# Scottish Medicines Consortium

## ibandronic acid (also known as ibandronate), 150mg, film-coated tablet (Bonviva®) No. (228/05)

## Roche/GSK

## New formulation

6 January 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**Ibandronic acid (Bonviva®)** is accepted for use within NHS Scotland for the treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Ibandronic acid 150mg monthly is superior to daily ibandronic acid in terms of lumbar spine bone mineral density at 1 year. Compared with placebo, daily administration of ibandronic acid results in a relative risk reduction for vertebral fractures of 62%. Unlike some other bisphosphonates, efficacy in reducing femoral neck fractures (and other non-vertebral fractures) has not been established.

Overleaf is the detailed advice on this product.

**Chairman**
**Scottish Medicines Consortium**

**Ibandronic acid (ibandronate) 150mg film-coated tablets (Bonviva®)**

## Indication

Treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established.

## Dosing information

Ibandronic acid 150mg film-coated tablet once a month. The tablet should preferably be taken on the same date each month. It should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water) of the day or any other oral medicinal products or supplementation (including calcium).

## UK launch date

September 2005

## Comparator medications

Alendronate, risedronate sodium, raloxifene, disodium etidronate, calcitonin and teriparatide are included in the Scottish Intercollegiate Guidelines Network (SIGN) guideline, *Management of Osteoporosis* and the National Institute of Health and Clinical Excellence (NICE) appraisal, *Bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.* Strontium ranelate was accepted for restricted use by the SMC in July 2005.

## Cost of relevant comparators

| Drug | Dose | Cost * per year (£) |
|---|---|---|
| **Ibandronic acid** | **150mg once monthly** | **257** |
| teriparatide solution for injection | 20 micrograms once daily by subcutaneous injection | 3544 |
| calcitonin nasal spray | 200IU once daily | 547 |
| strontium ranelate granules | 2g once daily | 334 |
| alendronic acid tablets | 70mg once weekly | 293 |
| risedronate sodium tablets | 35mg once weekly | 264 |
| raloxifene tablets | 60mg once daily | 259 |
| disodium etidronate tablets (90 day cycles) Didronel PMO® | etidronate 400mg for 14 days, followed by cacit 500mg for 76 days | 150 |

* Costs from eVADIS drug dictionary accessed on 3/10/05

## Summary of evidence on comparative efficacy

Bisphosphonates act by reducing osteoclast-mediated bone resorption, which results in a decrease in bone turnover, an increase in bone mineral density (BMD) and a reduction in fracture risk.

Two phase III randomised double-blind parallel group studies have been conducted with ibandronic acid; one comparing placebo, daily administration and an intermittent administration regimen and the second study comparing daily administration with three different monthly regimens.

The first study recruited women aged between 55 and 80 years, who were post-menopausal for = 5 years with a lumbar BMD T-score between -2 and -5 in at least one vertebra and 1-4 prevalent vertebral fractures. Patients were randomised in blocks of six to ibandronic acid 2.5mg once daily, ibandronic acid 20mg every other day for 12 doses every three months (intermittent ibandronic acid) or placebo, all for three years. All women received calcium 500mg and vitamin D 400 IU daily supplements.

The intention-to-treat (ITT) population included 975, 977 and 977 patients in the placebo, daily ibandronic acid and intermittent ibandronic acid groups, respectively and comprised all patients who received at least one dose of study medication and who attended at least one follow-up visit. The primary endpoint was the rate of patients with new morphometric vertebral fractures at 3 years and was estimated, by life-table analysis, to be 9.6%, 4.7% and 4.9% for the placebo, daily ibandronic acid and intermittent ibandronic acid groups, respectively. The relative risk reduction compared with placebo was 62% (95% Confidence Interval (CI) 41-75) and 50% (95% CI 26-66) for the daily and intermittent ibandronic acid groups respectively.

There were significant differences in favour of daily and intermittent ibandronic acid compared with placebo for the following secondary end points; reduction in height loss, increases in BMD at the lumbar spine and hip, and changes in biochemical markers of bone turnover. However, the incidence of clinical non-vertebral fractures was similar for the three groups. The study population was at relatively low risk for new non-vertebral fractures as the mean proximal femur BMD was relatively high. A retrospective analysis showed that, when a high-risk subgroup of patients with a baseline femoral neck BMD T score < -3.0 was analysed, the relative risk reduction for non-vertebral fractures compared with placebo was 69% and 37% for the daily and intermittent ibandronate groups. This reached statistical significance for the daily ibandronate group only (p=0.013).

The second study was a two-year non-inferiority trial recruiting women between 55 and 80 years, who were post-menopausal for = 5 years and had osteoporosis (mean lumbar spine BMD T-score between -2.5 and -5.0). Stratification before randomisation by centre and baseline lumbar spine BMD T-score was done to ensure comparable distribution of baseline BMD across treatment arms. Patients were randomised to ibandronic acid; 2.5mg daily, 50mg/50mg (single doses given on consecutive days) monthly, 100mg monthly or 150mg monthly. All women received calcium 500mg and vitamin D 400 IU daily supplements. The per protocol population was used for analysis of non-inferiority and comprised 1290 patients. The primary efficacy variability for the non-inferiority analysis was % change from baseline in lumbar spine BMD for the monthly regimens compared with daily administration, at 1 year. Increases in lumbar spine BMD at 1 year were 3.9%, 4.3%, 4.1% and 4.9% for the daily, 50mg/50mg monthly, 100mg monthly and 150mg monthly ibandronic acid groups respectively, and non-inferiority was shown for all monthly regimens versus the daily regimen.

If non-inferiority was shown, superiority of the monthly regimens versus the daily regimen for the primary efficacy variable was tested; ibandronic acid 150mg regimen was shown to be superior to the daily regimen (p=0.002). For the secondary endpoints, similar increases in hip BMD (total hip, trochanter and femoral neck) were observed across the treatment groups and in the responder (% patients with an increase in BMD above baseline) analysis significant differences for the ibandronic acid 150mg versus daily ibandronic acid comparison were observed for lumbar spine and total hip BMD. Two year findings for this study, recently published in abstract form, reported increases in lumbar spine BMD of 6.6% and 5.0% for the ibandronic acid 150mg monthly and 2.5mg daily groups respectively. The ibandronic aicd 150mg group continued to be superior to the 2.5mg daily group (p<0.001) in terms of lumbar spine BMD.

## Summary of evidence on comparative safety

In the second study the incidence of drug related and/or unrelated adverse events, as well as rates of adverse events resulting in withdrawal from the study, were similar for the daily and monthly arms. Patients with controlled dyspeptic symptoms, history of non-recurring peptic ulcers and/or taking medications with potential for gastrointestinal (GI) irritation were included in the study. Upper GI adverse events in all patients and those patients with prior history of an upper GI disorder occurred in 18% and 38% of patients in the ibandronic acid daily arm and 17% and 20% in the ibandronic acid 150mg monthly arm. The summary of product characteristics for ibandronic acid (Bonviva®) recommends caution when using NSAIDs and ibandronic acid concomitantly. There was a higher reporting by patients of influenza-like symptoms in the ibandronic acid 150mg arm (8.3%) compared with ibandronic acid 2.5mg daily (2.8%).

## Summary of clinical effectiveness issues

There are no comparative trials of ibandronic acid with other standard treatments for osteoporosis in postmenopausal women.

The Committee for Proprietary Medicinal Products (CPMP) guidelines for the evaluation of new drugs for the prevention and treatment of postmenopausal women states that a suitable study population for the indication “treatment of osteoporosis” would be women with a BMD T-score at the spine or hip -2.5, with or without a history of fragility fractures, which concurs with the WHO definition of osteoporosis. In the first trial the inclusion criteria included women with a lumbar BMD T-score between -2 and -5 in at least one vertebra. Thus the study population in this trial included women who, according to the WHO definition, did not have osteoporosis. The mean lumbar BMD T-score for the placebo, daily and intermittent ibandronic acid groups was -2.8, -2.8 and -2.7.

While studies have shown that changing from daily to weekly dosing improves both compliance and efficacy with bisphosphonates, the evidence in terms of monthly dosing is less clear. One of the criteria for exclusion from the efficacy analysis in the second study was poor compliance, but details regarding the reasons for exclusion and hence the numbers of non-compliant patients in each arm have not yet been published. This makes it difficult to assess whether compliance would be improved by monthly dosing. The manufacturer has undertaken several studies looking at patient preference and these suggest that between 71 and 83% of patients prefer monthly to either daily or weekly bisphosphonates. The manufacturer has also undertaken to provide a free telephone helpline service to encourage long-term adherence to therapy.

A meta-analysis of 32 randomised clinical trials suggests that ibandronic acid is broadly equivalent to other bisphosphonates in terms of vertebral fracture reduction. However, it has not demonstrated equivalence in terms of hip fracture reduction.

## Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing only direct costs. The rationale for a cost minimisation model is that equivalent clinical effectiveness has been demonstrated with competitor products. This was determined by a literature review and formal meta-analysis of 32 randomised control trials relating to bisphosphonates. However, only two were head-to-head trials, these involving alendronate and risedronate. The meta-analyses appeared to indicate approximate equivalence or superiority in terms of preventing vertebral fractures. The different effects on femoral neck fractures are not considered and potentially undermine the cost-minimisation approach.

Given the cost-minimisation approach, the annual direct drug cost of ibandronic acid is estimated at £257. This compares with an annual cost of £293 for alendronate and £264 for risedronate, which when weighted by their market shares give an average cost of £287. Note that this excludes etidronate, which has an annual cost of £150 and a market share of around 11%. Its inclusion would reduce the current market share weighted cost of bisphosphonates to around £272. As a consequence, the manufacturer claims that ibandronic acid will be cost saving within NHS Scotland.

## Patient and public involvement

Patient Interest Group Submission: National Osteoporosis Society

## Budget impact

The eligible population is estimated as 55,000, comprising 49,000 currently being prescribed bisphosphonates coupled with an annual number of new patients of 5,589. The manufacturer estimates that 10% will switch to ibandronic acid in year 1. In year 2, 20% of the remaining population on other bisphosphonates is estimated as switching to ibandronic acid. This accelerates each year, until in year 5, of the few patients remaining on other bisphosphonates, 50% switch to ibandronate.

Given an annual cost of £257 per patient for ibandronic acid, on manufacturer assumptions this appears to indicate a gross direct drug cost of £500,000 in year 1, rising to £7,900,000 by year 5. This gross estimate implies near market dominance by year 5 which may be optimistic, but given the similarity in price with other competitor products, ibandronic acid is likely to be broadly cost neutral in terms of the direct drug costs and possibly even cost saving.

## Guidelines and protocols

SIGN issued guideline 71: *Management of Osteoporosis* in June 2003.[5] Treatment options include alendronate, risedronate, raloxifene, cyclical etidronate and calcitonin. This guideline predates the availability of ibandronic acid.

NICE have published an appraisal entitled *Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women* in January 2005.[6] This guideline predates the availability of ibandronic acid.

## Additional information

The Scottish Medicines Consortium has issued advice on risedronate sodium, teriparatide and strontium ranelate. In May 2003 risedronate sodium was recommended for general use for the prophylaxis and treatment of osteoporosis in post-menopausal women. This was in response to an abbreviated submission for a new once weekly formulation.

In December 2003, teriparatide was accepted for restricted use for the treatment of established (severe) osteoporosis in post-menopausal women. The medicine was restricted to initiation by specialists experienced in the treatment of osteoporosis following assessment of fracture risk, including measurement of BMD.

In July 2005 strontium ranelate was accepted for restricted use for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures when bisphosphonates are contra-indicated or not tolerated, and then only in women aged over 75 with a previous fracture and T-score < -2.4 or other women at equivalent high risk.

The Scottish Medicines Consortium has also issued advice on ibandronic acid (Bondronat®). In October 2004 ibandronic acid (Bondronat®) was accepted for use for the treatment of tumour-induced hypercalcaemia with or without metastases, and for the prevention of skeletal events in patients with breast cancer and bone metastases.

***Advice context:***

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 11 November 2005.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.*

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

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