200 mg

In the absence of new clinical data, the transparency Committee confirms that the actual benefit of DIDRONEL 200 mg, in comparison with the treatments that are already available, is not sufficient to allow it to be refundable by National Health Insurance.

DIDRONEL 400 mg

Osteoporosis is a serious disorder because of the risk of fractures.
In particular, fractures of the femoral neck can be life-threatening.

Unlike other proprietary drugs in the same class (alendronate, risedronate and zoledronate in particular), DIDRONEL has not been shown to be effective in preventing femoral neck fractures. Consequently, its efficacy/adverse effects ratio is inferior to that of these alternatives.

The proprietary drug DIDRONEL is not shown by the data available to offer any public health benefit.

As alternative treatments exist (in particular, other bisphosphonates such as alendronic acid, risedronic acid and zoledronic acid) which have been shown to be effective in preventing vertebral and peripheral fractures due to osteoporosis, including fractures of the neck of the femur, the use of DIDRONEL could be a lost opportunity, especially for patients at greater risk of peripheral fracture (such as individuals over 80 years of age).
Consequently, the transparency Committee is of the opinion that this proprietary drug no longer has a role to play in the current management of osteoporosis.

In view of all these factors, the actual benefit of this proprietary drug must be regarded as insufficient to justify public funding in view of the other treatments available.

5.2. Transparency Committee recommendations

The transparency Committee does not recommend maintaining inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

The transparency Committee recommends removal from the list of medicines refundable by National Health Insurance and the list of medicines approved for hospital use and various public services in the indications and at the dosages given in the Marketing Authorisation.