

# NEW DRUG EVALUATION

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## ONCE-MONTHLY IBANDRONIC ACID

Ibandronic acid 150 mg (Bonviva®) is a bisphosphonate licensed for the treatment of osteoporosis in postmenopausal women. Ibandronic acid 2.5 mg daily has been shown to significantly reduce the risk of vertebral fractures but the effect of 150 mg once-monthly on fracture risk has not been directly assessed. The 150 mg once-monthly and 2.5 mg daily regimens showed improvements in lumbar bone mineral density, a surrogate marker of osteoporosis. There are no data on hip fractures or hip fracture risk. The most frequent adverse effects in clinical trials were dyspepsia, abdominal pain, influenza-type illness and nausea. The incidence of influenza-like symptoms appears to be increased compared with other bisphosphonates. Although some women may prefer this approach there is currently no evidence of important advantages in clinical outcome for once-monthly ibandronic acid 150 mg compared with other bisphosphonates regimens.

### What is it?

Ibandronic acid 150 mg (Bonviva®, Roche), a bisphosphonate, is the first once-monthly tablet for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral fractures. It is not licensed to reduce the risk of hip fractures or for primary prevention of osteoporosis.<sup>1</sup> The recommended dose is 150 mg once a month, to be taken preferably on the same date each month. Tablets must be taken one hour before the first food or drink of the day. The manufacturers claim that once-monthly dosing may result in better compliance than other regimens, and is preferred to weekly regimens by most women (data only available as an abstract).<sup>2</sup>

Ibandronic acid is also available orally for the reduction of bone damage in bone metastases in breast cancer and parenterally for hypercalcaemia of malignancy.

### How effective is it?

The effect of a once-monthly ibandronic acid dosage regimen on the occurrence of fractures has not been directly assessed. Ibandronic acid for the treatment of osteoporosis has been studied in two large clinical trials. The first of these (BONE) assessed the effect of ibandronic acid on vertebral fracture risk, but did not use a once-monthly dosage schedule.<sup>3</sup> The second (MOBILE) demonstrated that ibandronic acid 150 mg once-monthly and 2.5 mg daily had equivalent effects on increasing lumbar bone mineral density (BMD) (a surrogate marker of osteoporosis), but did not measure fracture risk.<sup>4</sup>

BONE (n = 2946), a three-year randomized, double-blind, placebo-controlled, parallel-group trial, assessed the difference between ibandronic acid 2.5 mg daily and intermittently (20 mg every other day for 12 doses, every three months). The primary endpoint was the incidence of new vertebral fractures after three years of treatment.<sup>3</sup> Postmenopausal women (55-80 years) with one or more existing vertebral fractures (and a BMD T-score of -2.0 to -5.0 in at least one vertebra) were included in the study.<sup>3</sup> Significant differences were quoted between each treatment group and placebo, with relative risk reduction values of 62% (p = 0.0001) for the daily regimen, and 50% (p = 0.0006) for the intermittent regimen. The absolute incidence of new fractures at year three was 9.6% for placebo, and 4.7% and 4.9% for daily and intermittent regimens respectively, which equate to absolute risk reduction values of 4.9% and 4.7%, or NNT values of 20 and 21 over three years.<sup>3</sup> There was no significant difference between the two treatment groups (p = 0.28).

The two-year MOBILE study (n = 1609) compared the effect of

ibandronic acid 150 mg once-monthly with other oral ibandronic acid regimens; the one-year efficacy results are published.<sup>4</sup> The study was of a randomised, double blind, multi-centre, non-inferiority design.<sup>4</sup> The aim was to assess the effects of 50 mg daily for two consecutive days each month (50 mg/50 mg), 100 mg monthly and 150 mg monthly ibandronic acid regimens on BMD compared with 2.5 mg daily. The primary endpoint was percentage change from baseline in mean lumbar spine BMD.<sup>4</sup> One-year results showed non-inferiority of all intermittent therapies on the primary endpoint; there was a 4.3%, 4.1% and 4.9% increase in BMD in the 50 mg/50 mg, 100 mg and 150 mg monthly groups respectively, compared to 3.9% in the daily treatment group.<sup>4</sup> The increase in BMD in the 150 mg monthly group compared to the daily regimen was statistically significant (p = 0.002).<sup>4</sup> This trial did not assess the effect of once-monthly ibandronic acid on fracture rate or risk. Preliminary two year results have been described and showed similar non-inferiority across all groups.<sup>5</sup> Details of these results are only available in abstract form.

There are no published studies which compare efficacy of once-monthly ibandronic acid with other bisphosphonates, although Roche and GSK have recently announced the start of a large-scale trial (MOTION) comparing once-monthly ibandronic acid to weekly alendronic acid.<sup>6</sup>

### How safe is it?

There are no published studies to date which compare the safety of once-monthly ibandronic acid with other bisphosphonates. The most frequently reported adverse events after one year in the MOBILE study were abdominal pain (3.5%), dyspepsia (3.3%) and nausea (3.3%).<sup>1</sup> These common adverse effects have also been reported for the other oral bisphosphonates.<sup>7-9</sup> Influenza-like illness (myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite or bone pain) was reported more frequently with ibandronic acid 150 mg monthly than the other ibandronic acid dosage schedules (3.3% in 150 mg monthly versus 0.3% in the 2.5 mg daily schedule);<sup>1</sup> no statistical analysis of this difference was reported.<sup>4</sup> The frequency of influenza-like illness (myalgia, malaise and fever) was < 0.1% in clinical trials with alendronate.<sup>9</sup>

### What other options are there?

Three other bisphosphonates are licensed for use in postmenopausal osteoporosis. Cyclical disodium etidronate with calcium carbonate, risedronate and alendronate are all licensed for prevention of fractures in postmenopausal women with

osteoporosis, and for primary prevention of osteoporosis.<sup>7,8,10</sup> Alendronate and risedronate are both available as once-weekly preparations. Alendronate is also licensed for the treatment of osteoporosis in men.<sup>10</sup>

Strontium ranelate (reviewed in New Drug Evaluation No. 69) has a novel mechanism of action and is also licensed for the treatment of postmenopausal osteoporosis.<sup>11</sup> An injectable formulation of ibandronic acid to be given quarterly by a health professional has recently been approved for postmenopausal osteoporosis by the FDA.<sup>12</sup> Calcium and vitamin D should be used as adjuncts to bisphosphonates unless the patient is considered to have adequate dietary levels (Drug Update No. 47).

### When should it be used?

The National Institute for Clinical Excellence (NICE) currently recommends bisphosphonates for the secondary prevention of osteoporotic fractures in postmenopausal women who have sustained a clinically apparent fracture.<sup>13</sup> Guidance on the primary

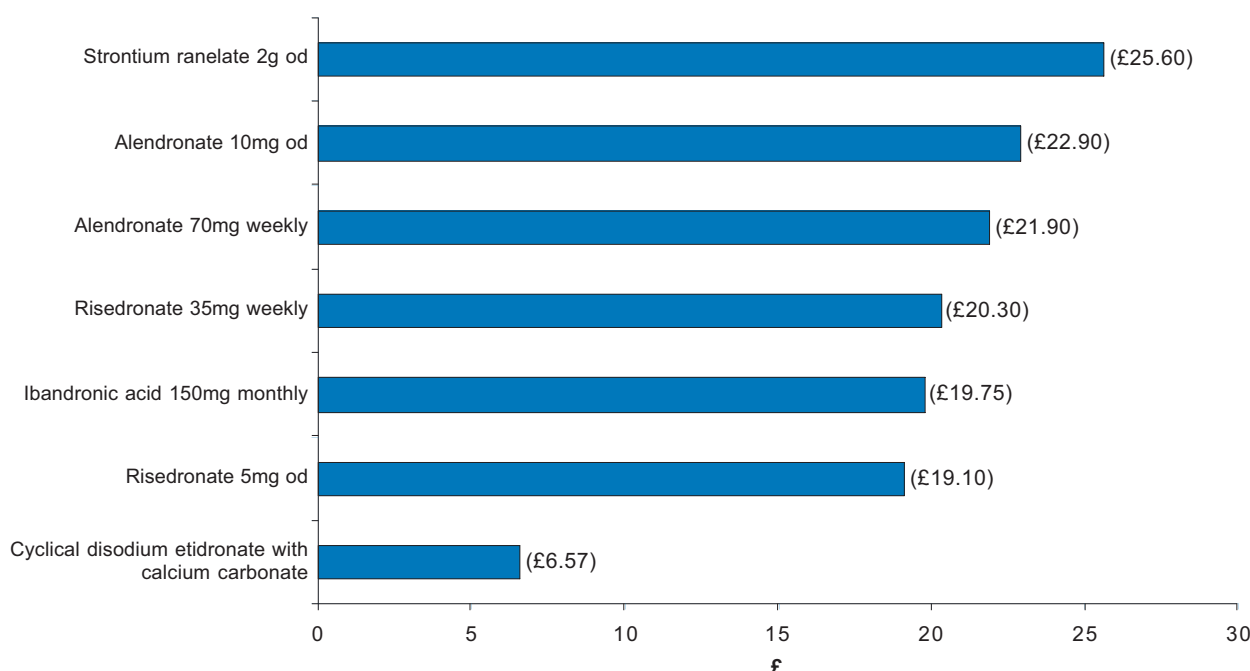
prevention of fractures in postmenopausal women is in development. Ibandronic acid and strontium ranelate are not licensed for primary prevention of osteoporosis.

There is currently no evidence available to conclude whether once-monthly ibandronic acid 150 mg is more effective or better tolerated than other bisphosphonates. The effect of ibandronic acid on hip fractures, which are associated with the highest rates of mortality and morbidity, has not been assessed. Once-monthly ibandronic acid may be an alternative in women who prefer to take once-monthly doses or who are intolerant of other bisphosphonates.

Between April and September 2005, 117,000 items at a cost of £3 million and 326,000 items at a cost of £9 million were prescribed in Greater Manchester Strategic Health Authority and the Former Northern and Yorkshire Region respectively. In these areas, the total spend on bisphosphonates for the treatment of postmenopausal osteoporosis has approximately doubled since 2002.

### How much does it cost?

Cost for 28 days treatment (prices from Drug Tariff/eMIMs March 2006)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, G-guideline, Abs- abstract.

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