

**ibandronic acid (also known as ibandronate),  
3mg in 3ml solution for injection in prefilled syringe  
(Bonviva<sup>o</sup>)** **No. (301/06)**

---

**Roche/GlaxoSmithKline**

4 August 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

**Intravenous ibandronic acid (Bonviva<sup>o</sup>)** is accepted for restricted use within NHS Scotland for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established.

Intravenous ibandronic acid is restricted to use in patients who are unsuitable for or unable to tolerate oral treatment options for osteoporosis. Treatment initiation should be under specialist supervision.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

**Ibandronic acid 3mg in 3ml  
solution for injection  
(Bonviva®)**

**Indication**

For the 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**

3mg administered as an intravenous injection over 15-30seconds, every three months. Strict adherence to the intravenous route is required. Patients must receive supplemental calcium and vitamin D.

**UK launch date**

5 April 2006

**Comparator medications**

Oral bisphosphonates, raloxifene, calcitonin, teriparatide, intravenous (IV) pamidronate (off licence use) and IV zoledronic acid (off licence use but in phase III trials for postmenopausal osteoporosis)

**Cost of relevant comparators**

Drug	Dose	Cost * per year (£)
<b>Ibandronic acid injection</b>	<b>3mg IV every three months</b>	<b>320</b>
Teriparatide injection	20 micrograms once daily by subcutaneous injection	3544
Calcitonin nasal spray	200IU once daily	547
Strontium ranelate granules	2g once daily	334
Risedronate sodium tablets	5mg daily or 35mg once weekly	249-264
Raloxifene tablets	60mg once daily	222
Ibandronic acid tablets	150mg once monthly	257
Alendronic acid tablets	10mg daily or 70mg once weekly	256-301
Pamidronate injection	30mg-60mg IV every three months	220-440
Disodium etidronate tablets then calcium carbonate tablets (90 day cycle) Didronel PMO®	400mg for 14 days, followed by 500mg for 76 days	86

\* Costs from eVADIS drug dictionary accessed on 6/6/2006; doses do not indicate therapeutic equivalence

## Summary of evidence on comparative efficacy

Postmenopausal osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue resulting in an increase in bone fragility and susceptibility to fracture. 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. Their exact mode of action is not fully understood.

The phase III, double-blind comparator study to establish the non-inferiority of IV to oral ibandronate, randomised 1395 postmenopausal women with osteoporosis (defined as mean lumbar (L2-L4) BMD T-score between -2.5 and -5.0) to daily oral ibandronate 2.5mg (n=470) or intravenous ibandronate: 2mg every 2 months (n=454) or 3 mg every 3 months (n=471), for two years. Patients were stratified for baseline BMD. The primary outcome measure was the mean percentage change from baseline in mean lumbar (L2-L4) BMD at one year. The analysis of non-inferiority was in the per protocol population at two years. Secondary outcomes included mean percentage change from baseline in mean lumbar BMD, in total hip BMD and the percentage of BMD responders. Non-inferiority was clearly demonstrated with a =-1.3% difference in the one-sided confidence interval for the mean percentage change from baseline in lumbar spine between treatments at two years. Compared with oral ibandronate, 3mg IV ibandronate every three months (the licensed dose) provided significantly greater increases in mean lumbar spine BMD at one and two years, 3.8% vs 4.8% and 4.8% vs 6.3%, respectively (p < 0.001). The IV formulation also achieved significantly greater gains in mean total hip BMD at one and two years, 1.8% vs 2.4% and 2.2% vs 3.1%, respectively (p < 0.05). The percentage of patients with no change or an increase in lumbar BMD, total hip BMD and both lumbar and total hip BMD, at one and two years was significantly greater for the IV versus the oral formulation of ibandronate for all measures at all time points. Bone turnover was similar in both groups. Additional data are presented below.

### Mean percentage change from baseline in bone mineral density in postmenopausal women with osteoporosis with oral and intravenous ibandronate (PP population)

	Analysis at 1 year		Analysis at 2 years	
	2.5mg oral daily N=377	3mg iv 3-monthly N=365	2.5mg oral daily N=334	3mg iv 3-monthly N=334
Mean (95% confidence intervals) percent change from baseline in bone mineral density				
Femoral neck	1.6% [1.2,2.0]	2.3% [1.9,2.7]	2.2% [1.8,2.7]	2.8%[2.3,3.3]
Trochanter	3.0% [2.6,3.4]	3.8% [3.2,4.4]	3.5% [3.0,4.0]	4.9% [4.1,5.7]
Percentage of patients with no change or increase from baseline in bone mineral density				
Lumbar spine	85%	92%	85%	93%
Total hip	75%	83%	77%	86%

## Summary of evidence on comparative safety

In clinical trials for postmenopausal osteoporosis, no new adverse events were reported that were not already known for oral or intravenous ibandronate. Most cases of adverse reactions did not lead to cessation of therapy. Acute phase reactions are often associated with IV bisphosphonates. The reported incidence over one year in the above comparator trial was 14% and 4% for the IV and oral formulations, respectively. Over 80% of patients who experienced an initial reaction did not report symptoms with subsequent doses. The majority of cases were mild and did not lead to discontinuation of therapy.

## Summary of clinical effectiveness issues

Registration of a new formulation for an already established treatment for postmenopausal osteoporosis does not require demonstration of a reduction in fracture rate, only to show non-inferiority to the existing formulation in terms of the effects on BMD. Daily and intermittent oral ibandronate are already licensed in postmenopausal osteoporosis and have previously been shown to reduce risks of vertebral fractures, although, unlike some other bisphosphonates, efficacy in reducing femoral neck (and other non-vertebral fractures) has not been established. Intravenous ibandronate 3mg every three months has been shown to be non-inferior to oral ibandronate 2.5mg daily in increasing BMD. Although not required for registration, in a prospectively specified test in the key comparative study, IV ibandronate was shown to be not only non-inferior to but also superior to the oral formulation.

In practice intravenous dosing may offer better compliance, which can be an issue due to the problems with adhering to the oral dosing requirements of bisphosphonates. It will also deliver a defined dose and is not affected by variable exposure due to erratic oral absorption. The quarterly IV regimen will therefore be useful for those patients who have difficulty complying and those who are unable to comply with the instructions for administration of oral bisphosphonates, such as remaining upright for 30-60 minutes after ingestion. The administration of a 15-30second injection should offer practical advantages over the infusion of the 'off licence' bisphosphonates used at present.

## Summary of comparative health economic evidence

The manufacturer presents a cost minimisation analysis, comparing ibandronate IV with pamidronate IV. This is justified on the basis of an informal indirect comparison. As pamidronate is being used off licence the evidence base for this is poor, and it is difficult to draw firm conclusions as to relative efficacy.

The key inputs to the cost minimisation analysis appear to be largely based on assumptions rather than on hard data sources.

The direct drug acquisition costs for ibandronate are greater than for pamidronate 30mg, but less than for pamidronate 60mg. The manufacturer combines these pamidronate doses on a 50:50 basis to estimate the average cost of pamidronate. On this basis, the average cost of pamidronate is £338 as against £320 for ibandronate. As a consequence, ibandronate is cost saving against this average.

When administration costs are taken into account, ibandronate is cheaper than both the 30mg and 60mg formulations of pamidronate.

Given the assumptions as to administration costs and the 50:50 split between 30mg and 60mg pamidronate, ibandronate is cost saving. The staff time dedicated to infusion of pamidronate has to fall to around 25-30 minutes for the entire infusion episode for each patient for this conclusion to be reversed for the lower cost 30mg pamidronate dose, and ibandronate remains cheaper than higher cost 60mg pamidronate dose regardless of the staff time required per infusion.

## Patient and public involvement

Patient Interest Group Submission: National Osteoporosis Society

## Budget impact

The manufacturer estimated that 450 patients are assumed to be eligible for treatment with ibandronate IV. With a market penetration of 70% or 315 patients transferring at the six month point in year 1, the direct drug cost is estimated as around £50K. With 100% of the market in year 3 this cost rises to £137K. Given the assumed 50:50 split between 30mg and 60mg pamidronate, ibandronate is anticipated to provide a net saving of around £3K in year 1, rising to £8K in year 5.

## Guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) issued guideline 71: *Management of Osteoporosis* in June 2003. Treatment options included alendronate, risedronate, raloxifene, cyclical etidronate and calcitonin. This guideline predates the licensing of ibandronic acid for treatment of postmenopausal osteoporosis.

The National Institute for Health and Clinical Excellence (NICE) have published a technology appraisal on Osteoporosis – secondary prevention 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. This guideline predates the licensing of ibandronic acid for treatment of postmenopausal osteoporosis.

NICE have also a clinical guideline in development for which a publication date is still to be confirmed, entitled *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk*.

## Additional information

After review of an abbreviated submission, the Scottish Medicines Consortium (SMC) issued advice in May 2003 that risedronate sodium (Actonel<sup>®</sup>) is recommended for general use within NHS Scotland. It is a one weekly formulation which offers a convenient, cost neutral alternative to once daily medication for the prophylaxis and treatment of osteoporosis in post-menopausal women.

After review of a full submission, SMC issued advice in December 2003 that teriparatide (Forsteo<sup>®</sup>) is accepted for restricted use within NHS Scotland for the treatment of established (severe) osteoporosis, in post-menopausal women. The medicine should be restricted to initiation by specialists experienced in the treatment of osteoporosis following assessment of fracture risk, including measurement of BMD. It is the first product to be licensed specifically for established (severe) post-menopausal osteoporosis. It has shown efficacy in reducing vertebral and non-vertebral fractures post-menopausal women with prior vertebral fractures, particularly in a sub-group with documented severe osteoporosis. At the recommended daily

dose it is expensive but appears to be cost-effective in women with proven osteoporosis who have developed fractures.

After review of a full submission, SMC issued advice in July 2005 that strontium ranelate (Protelos<sup>®</sup>) is accepted for restricted use within NHS Scotland 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. In the trial population of postmenopausal women, strontium ranelate reduced the risk of developing a vertebral fracture by 41%. In women  $\geq 74$  years with a femoral neck BMD T-score < -2.4 the risk of fractures was reduced by 36%. However, equivalent cost-effectiveness to bisphosphonate therapy has not been demonstrated.

After review of a full submission, SMC issued advice in October 2004 that ibandronic acid (Bondronat<sup>®</sup>) is accepted for use within NHS Scotland for the treatment of tumour-induced hypercalcaemia with or without metastases. It has been shown to be a cost-effective option in reducing serum calcium in patients with hypercalcaemia of malignancy.

After review of full submission, SMC issued advice in October 2004 that ibandronic acid (Bondronat<sup>®</sup>) is accepted for use within NHS Scotland for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. It reduces the rate of skeletal events consisting of a composite of vertebral fractures, pathological non-vertebral fractures and the need for radiotherapy or surgery to deal with bone complications. It can be given both by the oral and intravenous route.

After review of a full submission, SMC issued advice in January 2006 that ibandronic acid (Bonviva<sup>®</sup>) 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 BMD at 1 year. Compared to 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) was not established.

**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 14 July 2006.*

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

*The undernoted references were supplied with the submission.*

*Emkey R, Zaidi M, Lewiecki EM et al. Two-year efficacy and tolerability of intermittent intravenous ibandronate injections in postmenopausal osteoporosis: the DIVA study  
Arthritis Rheum 2005;52;4060 (Abstract)*

*Reid DM, Eisman J, Emkey R et al. Intermittent intravenous ibandronate infections show similar safety to daily oral ibandronate: 1-year results from DIVA  
Osteoporosis Int 2005;16(suppl 3):S80 (Abstract P308)*