HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 November 2006

Bonviva 3 mg/3 ml injectable solution in pre-filled syringe
Box of 1 pre-filled 3 ml glass syringe with 1 needle: 376 871.8
Box of 4 pre-filled 3 ml glass syringes with 4 needles: 569 956.5

Applicant: Roche

ibandronic acid

list I

Date of Marketing Authorisation (MA): 19 march 2006.

Rectification of MA 28 August 2006 (indication and pharmacodynamic properties)

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

Health Technology Assessment Division

1 CHARACTERISTICS OF MEDICINAL PRODUCT

1.1. Active ingredient

Ibandronic acid

1.2. Background

The first bisphosphonate, administered intravenously every 3 months, indicated for the treatment of post-menopausal osteoporosis.

1.3. Indication

Treatment of post-menopausal osteoporosis in women with an increased risk of fracture. Reduced risk of vertebral fractures has been demonstrated, but efficacy on femoral neck fractures has not been established.

1.4. Dosage

The recommended dose of ibandronic acid is 3 mg, administered intravenously within 15 to 30 seconds, every 3 months.

- Strictly the intravenous route should be used.
- Patients must be given a calcium and vitamin D supplement.
- If an injection is missed, it must be given as soon as possible. The subsequent injections must then be scheduled every 3 months after the date of the last injection.

Kidney failure
No dose adaptation is required in patients with slight or moderate kidney failure, characterised by a serum creatinine level of less than or equal to 200 µmol/l (2.3 mg/dl) or a creatinine clearance (measured or estimated) greater than or equal to 30 ml/min.

Considering the limited data in these patients during clinical trials, the use of Bonviva i.v. is not recommended in patients with a serum creatinine level exceeding 200 µmol/l (2.3 mg/dl) or with a creatinine clearance (measured or estimated) of less than 30 ml/min.

Liver failure
No dose adaptation is necessary.

Elderly
No dose adaptation is necessary.

Children and adolescents
The drug has not been tested on children.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2006)

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

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

No other injectable bisphosphonate has an MA for the treatment of post-menopausal osteoporosis.

Oral bisphosphonates indicated for the treatment of post-menopausal osteoporosis:

- Didronel 400 mg tablet and its generics (etidronate)
- Actonel 5 mg and 35 mg tablet (risedronate)
- Fosamax 10 mg and 70 mg tablet and other drugs based on alendronate 10 mg and 70 mg, Fosavance tablet (alendronate or combination of alendronate + vitamin D)
- Bonviva 150 mg and 2.5 mg tablet (ibandronate).

2.3. Medicines with a similar therapeutic aim

Other drugs indicated for post-menopausal osteoporosis:

- Evista and Optruma (raloxifen),
- Protelos (strontium ranelate)
- Forsteo (teriparatide).

Calcium and vitamin D are most often used as adjuvant treatment.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The development plan of Bonviva i.v. 3 mg/3 months is based on:

- the BONE study, which demonstrated the anti-fracture effect of the daily oral form (Bonviva 2.5 mg tablet), and
- the DIVA study, which demonstrated the non-inferiority of Bonviva i.v. 3 mg/3 months in terms of Bone Mineral Density (BMD) compared with Bonviva 2.5 mg.

Results of the BONE pivotal study (MF4411)[1]

The efficacy against vertebral fractures of Bonviva at the daily dose of 2.5 mg and the intermittent dose of 20 mg during 12 days every 3 months was demonstrated in placebo-controlled studies conducted on 2929 women under 80 years old suffering from post-menopausal osteoporosis with at least one prevalent vertebral fracture (1-4).

All patients received a calcium (500 mg/day) and vitamin D (400 I/day) supplement.

The primary efficacy endpoint was the number of patients in whom a new vertebral fracture appeared after a 3 years treatment.

Results: (Analysis was on an intention-to-treat analysis)

Number and percentage of patients in whom a new vertebral fracture appeared after a 3 years treatment:

Placebo N = 975	Bonviva 2.5 mg / day N = 977	Bonviva 20 mg/day during 12 days every 3 months N = 977
73 9.6% [7.47%;11.66%]	37 4.7% [3.20%; 6.16%]	39 4.9% [3.39%; 6.41%]

Bonviva performed better than the placebo in reducing the incidence of new vertebral fractures[2]. The reduction in the relative risk of vertebral fractures was 62% [40.89% ; 75.08%] in the group treated with Bonviva 2.5 mg/day (p= 0.0001) and 50% [25.66% ; 66.20%] in the group treated with Bonviva 20 mg (p= 0.0006) compared with the placebo.

In the global population, no efficacy was demonstrated on non-vertebral fractures (incidence: 9.1% and 8.9% with Bonviva, vs 8.1% with only the placebo).

However, in a post-hoc analysis (i.e. purely exploratory) conducted on a sub-group of patients with a BMD in the neck of femur of <-3, a 69% reduction in the risk of non-vertebral fractures was observed with the daily form of Bonviva (2.5 mg).

Safety:

In this study, the incidence of adverse drug reactions in the three groups was similar, except from dyspepsia which was more common with Bonviva 2.5 mg/day (11%) than with placebo (9%) or Bonviva 20 mg (9%).

DIVA pivotal study (Delmas et al 2006)[2]

DIVA is a randomised, double-blind trial. The objective was to demonstrate the non-inferiority of the i.v. form at the dose of 3 mg every 3 months or 2 mg every 2 months compared with the 2.5 mg daily oral form of Bonviva in terms of variations in lumbar BMD in 1386 women aged 55 to 80 years suffering from post-menopausal osteoporosis.

Primary efficacy endpoint: variation (%) in mean lumbar BMD (L2-L4) compared with the baseline value after 1 year of treatment.

[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.

[2] Delmas et al. Intravenous Ibandronate Injections in Postmenopausal Women with osteporosis. Arthritis & Rheumatism 2006; 54 (6) : 1838-1846

The main secondary endpoints were:

- Relative (%) and absolute (g/cm²) variation in mean lumbar BMD (L2-L4) compared with baseline values after 2 years,
- Absolute variation in mean lumbar BMD (L2-L4) compared with baseline values after 1 year,
- Relative and absolute variation in BMD at proximal femur (total hip, trochanter, femoral neck) after years 1 and 2 compared with baseline values,
- Rate of response: patients with a lumbar or total hip BMD ≥ the baseline value after year 1 and year 2 were considered as responders.
- Absolute and relative variation of serum CTX levels (C telopeptide) after 6, 12 and 24 months.

It was hypothesised that ibandronate i.v. (2 mg/2 months and 3 mg/3 months) could be considered as non-inferior to the daily oral treatment if the lower limit of the 95% confidence interval of the difference in relative variation (%) of the lumbar BMD compared with the baseline value was greater than or equal to -1%.

This non-inferiority limit, fixed at 1%, corresponded to an allowed loss of 30% of the minimal effect of Bonviva 2.5 mg/day on lumbar BMD compared with the placebo after 1 year. Conversely, better digestive tolerance was expected with Bonviva 3 mg/3 month.

The protocol required application of a superiority test if non-inferiority was demonstrated and a confirmation test after 2 years. The non-inferiority limit was defined at -1.3% in this case.

The patients were divided into 4-3 groups, and received Bonviva at the dose of:

- 2.5 mg per os per day (n= 469)
- 2 mg i.v. every 2 months (n = 454)
- 3 mg i.v. every 3 months (n = 472)

The study used a double placebo (per os and i.v).

All patients received a daily supplement of 500 mg of calcium and 400 IU of vitamin D.

The inclusion criteria were:

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

Results: (per protocol analysis)

Patient's characteristics at baseline

	Bonviva 2.5 mg/day n =465	Bonviva i.v. 2mg/2 months n =448	Bonviva i.v. 3 mg/3 months n =469
Age (m±Sd)	65.7±6.08	66.6±6.26	65.8±6.3
History of fractures (%)	202 (43.5)	187 (42.1)	206 (43.9)
Mean lumbar T-score (L2-L4) (m±Sd)	-3.26±0.55	-3.27±0.57	-3.27±0.59
Total hip T-score (m±Sd)	-1.99±0.88	-1.90±0.87	-1.96±0.91

Results on the primary efficacy endpoint:

Relative % variation in lumbar BMD after 1 year's treatment (per protocol analysis)

	Bonviva 2.5 mg/ day **n =377**	Bonviva i.v. 2 mg / 2 months **n =353**	Bonviva i.v. 3 mg/3 months **n =365**
Mean increase in lumber BMD after 1 year (%)	3.8 (3.4-4.2)	5.1 (4.7- 5.5)	4.8 (4.5-5.2)
95% CI of difference compared with Bonviva 2.5 mg/day	--	1.3 [0.76 ,1.86]	1 [0.49, 1.58]

Source: report on DIVA study after 1 year

Bonviva i.v. 2 mg/2 months and 3 mg/3 months proved not to be inferior to Bonviva 2.5 mg/day in terms of increase in BMD after 1 year.

These results were confirmed by analysis of the data after 2 years:

	Bonviva 2.5 mg/day **n =334**	Bonviva i.v. 2 mg/2 months **n =320**	Bonviva i.v. 3 mg/3 months **n =334**
Mean increase in lumbar BMD after 2 years (%)	4.8 (4.3-5.4)	6.4 (5.9 -6.9)	6.3 (5.7-6.8)*
97.5% CI of difference compared with Bonviva 2.5 mg/day	--	1.6 [0.80 , 2.28]	1.5 [0.76, 2.23]

Source: Report on DIVA study after 2 years

Moreover, in a prospective analysis, Bonviva i.v. 2 mg/2 months and 3 mg/3 months proved superior to Bonviva 2.5 mg/day in terms of the increase in lumbar BMD after 1 year and 2 years, p <0.001.

These results were confirmed by intention-to-treat analysis.

Results on the secondary endpoints:

- BMD

  Increase in BMD compared with baseline (%) after 1 year and 2 years, 95% CI (population PP)

	year			**2 years1**		
	2.5 mg/day per os **(373)**	2 mg/2 months i.v. **(346)**	3 mg/3 months i.v. **(362)**	2.5 mg/day per os **(330)**	2 mg/2 months i.v. **(316)**	3 mg/3 months i.v. **(333)**
Total hip	1.8 (1.5-2.1)	2.6 * (2.3-2.8)	2.4 * (2-2.7)	2.2 (1.8-2.6)	3.4* (3-3.7)	3.1* (2.6-3.6)
Neck of femur	1.6 (1.2-2)	2 * (1.6-2.4)	2.3 * (1.9-2.7)	2.2 (1.8-2.7)	2.7 (2.3-3.2)	2.8 (2.3-3.3)
Trochanter	3 (2.6-3.4)	4.1 (3.7-4.5)	3.8* (3.2-4.4)	3.5 (3-4)	5.0* (4.5-5.5)	4.9 * (4.1-5.7)

* significant difference compared with the daily oral group

➢ <u>% of responders</u>

A higher response rate was observed in the groups treated with Bonviva i.v. than with the daily treatment.

% of responders	1 year			2 years		
	2.5 mg/day per os	2 mg/2 months i.v.	3 mg/3 months i.v.	2.5 mg/day per os	2 mg/2 months i.v.	3 mg/3 months i.v.
lumbar BMD	84.9	92.6*	92.1*	84.7	92.8*	92.8*
total hip BMD	75.1	86.4*	82.3*	77	88.6*	85.6*

* significant difference compared with the daily oral group

➢ <u>Serum CTX[3]</u>

Median variation compared with baseline value (%) (per protocol analysis)

	Bonviva 2.5 mg/day	Bonviva 2 mg i.v./2 months	Bonviva 3 mg i.v./3 months
2 months	-45	-47	-
3 months	-54	-	-43
4 months	-57	-61	-
6 months	-62	-65	-58
12 months	-63	-65	-59
24 months	-60	-56	-53

Source: reports on DIVA study after 1 year and 2 years

3.2. Adverse effects

In the DIVA study, the global safety after 2 years of Bonviva i.v. 3 mg/3 months and Bonviva oral 2.5 mg was similar: the incidence of adverse drug reactions was 22.6% with the oral form, versus 28.6% with the three-monthly i.v. form.

Transient influenza-like symptoms were reported in the patients who received Bonviva i.v. 3 mg every 3 months, usually at the time of the first injection. The influenza-like syndrome included muscle pain, joint pain, fever, shivering, fatigue, nausea, loss of appetite or bone pain. These symptoms were generally short-lived, of mild to moderate intensity, and disappeared as the treatment continued, with no need for any particular measures.

However, two patients in the Bonviva i.v. 3 mg/3 months group discontinued the treatment due to influenza-like syndrome.

[3] serum C-telopeptides

Adverse drug reactions with a frequency of > 1% considered by the investigator to be possibly or probably associated with the treatment under study in DIVA 2 years

Percentages of patients with at least one adverse effect	**DIVA 2 years**		
	2.5 mg/day per os N=465	**2 mg/2 months i.v. N=448**	**3 mg/3 months i.v. N=469**
Digestive			
Gastritis	0.9	1.1	1.3
Diarrhoea	0.6	0.7	1.1
Abdominal pain	4.5	4.2	3.6
Dyspepsia	4.1	4.0	3.0
Nausea	2.8	2.7	1.7
Constipation	1.5	0.9	1.1
Musculoskeletal system			
Musculoskeletal pain	0.4	0.7	1.1
Joint pain	0.9	2.2	2.8
Muscle pain	0.9	3.3	1.7
Back pain	0.2	0.4	1.1
General disorders			
Influenza-like syndrome*	0.9	4.7	4.5
Fatigue	0.4	1.3	1.1
Nervous system			
Headache	0.6	2.0	1.3
Skin disorders			
Rashes	0.9	0.2	0.9

Source: SPC

- Clinical fractures

N (%)	2.5 mg oral daily		2 mg i.v./2 months		3 mg i.v./3 months	
	1 year	2 years	1 year	2 years	1 year	2 years
Clinical osteoporotic fractures	15 (3.2)	29 (6.2)	10 (2.2)	21 (4.7)	12 (2.6)	23 (4.9)
Clinical non-vertebral fractures	11(2.4)	28 (6.0)	7(1.6)	21 (4.7)	5(1.1)	18 (3.8)

3.3. Conclusion

The efficacy of oral Bonviva on vertebral fractures was demonstrated with the daily dose of 2.5 mg in the BONE clinical trial, conducted on 2,929 women under 80 years old suffering from post-menopausal osteoporosis with a vertebral fracture. There was no demonstration of efficacy on femoral neck fractures.

In a non-inferiority study (DIVA), the i.v. regimen of 3 mg every 3 months proved to be non-inferior to oral treatment with 2.5 mg once a day in terms of increase in lumbar BMD after 1 and 2 years. The non-inferiority threshold was fixed at 1%, which corresponded to a loss of 30% of the minimal effect of 2.5 mg/day per os compared with placebo on lumbar BMD.

Moreover, a prospective analysis demonstrated the superiority of Bonviva 3 mg every 3 months to oral Bonviva 2.5 mg/day in terms of increased lumbar BMD after 1 and 2 years ($p < 0.001$).

Bonviva 3 mg/3 months intravenous route of administration, was supposed to be associated with better digestive tolerance, thus allowing its administration to women intolerant to oral bisphosphonates or at increased risk of digestive intolerance. In the DIVA pivotal study, abdominal pain, dyspepsia, nausea and constipation were less frequent with the intravenous form Bonviva 3 mg/3 months, but gastritis and diarrhoea were more frequent than with Bonviva 2.5 mg.

Moreover, influenza-like syndromes were more frequent with Bonviva i.v. 3 mg/3 months (4.5%) than with the daily form (0.9%). These symptoms were generally short-lived, of mild to moderate intensity, and disappeared as the treatment continued, with no need for any particular measures.

The Transparency Committee regrets that no efficacy against fractures has been directly demonstrated with Bonviva i.v. 3 mg/3 months, and that there is no comparative study with other oral bisphosphonates (alendronate and risedronate).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit (AB)

Osteoporosis is a disorder whose severity is linked to the risk of fractures. Especially, femoral neck fractures can be life-threatening.

Bonviva i.v. 3 mg/3 months is a preventive treatment of osteoporotic fractures.

However, its efficacy on femoral neck fractures has not been established.

Public health benefit:
Considering the high frequency of post-menopausal osteoporosis and the severity of its consequences, the disorder constitutes a major public health burden.

There is a public health need which is insufficiently covered in osteoporosis.

The expected impact of Bonviva 3 mg/3 months on the reduction of morbidity and mortality associated with post-menopausal osteoporosis cannot be assessed, particularly in terms of anti-fracture effect, due to the absence of a clinical trial comparing this three-monthly injectable form of ibandronate with other oral bisphosphonates. Moreover, the results of the studies do not support the hypothesis of better compliance associated with fewer adverse digestive effects.

The available data are therefore insufficient to suggest that Bonviva 3 mg/3 months would offer a response to the public health need in addition to that provided by other bisphosphonates.

Consequently, in the current state of knowledge, no public health benefit is expected from Bonviva 3 mg/3 months.

The efficacy/safety ratio of Bonviva i.v. 3 mg/3 months is high.

Bonviva i.v. 3 mg/3 month is a first-line drug.

There are alternative therapies, especially other oral bisphosphonates whose efficacy has been demonstrated in the prevention of vertebral and peripheral osteoporotic fractures.

The AB offered by this medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

Bonviva i.v. 3 mg/3 months does not offer any IAB (level V) in the management of post-menopausal vertebral osteoporosis.

4.3. Therapeutic use

Osteoporosis is defined by a T-score of ≤ -2.5 in the absence of any other cause of demineralising or fragilising bone disease.

The aim of treating osteoporosis is to prevent fractures.

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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.

According to AFSSAPS recommendations published in January 2006, treatment is systematically recommended in the case of osteoporosis complicated by a fracture. In the absence of fractures in menopausal women, the indication for the treatment will be discussed case by case, according to the individual fracture risk. This risk is evaluated on the basis of the T-score and any other fracture risk factors. Treatment should be given to women with:

- a major reduction in bone density (T score < -3) or
- a T score ≤ -2.5 associated with other fracture risk factors, especially: age > 60 years, previous or current systemic corticosteroid treatment at the dose of ≥ 7.5 mg/day prednisone equivalent, a body mass index < 19 kg/m², a history of femoral neck fracture in a first-degree relative (mother), and early menopause (before the age of 40).

Without any direct comparison between the various anti-osteoporosic drugs (bisphosphonates, raloxifen, teriparatide and strontium ranelate), the choice of treatment will depend on the risk of vertebral and/or non-vertebral fractures, age, number and location of fractures, the patient's general condition and the contraindications to any of the drugs.

Among the bisphosphonates indicated for the treatment of post-menopausal osteoporosis, ibandronic acid (Bonviva®) reduces the risk of recurrences of vertebral fractures in women under 80 years old with post-menopausal osteoporosis. But it has not shown its effectiveness on femoral neck fractures.

At present, three drugs containing ibandronic acid have received MA for the treatment of post-menopausal osteoporosis, two of which are oral drugs: Bonviva 2.5 mg to be taken daily, Bonviva 150 mg to be taken monthly, and BONVIVA i.v. 3 mg/3 months.

The occurrence of a fracture after the first year of treatment, despite satisfactory compliance, should lead to reconsideration of the treatment. Another drug included in the same pharmacological class could be proposed.

4.4. Target population

The target population of Bonviva i.v. 3 mg/3 months is identical to that of Bonviva 2.5 mg and 150 mg. It is represented by women with vertebral post-menopausal osteoporosis at low risk of fractures of the femoral neck.

The population of women with osteoporosis can be estimated on the basis of the following data:

- approximately 25% of women aged 65 and 50% of women aged 80 suffer from osteoporosis (GTNDO, 2003).
- according to INSEE (the French National Statistics and Studies Institute) (www.insee.fr), the female population on 1 January 2005 consisted of 11.5 million women over 50 years old, 6 million women over 65 years old, and 1.9 million women over 80 years old.

According to these data, the population presenting post-menopausal osteoporosis can be estimated at around 3 to 3.3 million women.

Considering the population included in the study and the absence of proven efficacy on femoral neck fractures, women over 80 years old should be excluded from the target population of Bonviva 3 mg/3 months.

The target population of Bonviva 3 mg/3 months is consequently between 2 and 2.4 million.

4.5. Transparency Committee recommendations

The Committee recommends inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals and various public services in the Marketing Authorisation.

4.5.1. Indications reimbursed

Treatment of post-menopausal vertebral osteoporosis:

- in patients who have suffered a fracture due to 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 femoral neck in a first-degree relative (mother), early menopause (before the age of 40).

4.5.2. Packaging: Appropriate for the prescription conditions

4.5.3. Reimbursement rate: 65%