HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

21 June 2006

Bonviva 150 mg, film-coated tablet
B/1: 371 657.8
B/3: 371 658.4

Applicant: Roche

Ibandronic acid

List I

Date of Marketing Authorisation: 15 September 2005

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

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Ibandronic acid

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.

1.4. Dosage

Oral route
The recommended dose is one 150 mg film-coated tablet once.a month
The tablet should be taken on the same date every month.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

M: Musculo-skeletal system
05: Medicinal products for the treatment of bone disorders
B: Medicinal products acting on mineralisation
A: Bisphosphonates
06: Ibandronic acid

2.2. Medicinal products in the same therapeutic category

Comparator drugs
Other oral bisphosphonates:

- risedronic acid - Actonel 5 mg and 35 mg tablets
- etidronic acid - Didronel 400 mg tablets
  sodium etidronate 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.

2.3. Medicinal products with the same therapeutic aim

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

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy and safety

The efficacy and safety data submitted by the company concerned:

- the BONE trial, already examined in the opinion on Bonviva 2.5 mg, issued on 10 May 2006,
- the MOBILE trial,
- the MOPS dose-ranging study and the EMKEY (2005) preference study comparing Bonviva 150 mg with Fosamax 70 mg were not taken into account by the Committee.

- ***Reminder of the results of the pivotal BONE trial (MF4411)[1]***

The efficacy against vertebral fractures of ibandronate at a daily dose of 2.5 mg and an intermittent dose of 20 mg for 12 days every 3 months was demonstrated against placebo in 2929 women with postmenopausal osteoporosis with at least one prevalent vertebral fracture (1-4) and aged at least 80 years.

All patients received supplements of calcium (500 mg/day) and vitamin D (400 IU/day).

The primary endpoint was the number of patients experiencing a new vertebral fracture after 3 years of treatment.

Results for efficacy (ITT analysis)

Patients experiencing a new vertebral fracture after 3 years of treatment

	Placebo N = 975	Ibandronate 2.5 mg/day N = 977	Ibandronate 20 mg/day for 12 days every 3 months N = 977
Number and percent (IC95%) 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 with 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).

No efficacy was shown against nonvertebral fractures (incidence: 9.1% and 8.9% for ibandronate vs. 8.1% for placebo).

Safety

In this trial, the incidence of undesirable effects was similar in all three groups, apart from dyspepsia which was more common in the ibandronate 2.5 mg/day group (11%) than under placebo (9%) or ibandronate 20 mg (9%).

The Transparency Committee noted that the doses of ibandronate tested in this trial (2.5 mg/day and 20 mg intermittently) do not correspond to the dose which is the subject of the application for inclusion, i.e. 150 mg once a month.

[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.

- ***Pivotal trial: MOBILE (BM 16549)***[2]

Randomised double-blind trial to demonstrate the non-inferiority of two monthly doses (100 mg and 150 mg) compared with a daily dose (2.5 mg) of ibandronate on lumbar BMD (bone mineral density) change in 1609 female patients with postmenopausal osteoporosis.

Patients were divided into 4 groups and received:

- 2.5 mg/day of ibandronate = 402
- 100 mg in two doses of 50 mg /month of ibandronate = 404
- 100 mg in a single dose/month of ibandronate = 402
- 150 mg/month of ibandronate = 401

All patients received supplementation in the form of 500 mg of calcium and 400 IU of vitamin D a day.

Inclusion criteria:

- Menopaused for at least 5 years
- age between 55 and 80years,
- mean lumbar BMD (L2-L4): T-score between -2.5 and -5.0.

Primary efficacy endpoint:

Change (%) in mean lumbar BMD (L2-L4) compared with value at inclusion after 1 year of treatment.

It was hypothesised that monthly doses of ibandronate could be regarded as non-inferior to a daily dose of 2.5 mg if the lower limit of the 97.5% confidence interval of the difference in relative change (%) in lumbar BMD compared with baseline value was ≥1%. If non-inferiority was demonstrated, the protocol planned to assess the superiority of monthly treatment groups compared with the daily treatment group

Secondary endpoints:

- Change in BMD in the proximal femur (whole hip, trochanter, femoral neck) at one year compared with baseline values,
- % of responders (proportion of patients with lumbar BMD ≥ 6% or hip BMD ≥ 3% compared with baseline value),
- bone markers: change in serum levels of CTX[3].

Results (Per-protocol analysis)

Characteristics at inclusion were only available for the population who received at least one dose of treatment and who was assessed at least once.

Patient characteristics at inclusion

	Ibandronate 2.5 mg / day N = 395	Ibandronate 100 mg in two doses / month N = 396	Ibandronate 100 mg in one dose / month N = 396	Ibandronate 150 mg / month N = 396
Age(m ± SD)	65.8 ± 6.61	66.0 ± 6.71	66.2 ± 6.38	66.2 ± 6.64
History of fracture - n (%)	192 (48.9)	183 (46.3)	180 (45.5)	185 (47.0)
Mean lumbar T-score (L2-L4) (m±SD)	-3.28 ± 0.57	-3.28 ± 0.60	-3.27 ± 0.59	-3.28 ± 0.59
Total hip T-Score (m±SD)	-1.79±0.85	-1.78±0.87	-1.85± 0.84	-1.85±0.85

Primary endpoint

[2] Miller et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res 2005;20 (8):1315-1322.

[3] serum C-telopeptide

Relative change as % of lumbar BMD after 1 year of treatment (per-protocol population)

	Ibandronate 2.5 mg/day N=318	Ibandronate 50/50 mg / month N=328	Ibandronate 100 mg / month N=311	Ibandronate 150 mg / month N=320
Mean increase in lumbar BMD at 1 year (%)	3.9	4.3	4.1	4.9
97.5% CI of difference vs ibandronate 2.5 mg/day	--	[-0.09, 1.12]	[-0.42, 0.81]	[0.38, 1.60]

The non-inferiority of the three monthly doses of ibandronate compared with the 2.5 mg daily dose was demonstrated in the per-protocol analysis.

In addition, ibandronate 150 mg/month was superior to ibandronate 2.5 mg/day for lumbar BMD at 1 year (p=0.002).

These results were confirmed by an ITT analysis and were maintained at 2 years.

A *post-hoc* subgroup analysis compared the 150 mg and 100 mg doses: a statistically superior mean increase in lumbar BMD at 1 year was demonstrated for ibandronate 150 mg compared with ibandronate 100 mg (PP: p=0.001; ITT: p=0.002).

Secondary endpoints

BMD

A statistically significant increase in hip and trochanter BMD was demonstrated in the group treated with the 150 mg dose compared with the group treated with the 2.5 mg/day dose. There was no statistically significant difference for femoral neck between the 2 groups.

Response rate at 1 year (%) (per-protocol population)

	Ibandronate 2.5 mg/day 318	Ibandronate 50/50 mg / month 330	Ibandronate 100 mg / month 315	Ibandronate 150 mg / month 327
Lumbar BMD ≥ 6%	24.2	30.5	32.2	35.3
Hip BMD ≥ 3%	34.9	38	43.4	48.4

response rate was higher in the groups treated with monthly doses of ibandronate (100 or 150 mg) than with daily treatment.

Effects of treatment on serum CTX[4] at 1 year (per-protocol population)

Median change from baseline value (%)	Ibandronate 2.5 mg/day	Ibandronate 50/50 mg / month	Ibandronate 100 mg / month	Ibandronate 150 mg / month
At 3 months, n	269	283	273	279
%	-53.62	-50	-53.19	-66.13
At 6 months, n	270	278	276	282
%	-63.45	-60.67	-63.19	-73.41
At 12 months, n	272	279	278	272
%	-67.26	-62.79	-66.67	-75.76

All doses of ibandronate significantly decreased bone resorption: rapid and marked reduction in serum CTX after 3 months of treatment, the lowest levels were observed at 6 months and were maintained at one year.

[4] serum C-telopeptide

Safety

At both 1 and 2 years, the incidence of flu-like symptoms was higher in the ibandronate 150 mg/month group than in the ibandronate 2.5 mg group. These flu-like symptoms were generally of short duration, mild to moderate in severity and resolved while treatment continued, without requiring special measures.

The incidence of musculoskeletal side-effects (arthralgia, low back pain, osteoarthritis, pain in the extremities, myalgia, bone pain) was greater in the ibandronate 150 mg/month group than in the ibandronate 2.5 mg group.

Incidence of arthralgia was 1% under ibandronate 150 mg at 1 year and at 2 years versus 0.3% at 1 year and 0.5% at 2 years under ibandronate 2.5 mg.

Incidence of myalgia was 1.5% under ibandronate 150 mg versus 0.3 % under ibandronate 2.5 mg at 1 year and 2 years.

Incidence of fractures under Bonviva at 1 year and at 2 years

	Ibandronate 2.5 mg/day	Ibandronate 100 mg / month	Ibandronate 150 mg / month
All clinical fractures			
at 1 year (%)	2.5	3.3	4
at 2 years (%)	6.6	6.3	7.3
Non-vertebral fractures			
at 1 year (%)	2.3	3.3	3.8
at 2 years (%)	5.1	5.1	5.3

A *post-hoc* analysis (conducted purely for information purposes) did not reveal any statistically significant difference between treatments on fracture incidence after 1 and 2 years.

Renal and gastrointestinal side-effects were similar for all forms of treatment.

- ***Indirect comparisons***

The company submitted an indirect comparison:

– *in terms of efficacy*, comparing Bonviva 150 mg with risedronate and alendronate, in:
  - the BONE trial (ibandronate)
  - the VERT US and MN trials (risedronate)
  - the FIT 1 trial (alendronate)

– *in terms of safety*, between Bonviva 150 mg (BONE trial) and alendronate 70 mg (Schnitzer[5] trial).

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).

[5] Schnitzer T et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Aging Clin Exp Res.2000;12:1-12.

- ***Post marketing data***

According to the company, between 1 April and 31 December 2005, 301 104 patients worldwide were exposed to Bonviva 150 mg. Of the 5 fractures reported, only 1 was observed after more than 3 months (at 6 months precisely), the period after which Bonviva 150 mg might reasonably be expected to have an effect against fractures. The other osteoporosis-induced fractures were observed after periods of between 5 days and 2 months. Overall, 320 musculoskeletal side effects and 28 cases of flu-like syndrome were reported in patients treated with Bonviva 150 mg. None of these effects led to treatment discontinuation.

3.2. Conclusion

One clinical trial (BONE) carried out in 2929 postmenopausal women for at least 5 years showed that Bonviva given at a daily dose of 2.5 mg or an intermittent dose of 20 mg a day for 12 days every 3 months, reduced the risk of vertebral fractures in women aged under 80 years with osteoporosis and a prevalent vertebral fracture.

There was no evidence of efficacy against peripheral fractures, in particular femoral neck fractures with these doses.

A pivotal trial (MOBILE) demonstrated the non-inferiority on bone mineral density of monthly doses of 100 mg and 150 mg compared with a daily dose of 2.5 mg.

During the first year of treatment, musculoskeletal side-effects, flu-like syndrome and clinical fractures were more common with ibandronate 150 mg/month than with ibandronate 2.5 mg/day.

At 2 years, the incidence of musculoskeletal side-effects and flu-like symptoms remained higher with the monthly dose of 150 mg. The Committee regretted that no efficacy against fractures was demonstrated directly with the monthly dose of Bonviva 150 mg, and the absence of comparative trials with other bisphosphonates.

The Committee also noted that Bonviva 150 mg had not been shown to be effective in reducing the risk of onset of nonvertebral fractures. Finally, according to current data, the Committee considered that the efficacy/safety ratio for this bisphosphonate has not been shown to be equivalent to that of alendronate or risedronate.

4 REMINDER OF THE COMMITTEE'S OPINION AND CONDITIONS OF INCLUSION OF 18 JANUARY 2006

4.1. Actual benefit

- The seriousness of osteoporosis lies in the risk of fracture. Femoral neck fractures in particular can be life-threatening.
- Bonviva 150 mg reduces the risk of onset of new vertebral fractures. Its efficacy against femoral neck fractures has not been demonstrated, irrespective of the dose or dosage regimen used.
- The efficacy/side effects ratio for Bonviva 150 mg is moderate.
- Bonviva 2.5 mg is a drug whose role in the treatment strategy is difficult to establish.

- There are alternative forms of treatment, notably other bisphosphonates that have demonstrated their efficacy in preventing vertebral and peripheral fractures caused by osteoporosis.

The Committee regretted the lack of clinical data proving that compliance was improved under Bonviva 150 mg once a month compared with weekly or daily use of bisphosphonates.

- 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 related to osteoporosis is insufficiently covered. There is no evidence to suggest that Bonviva will provide any additional response to this need over that provided by other bisphosphonates.
  - The anticipated impact of Bonviva in reducing morbidity and mortality related to postmenopausal osteoporosis cannot be established in view of the absence of:
    - clinical trials comparing ibandronate with other oral bisphosphonates, particularly in terms of preventing fractures;
    - any confirmed improvement in compliance with a bisphosphonate given monthly compared with weekly or daily doses of bisphosphonates.
  - In addition, it is difficult to identify those patients likely to benefit particularly from the monthly form.
  - In the current state of knowledge it is therefore not expected that Bonviva will benefit public health.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit:

Bonviva 150 mg does not contribute any improvement in actual benefit (level V) over Bonviva 2.5 mg in the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fracture. Efficacy against femoral neck fractures has not been established.

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 if compliance is excellent.

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

The drugs indicated for treating postmenopausal osteoporosis are bisphosphonates, selective oestrogen receptor modulators (SORMs/SERMs), parathormone derivatives (teriparatide) and strontium ranelate.

Bonviva 150 mg reduces the risk of onset of new vertebral fractures, but its efficacy against femoral neck fractures has not been demonstrated, irrespective of the dose or the dosage regimen used.

The place of Bonviva 150 mg in the range of treatments for osteoporosis is difficult to establish as there are already bisphosphonates taken daily or weekly that have

demonstrated their efficacy both in preventing vertebral fractures and femoral neck fractures, and which may have a better efficacy/safety ratio.

Although it has been established that, as with all chronic disease, treatment of osteoporosis is only effective if compliance is excellent, there are no trials confirming that a monthly dose of one Bonviva 150 mg tablet improves compliance compared with weekly or daily forms of treatment.

4.4. Target population

The target population for Bonviva is women with postmenopausal osteoporosis with vertebral fractures and at low risk of femoral neck fracture, and can be estimated from 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 there were 11.5 million women over 50 in France; 6 million over 65; and 1.9 million over 80.

The estimated population with postmenopausal osteoporosis is thus around 3 to 3.3 million women including around 930 000 over 80.

Drug therapy is appropriate in only part of this population.

As bone densitometry has only recently become eligible for reimbursement in France, there are no data that could be used to estimate the subpopulation of patients with osteoporosis with no fractures and with a T score < -3 or T score ≤ -2.5 combined with other risk factors for fracture.

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 150 mg.

The target population for Bonviva 150 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 on the list of medicines approved for use by hospitals and various public services.

4.5.1. Indications reimbursed

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

- in female patients who have had one fracture caused by bone fragility,
- in the absence of fractures, in women with substantially reduced bone density (T score < -3) or with a T score ≤ -2.5 combined with other risk factors for fracture, particularly age > 60 years, previous or current use of systemic corticosteroids at a daily dose of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², history of fracture of the end of the femoral neck in a first-degree relative (mother), early menopause (before the age of 40).

4.5.2. Packaging: the packaging is appropriate for the prescription conditions

4.5.3. Reimbursement rate: 65%