HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 May 2006

Bonviva 2.5 mg, film-coated tablet
PVC-Aluminium blister packs
Box of 28 tablets
CIP Code: 371 657-8

Applicant: Roche

ibandronic acid

list I

Date of Marketing Authorisation (AMM): 23 February 2004

Reason for request: inclusion on the list of drugs reimbursed by National Insurance and approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

ibandronic acid as ibandronic sodium monohydrate

1.2. Background

Not applicable

1.3. Indications

- **Treatment** of postmenopausal osteoporosis to reduce the risk of vertebral fractures. Efficacy against femoral neck fractures has not been established.
- **Prevention** of postmenopausal osteoporosis in women at risk of developing osteoporosis.

1.4. Dosage

The recommended dose is one 2.5 mg film-coated tablet once daily.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

M: Musculo-skeletal system
05: Drugs for treatment of bone diseases
B: Drugs affecting bone structure and mineralization
A: Bisphosphonates
06: Ibandronic acid

2.2. Medicines in the same therapeutic category

Treatment of postmenopausal osteoporosis

Comparator medicines

Other oral bisphosphonates:

- risedronic acid - Actonel 5 mg and 35 mg tablets
- etidronic acid - Didronel 400 mg tablets
  etidronate de sodium GGAM 400 mg
  etidronate MERCK 400 mg
  etidronate SANDOZ 400 mg
- alendronic acid - Fosamax 10 mg tablets and generics, Fosamax 70 mg tablets
- alendronic acid + vitamin D – Fosavance tablets.

Medicines in the same therapeutic area

- raloxifene - Evista, Optruma
- strontium ranelate – Protelos
- teriparatide - Forsteo
- calcium and vitamin D are used as adjuvant therapy.

Prevention of postmenopausal osteoporosis

Comparator medicines

Other oral bisphosphonates:
- risedronate – Actonel 5 mg tablets*
- alendronate – Fosamax 5 mg*.

Medicines in the same therapeutic area
- hormone replacement therapy
- raloxifene – Evista*, Optruma *.

*Note:
These medicines are not currently reimbursed for the indication “Prevention of osteoporosis”.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Treatment of postmenopausal osteoporosis

Pivotal trial: BONE (MF4411)[1]

A randomised double-blind placebo-controlled comparative trial in 2929 patients with postmenopausal osteoporosis, to assess the efficacy and safety of ibandronate administered continuously (2.5 mg/day) or intermittently (20 mg/day for 12 days every 3 months) for 3 years.
All patients received supplements of calcium (500 mg/day) and vitamin D (400 IU/day).

Inclusion criteria
- women aged 55 to 80, menopausal for at least 5 years with,
- mean lumbar BMD (L2-L4): T-score between -2 and -5 in at least one lumbar vertebra, and
- 1 to 4 vertebral fractures (T4-L4).

Primary endpoint: rate of patients with new vertebral fractures during the 3 years of the trial.

[1] Chesnut *et al*. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19 (8):1241-1249.

Characteristics of the population at inclusion

	Placebo N = 975	Ibandronate 2.5 mg/day N = 977	Ibandronate 20 mg/day for 12 days every 3 months N = 977
Age (years)	69 ± 6	69 ± 6	69 ± 6
History of fracture (N,%)	906 (93%)	920 (94%)	917 (94%)
Mean lumbar T-score (L2-L4)	-2.8 ± 0.9	-2.8± 0.9	-2.7± 0.9
Femoral neck T-Score	-2 ± 0.9	-2 ± 0.9	-2 ± 0.9
Total hip T-Score	-1.7 ± 0.9	-1.7 ± 0.8	-1.7 ± 0.9
Time since menopause	20.8 ± 7.8	20.9 ± 8	20.8 ± 8

The main statistical analysis covered the ITT population.

Results

	Placebo N = 975	Ibandronate 2.5 mg/day N = 977	Ibandronate 20 mg/day for 12 days every 3 months N = 977
Number of patients with at least one new vertebral fracture after 3 years of treatment	73 9.6% [7.47%;11.66%])	37 4.7% [3.20%; 6.16%]	39 4.9% [3.39%; 6.41%]

Ibandronate was superior to placebo in reducing the incidence of new vertebral fractures. The relative risk reduction of vertebral fractures compared to placebo was 62% [40.89%; 75.08%] in the ibandronate 2.5 mg/day group (p= 0.0001) and 50% [25.66%; 66.20%] in the ibandronate 20 mg group (p= 0.0006).

Efficacy against nonvertebral fractures has not been shown (incidence: 9.1% and 8.9% for ibandronate vs. 8.1% for placebo).
Bonviva 2.5 mg/day and 20 mg/day for 12 days every 3 months was shown to be effective in preventing vertebral fractures, only in women with postmenopausal osteoporosis who have had a vertebral fracture and are under 80.

Safety
In this trial, the incidence of undesirable effects in the two ibandronate groups was similar to that of the placebo group.

Indirect comparison

The laboratory submitted an indirect comparison with risedronate and alendronate.
The comparison covered the following trials:

- BONE (ibandronate)[2]
- VERT US[3] and MN[4] (risedronate)
- FIT 1[5] (alendronate)

[2] Chesnut *et al*. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19 (8):1241-1249.
3 Harris *et al*. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. JAMA 1999;282:1344-1352.
4 Reginster *et al*. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. osteoporosis international 2000;11:83-91.

The committee could not take this indirect comparison into account as the populations enrolled in these trials had different characteristics (age, severity of osteoporosis – BMD and risk of fractures at inclusion).

Prevention of postmenopausal osteoporosis
The applicant did not submit any clinical data for this indication.

3.2. Conclusion

Efficacy and safety of Bonviva 2.5 mg were assessed in a clinical trial with 2929 women menopausal for at least 5 years. The trial showed that Bonviva at a daily dosage of 2.5 mg or an intermittent dosage of 20 mg daily for 12 days every 3 months reduces the risk of new vertebral fractures in women under 80 with osteoporosis and with a vertebral fracture.
There was no evidence of efficacy against peripheral fractures especially femoral neck fractures.
The committee regrets the fact that no comparative study with another bisphosphonate was available.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Treatment of postmenopausal osteoporosis
The seriousness of osteoporosis lies in the risk of fracture. Femoral neck fractures in particular can be life-threatening.
Bonviva 2.5 mg is a preventive therapy against osteoporotic fractures and their recurrence.
In women with postmenopausal osteoporosis and vertebral fractures, ibandronic acid reduces the risk of new vertebral fractures. Its efficacy against peripheral fractures including the femoral neck has not been established in this population.
The efficacy/safety ratio for this drug is substantial.

Public health benefit
Given that postmenopausal osteoporosis is common and has serious consequences, the disease represents a substantial burden on public health.
The public heath need caused by osteoporosis is insufficiently covered. There is no evidence to suggest that Bonviva will provide an additional response to this need that differs from that offered by other oral bisphosphonates.
In the absence of any clinical trial comparing ibandronate with other oral bisphosphonates, it is not possible to assess the impact of Bonviva on the reduction of morbidity and mortality related to postmenopausal osteoporosis.
In the current state of knowledge, it is therefore not expected that Bonviva will benefit public health.

Bonviva 2.5 mg is first-line therapy.
There are alternative therapies.
The actual benefit of this medicinal product is substantial.

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5 Black *et al*. Randomized trial of the effect of alendronate on risk of fracture in women with existing vertebral fractures. The Lancet 1996;348:1535-1541.

Prevention of postmenopausal osteoporosis

In the absence of data provided by the applicant, the actual benefit of this medicinal product in the indication “Prevention of postmenopausal osteoporosis” is insufficient.

4.2. Improvement in actual benefit

Bonviva 2.5 mg does not offer any improvement in actual benefit (level V) compared with other bisphosphonates in treating postmenopausal osteoporosis.

4.3. Therapeutic use

The aim of treating osteoporosis is to prevent fractures.

Before starting any anti-osteoporosis therapy, any calcium or vitamin D deficiency should be identified and treated. If necessary, calcium and vitamin supplements should be continued during anti-osteoporosis therapy.

As with any chronic disease, treatment for osteoporosis is only effective in case of optimal compliance.

In post-menopausal women, the choice of anti-osteoporosis therapy will depend on risk factors for fracture such as age, existence of fractures due to bone fragility, and osteodensitometry findings.

Bisphosphonates, selective oestrogen receptor modulators (SORMs/SERMs), parathormone derivatives (teriparatide) and strontium ranelate are the drugs indicated in treating postmenopausal osteoporosis.

Ibandronic acid reduces the risk of new vertebral fractures. It has not been shown to be effective against femoral neck fractures.

Unlike alendronate, risedronate, strontium ranelate and teriparatide, which have been shown to be effective against vertebral and peripheral fractures (including femoral neck fractures in the case of alendronate, risedronate and strontium ranelate), ibandronic acid should therefore be reserved for patients under 80 at risk of vertebral fractures and at low risk of peripheral fractures.

4.4. Target population

The target population of Bonviva includes the women with postmenopausal osteoporosis with vertebral fractures and at low risk of femoral neck fracture. It can be estimated on the basis of the following data:

- around 25% of women aged 65 and 50% of women aged 80 are thought to have osteoporosis (GTNDO, 2003).
- according to INSEE (www.insee.fr), on 1st January 2005, 11.5 million women were over 50 in France; 6 million over 65; and 1.9 million over 80.

According to these data, the estimated population with postmenopausal osteoporosis is around 3 to 3.3 million women including around 930 000 over 80.

In view of the population included in the trial and given that no effect was shown on femoral neck fractures, women over 80 should be excluded from the target population for Bonviva 2.5 mg.

The target population for Bonviva 2.5 mg is therefore 2 to 2.4 million.

4.5. Transparency Committee Recommendations

The Committee recommended inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals and various public services for the indication “Treatment of osteoporosis to reduce the risk of vertebral fractures”.

The Committee did not recommend inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals and various public services for the indication “Prevention of postmenopausal osteoporosis in women at risk of developing osteoporosis”.

4.5.1. Scope of reimbursement

Treatment of postmenopausal osteoporosis to reduce the risk of vertebral fracture.

- in patients who have had a fracture due to bone fragility
- in women who have experienced no bone fractures but
  - in whom there is a marked decrease in bone density (T score < -3)
  - or in whom a T score ≤ 2.5 is combine with other risk factors such as age > 0 years, previous or current systemic corticoid treatment at a dose corresponding to ≥7.5 mg/day of prednisone, a body mass index of <9 kg/m², a family history of hip fracture in a first-degree parent (mother), or early menopause (before 40 years of age).

Packaging: Suitable for conditions of prescription.

Reimbursement Rate: 65% (treatment of osteoporosis).