



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

21 July 2010

ACTONEL 5 mg, film-coated tablet
B/14 (CIP code: 354 362-3)

ACTONEL 30 mg, film-coated tablet
B/28 (CIP code: 354 366-9)

ACTONEL 35 mg, film-coated tablet
B/4 (CIP code: 361 577-1)
B/12 (CIP code: 366 668-5)

ACTONEL 75 mg, film-coated tablet
B/2 (CIP code: 384 568-9)
B/6 (CIP code: 384 570-3)

Applicant: PROCTER & GAMBLE PHARMACEUTICALS

risedronate sodium
ATC code: M05BA07

List I

Date of Marketing Authorisation:
ACTONEL 5 mg – 3 May 2000
ACTONEL 30 mg – 3 May 2000
ACTONEL 35 mg – 3 March 2003
ACTONEL 75 mg – 25 March 2008

Reason for request: Re-evaluation of the 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

risedronate sodium

1.2. Indications

“ACTONEL 5 mg, film-coated tablet

- Treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures.
- Treatment of confirmed postmenopausal osteoporosis to reduce the risk of hip fractures.
- Prevention of postmenopausal osteoporosis in women at increased risk of osteoporosis.
- Maintenance or augmentation of bone mass in postmenopausal women, requiring prolonged (more than 3 months’) systemic corticosteroid therapy with doses ≥ 7.5 mg/day prednisone equivalent.

ACTONEL 30 mg, film-coated tablet

Treatment of Paget’s disease of bone.

ACTONEL 35 mg, film-coated tablet

- Treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures.
- Treatment of confirmed postmenopausal osteoporosis to reduce the risk of hip fractures.
- Treatment of osteoporosis in men at high risk of fracture.

ACTONEL 75 mg, film-coated tablet

Treatment of postmenopausal osteoporosis in women at increased risk of fractures.”

1.3. Dosage

see SPC

2 UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION (11 June 2008)

2.1. Efficacy

The new efficacy data submitted by the company, chiefly from observational studies^{1,2,3,4}, from an open study⁵, from studies versus an active comparator based on densitometric criteria^{6,7,8} or bone-formation markers⁹, from meta-analyses^{10,11,12} or from a systematic literature review¹³, do not alter the conclusions of the transparency Committee's opinions.

2.2. Adverse effects

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

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

Osteonecrosis of the jaw¹⁴ (mandibular and/or maxillary):

Following the first re-evaluation of the class of bisphosphonates in respect of ONJ by the EMEA in 2005, the SPC of ACTONEL, in common with that 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 SPCs of bisphosphonates, cases of ONJ have continued to be reported. The EMA consequently undertook a second re-evaluation in December 2007, the conclusions of which were published in September 2009¹⁵.

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

¹ Delmas PD et al. bisphosphonate therapy and hip fractures within the risedronate and alendronate (REAL) cohort study: subgroup with prior fracture. *Calcif Tissue Int* 2008; 82(suppl 1).

² Curtis JR et al. Risedronate and alendronate intervention over three years (REALITY): minimal differences in fracture risk reduction. *Osteoporos Int* 2009; 20(6): 973-978.

³ Harris et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the evaluation of ibandronate efficacy (VIBE) database fracture study. *Bone* 2009; 44(5): 758-765

⁴ Cadarette SM et al. Relative Effectiveness of Osteoporosis Drugs for Preventing Nonvertebral Fracture. *Ann Intern Med* 2008; 148 (9): 637-646.

⁵ Ringe et al. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. *Rheumatol Int.* 2009; 29(3): 311-315

⁶ Van Poznak C et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. *J Clin Oncol.* 2010 Feb 20; 28(6): 967-975.

⁷ Reid DM et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet.* 2009 Apr 11; 373(9671): 1253-1263.

⁸ Mok CC et al. Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial. *Osteoporos Int.* 2008 Mar; 19(3): 357-364.

⁹ Miller et al. Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. *J Clin Endocrinol Metab.* 2008; 93(10): 3785-3793.

¹⁰ Wells et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev.* 2008.

¹¹ Zhong ZM et al. Anti-fracture efficacy of risedronic acid in men: A meta-analysis of randomized controlled trials. *Clin Drug Investig.* 2009; 29(5): 349-357

¹² Bolland et al. Effect of Osteoporosis Treatment on Mortality: A Meta-Analysis. *J. Clin. End. & Metab.* 2010; 95(3): 1174-1181.

¹³ Bianchi G et al. Oral nitrogen-containing bisphosphonates: a systematic review of randomized clinical trials and vertebral fractures. *Curr Med Res Opin.* 2008 Sep; 24(9): 2669-2677.

¹⁴ 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.

¹⁵ EMA. CHMP Assessment report on bisphosphonates and osteonecrosis of the jaw. 24/09/2009.

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 evaluation of the risk of ONJ through the creation of a European register and the performance of clinical studies.

Analysis of the available tolerance data since 2006 showed the frequency of ONJ reporting with risedronic acid to be 1.45 per 100,000 patient-years.

The transparency Committee draws attention to the recommendations on the oral and dental care of patients treated with bisphosphonates¹⁶: "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 data currently available, 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-evaluation 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-evaluation of the class as a whole in 2008¹⁷.

The EMA pharmacovigilance working group concluded that:

- stress fractures of 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 risk of stress fractures 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.

Concerning risedronic acid more particularly, cases of non-traumatic fractures associated with risedronic acid therapy were reported, but the number of atraumatic femoral fractures reported was small relative to the number of patients exposed. On the basis of the limited available data, it is not possible to establish a causal connection with risedronic acid. Monitoring of the cases of stress fracture was recommended with the addition of a specific analysis in the PSURs* but no modification of the SPC was deemed necessary.

- Atrial fibrillation (AF):

In June 2008, the EMA pharmacovigilance working group re-evaluated the benefit/risk ratio for bisphosphonates in respect of the risk of AF¹⁸. This re-evaluation 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.

¹⁶ AFSSAPS. Letter to healthcare professionals. Recommendations on the oral and dental care of patients treated with bisphosphonates. 18/12/2007

¹⁷ MHRA. Bisphosphonates and stress fractures. January 2009.

¹⁸ 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

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.

No increase in the risk of AF has been identified for risedronic acid.

3 USAGE DATA

Sales data:

	2005	2006	2007	2008	2009
ACTONEL 30 mg fct B/28	8533	7528	6156	5590	4856
ACTONEL 35 mg fct B/12	83,419	395,568	470,556	519,037	461,977
ACTONEL 35 mg fct B/4	3,082,798	2,531,364	2,333,096	1,813,905	1,411,962
ACTONEL 5 mg fct B/28	149,591	103,278	72,860	52,757	39,307
ACTONEL 75 mg fct B/2	0	0	0	25,747	150,240
ACTONEL 75 mg fct B/6	0	0	0	11,508	65,375
Total ACTONEL	3,324,341	3,037,738	2,882,668	2,428,544	2,133,717

4 TRANSPARENCY COMMITTEE CONCLUSIONS

Transparency Committee recommendations

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

ACTONEL is a preventive treatment for osteoporotic fractures. Its efficacy has been demonstrated in the prevention of vertebral and peripheral fractures, including femoral neck fractures.

In the light of the new tolerance data available, the transparency Committee considers that the efficacy/adverse effects ratio of the ACTONEL medicinal products, like that of all medicinal products of the bisphosphonates class, is moderate.

These medicinal products are first-line therapies.

Alternative medicinal products exist.

The actual benefit of these medicinal products remains substantial.