HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 May 2007

ACTONEL 35 mg, film-coated tablet
Box of 4 tablets – CIP Code: 361 577.1
Box of 12 tablets – CIP Code: 336 668.5

PROCTER & GAMBLE PHARMACEUTICALS FRANCE

Risedronate

List I

Date of Marketing Authorisation (MA): March 3, 2003

Date of latest revision of MA: January 30, 2007 (extension of indication)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the indication of “Treatment of osteoporosis in men at high risk of fracture”.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Risedronate Monosodium

1.2. Indications

Indications prior to the application

- Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures.
- Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.

New indication applied for
Treatment of osteoporosis in men at high risk of fracture

1.3. Dosage

The recommended dose in adults is one 35 mg tablet orally once a week. The tablet should be taken on the same day each week.

Food interferes with the absorption of risedronate monosodium.

For optimal absorption, patients should take ACTONEL® 35 mg before breakfast, and at least 30 minutes before the first food, other medicines, or beverages (other than water) of the day.

Patients should be instructed that if a dose of ACTONEL® 35 mg is missed, it should be taken on the day it is remembered. Thereafter, they should return to taking one tablet once a week on the day originally chosen. Two tablets should not be taken on the same day.

The whole ACTONEL® 35 mg tablet must not be swallowed at once, without chewing or allowing it to dissolve in the mouth. It should be swallowed with a large glass of slightly mineralised (calcium and magnesium) still water (≥ 120 ml), in a seated or standing position, to ease its transit to the stomach. Patients should not lie down for 30 minutes following tablet intake.

Supplemental calcium and vitamin D should be considered if the dietary intake is inadequate.

Elderly patients: No dosage adjustment is necessary since bioavailability, distribution and elimination are identical in elderly (>60 years) and younger patients. This has also been shown in very elderly menopausal patients, 75 years old and above.

Patients with renal impairment: No dosage adjustment is necessary in patients with mild to moderate renal impairment. The use of risedronate monosodium is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

M: Musculo-skeletal system
05: Drugs for treatment of bone diseases
B: Drugs affecting bone mineralisation
A: Bisphosphonates
07: risedronic acid

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines
FOSAMAX 10 mg (alendronic acid) and 10 mg alendronic acid-based medicinal products indicated for the treatment of male osteoporosis.

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

The indication extension to male osteoporosis is based on the results of a single bone densitometry study carried between June 2002 and May 2005 (unpublished).

3.1. Efficacy

A randomised, placebo-controlled, double-blind study was conducted to evaluate the efficacy of ACTONEL 35 mg in a single weekly dose in the treatment of male osteoporosis. Following randomisation (2:1), 284 patients were included in the study. All patients received daily calcium (1000 mg) and vitamin D (400 or 500 IU) supplements. Patients were at least 30 years old and had low bone mineral density (BMD):

- Femoral T-score of ≤ -2 and lumbar T-score of ≤ -1 or,
- Femoral T-score of ≤ -1 and lumbar T-score of ≤ -2.5.

In particular, among the exclusion criteria were:

- Recent osteoporotic fracture (< 6 months) or the existence of ≥ 2 vertebral fractures at baseline;
- Alcohol abuse;
- Non-compensated hypogonadism and other endocrine disorders likely to affect bone metabolism;
- History of extended corticosteroid therapy (≥ 3 months at a dosage > 7.5 mg of prednisone equivalent) or ongoing administration of prednisone > 5 mg/day;
- Anti-osteoporosis and/or osteomalacia treatments.

Duration of treatment: 24 months.

Primary endpoint: change in lumbar spine BMD at 24 months or at the last assessment (LOCF). An endpoint analysis on the ITT population was planned in the protocol

Results:
The protocol provided for an endpoint analysis of the ITT results. The ITT population was defined as all randomised patients having received at least one treatment dose.

Table 1: Patient characteristics at baseline (ITT population)

Parameters	**Placebo n = 93**	**ACTONEL 35 mg n = 191**
Mean Age (years)	61.5± 10.64	60.1± 10.66
Mean BMI (kg/m²)	24.9± 3.8	25± 3.5
Lumbar T-score	-3.13± 0.93	-3.25± 0.86
Femoral T-score	-2.00± 0.73	-1.96 ± 0.76
History of vertebral fracture (n,%)	28 /80 (35%)	59/173 (34,1%)

The analysis presented in the file was conducted on 87 (out of 93) patients in the placebo group and 188 (out of 191) in the ACTONEL 35 mg group.

Table 2: Change in lumbar spine BMD (primary endpoint) and femoral neck BMD at 24 months compared to initial score (%)

	Placebo (n =87)	**ACTONEL 35 mg** (n =188)	Difference	CI 95%
Initial BMD (g/m²) in L2-L4	0.82	0.81		
Change in lumbar spine BMD	+1.2 % IC95%: 0.2-2.2%	+5.75% IC95%: 5-6.5%	4.5 %	3.5-5.6%
Change in femoral neck BMD	+0.24% IC95%: -0.41;+0.9%	+1.7% IC95%: 1.2-2.2%	1.5 %	0.8-2.2%

* The analysed population does not correspond to the ITT population (n=93 in the placebo group, n = 191 in the ACTONEL 35 mg group)

Data on fracture-prevention effect
This study did not have the necessary statistical strength (limited number of subjects) to detect a difference in the incidence of fractures between the two groups.

The number of symptomatic fractures (all sites) was 3 (3,4%) for the placebo group, compared to 5 (2,7%) for the ACTONEL 35 mg group during the first year of treatment, and 6 (7,7%) versus 9 (4,9%), respectively, at the end of the trial.

3.2. Adverse events

Safety was similar in both treatment groups: 73% of the placebo group patients compared to 70% of the ACTONEL 35 mg group patients experienced adverse events. The most frequent of these were constipation and spine and joint pain. These adverse events are consistent with the known safety profile for this medicinal product.

3.3. Conclusion

This study demonstrated that ACTONEL 35 mg, in a single weekly dose, significantly increases bone mass compared to placebo in men, aged on average 60±10 years, with a mean T-score of -3,2 for the lumbar spine and of -2 for the femoral neck, 35% of whom had a prevalent vertebral fracture at baseline. The efficacy of ACTONEL 35 mg in preventing fractures was not shown in this study, the objective of which was to assess the effect on lumbar bone mineral density.

The adverse events observed are consistent with the known safety profile for this medicinal product.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Osteoporosis is a serious disorder which gravity is linked to the high risk of fracture. In particular, fractures of the femoral neck can be life-threatening.

In men, ACTONEL 35 mg increases lumbar bone density; its efficacy in preventing fractures has not been shown.

This efficacy/safety ratio is high.

> Public Health Benefit
> The burden on public health caused by male osteoporosis is difficult to quantify.
> Improving the femoral neck fracture prevention in elderly patients is a necessity to be managed within the scope of an identified public health priority (GTNDO).
> In light of the available data, the impact that this medicinal product might be expected to have in terms of morbi-mortality and quality of life cannot be quantified. Moreover, extrapolation of the study results to clinical practice is not guaranteed (in particular, the profile of patients treated in actual practice may differ from that of the patients included in the study, the majority of whom were not “at high risk of fracture”).
> Therefore, there is no basis for presuming that ACTONEL will provide an additional response to the identified need.
> Accordingly, in the current state of knowledge, ACTONEL 35 mg is not expected to have any public health benefit.

ACTONEL 35 mg is a medicinal product intended for first-line therapy.

The only treatment alternative is FOSAMAX 10 mg.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

In light of:

- the absence of a direct comparison between ACTONEL 35 mg and FOSAMAX 10 mg,
- the unreliability of an indirect comparison of these two medicines, the populations included in the placebo-controlled trials not being comparable,

the Transparency Committee considers that ACTONEL 35 mg does not provide any improvement in actual benefit compared to FOSAMAX 10 mg in the treatment of osteoporosis in men at high risk of fracture.

4.3. Therapeutic use

As male osteoporosis is “secondary” in more than 50% of cases, it is important to treat the associated causes (in particular endocrine disorders) and to achieve the removal of “toxic factors” (tobacco, alcohol). Regular load-bearing physical exercise and correction of any dietary intake insufficiencies in calcium and vitamin D are also recommended.

In addition to aetiological treatment and calcium and vitamin D supplements, bisphosphonates constitute the benchmark treatment for male osteoporosis.

Currently, two bisphosphonates, alendronate (FOSAMAX® 10 mg daily dose) and risedronate (ACTONEL® 35 mg weekly dose), have obtained Marketing Authorisations for the treatment of osteoporosis in men.

4.4. Target population

According to its Marketing Authorisation, the ACTONEL 35 mg target population comprises all men with osteoporosis at high risk of fracture.

This population includes osteoporosis patients who have had a fracture caused by bone fragility. In the absence of a personal history of fracture, the individual fracture risk must be assessed taking into account the following items:

- T-score
- Patient age
- Possible existence of additional risk factors such as a history of extended systemic corticosteroid therapy (> 3 months); primary or secondary hypogonadism, iatrogenic or not; a concomitant condition causing bone loss (chronic inflammatory rheumatism, CIBD, endocrine disorder, etc.); smoking and excessive consumption of alcohol; low BMI (< 20) and osteoporotic fracture in a parent.

In the absence of French epidemiological data, the prevalence of densitometric osteoporosis (T score < -2.5) may be estimated from an American study. It was found to be between 3% and 6% of men over 50 years of age[1]. By extrapolating these data to the French population (INSEE 1st January 2007), it would appear that 900,000 to 1,800,000 men are affected by osteoporosis in France.

However, the sub-population at high risk of fracture likely to benefit from ACTONEL 35 mg treatment is difficult to determine at the present time.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication “treatment of osteoporosis in men at high risk of fracture” and at the posology in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%

[1] Looker AC et al. Prevalence of low femoral bone density in older US adults from NHAES III. J Bone Mineral Res 1997; 12: 1761-8