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# Treating Osteoporosis with Bisphosphonates and Addressing Adherence

## A Review of Oral Ibandronate

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## Contents



## Abstract

Osteoporosis is a common, chronic condition, affecting approximately half of all postmenopausal Caucasian women in the US. Vertebral fractures occur as a result of osteoporosis and lead to increased hospitalisation and mortality, and adversely affect patient quality of life. The burden of osteoporosis on healthcare systems is expected to rise as the elderly population continues to grow. Yet there are many medications for preventing and treating osteoporosis.

Oral bisphosphonates are first-line treatment for osteoporosis, with demonstrated efficacy in increasing bone mineral density and reducing bone turnover, which reduces the incidence of fractures. However, adherence to medication is suboptimal, with approximately 40% of patients discontinuing treatment within 6 months. Recent reports have suggested simplifying the dosage regimen as a strategy to help address this issue.

Ibandronate is a potent, nitrogen-containing bisphosphonate which is administered once-monthly. Preclinical studies initially revealed the feasibility of extending the between-dose interval. Subsequent clinical studies have provided further evidence of the positive effects of extended-interval ibandronate administration in reducing the risk of vertebral fractures through increasing bone mineral density and reducing bone turnover without compromising bone quality. These studies have also demonstrated that ibandronate has a safety profile similar to placebo. Ibandronate has recently been approved for use in the US to treat postmenopausal osteoporosis.

This review summarises the efficacy and safety of once-monthly oral ibandronate and discusses the implications of such a treatment in primary care in the US.

## 1. Osteoporosis

### 1.1 The Burden

Osteoporosis is a degenerative skeletal disease, in which increased bone turnover, decreased bone mass and abnormal microarchitecture increase the risk of fractures.[1] In elderly women, it is a common chronic condition,[2] with low bone mass found in more than half of Caucasian women.[3] As a result, some investigators have estimated that a 50-year-old woman has a 40% risk of experiencing an osteoporotic fracture in her remaining lifetime,[3] while other models suggest that half of postmenopausal women will experience at least one osteoporotic fracture during their lifetime.[4]

Although nonvertebral fractures are associated with substantial pain and disability, vertebral fractures are responsible for considerable reductions in quality of life,[5] increased risk of hospitalisation and mortality,[6,7] and are the most frequent of all osteoporotic fractures.[8] Furthermore, patients with existing vertebral fractures are highly likely to experience additional vertebral fractures[9,10] and have substantially greater risk for subsequent fractures at all sites.[11]

### 1.2 Diagnosis

The diagnosis of osteoporosis has historically been based on the deviation below 'normal' bone mineral density (BMD), and was defined differently by the WHO[12] and the National Osteoporosis Foundation.[13] The level of deviation from normal BMD is conveyed using T-scores (standard deviations). However, it is recognised that BMD is only one of a number of clinical risk factors requiring consideration when deciding whether to treat patients. More recent professional guidelines[14-17] have incorporated other risk factors (summarised in table I) in their diagnostic algorithms, and the anticipated revision of the WHO guidelines for osteoporosis is also expected to place greater emphasis on these other risk factors[18] than on BMD T-score.

**Table I.** Factors recognised in treatment guidelines as providing increased risk for osteoporotic fracture

| |
|---|
| Personal and family history of low-trauma fracture as an adult |
| Low bodyweight |
| Current smoking |
| Corticosteroid use for more than 3 months |
| Age |
| Early estrogen deficiency |
| Lifelong low calcium intake |
| Low physical activity |
| High bone turnover |
| Tallness |
| Recent falls |
| General poor health |
| Dementia |
| Impaired vision or hearing |
| Excessive alcohol intake |

### 1.3 Management and Adherence to Medication

In managing postmenopausal osteoporosis, orally administered nitrogen-containing bisphosphonates are considered the standard of care by many clinicians.[12,15,19] The ability of oral daily bisphosphonates to increase BMD significantly and decrease biochemical markers of bone turnover has been widely demonstrated in large-scale, well designed clinical studies conducted in postmenopausal women with osteoporosis.[20-25] These BMD changes have been observed in association with significant reductions in the incidence of vertebral fractures.[20,21,25-27]

Adherence to any long-term therapy is known to be mediocre, around 50% at best, regardless of the disease and treatment.[28] This situation is no different with oral bisphosphonates,[29] which is not surprising given the stringent dosage requirements of this drug class. In addition, patients do not experience overt evidence of their condition, and consequently may not believe their diagnosis, accept the need for medication or perceive the threat to their health from their disease.[28,30,31] Evidence from clinical studies conducted in various therapeutic ar-

eas indicates that patients are more likely to be adherent when the frequency and complexity of administration is reduced.[32,33] This strategy for improving adherence has been demonstrated in osteoporosis by the better adherence seen with weekly (versus daily) bisphosphonate therapy after its introduction to the marketplace.[34,35]

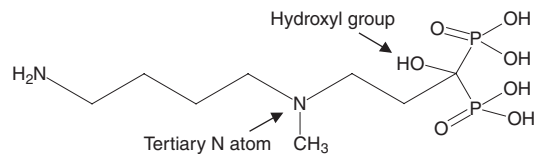
However, up to 40% of patients with osteoporosis still prematurely withdraw from available treatments within 6–7 months of beginning therapy.[36-38] This premature withdrawal of medication can lead to reduced efficacy, associated with up to a 26% increase in the risk of fracture, and may place a substantial burden on health service resources.[39,40] Preliminary patient database analyses reveal that, although weekly administration significantly improves persistence, it remains suboptimal. Only 45% of patients receiving weekly treatments maintained adequate refill compliance (treatment for >80% of the time) over 1 year[35] and only 57% were still persisting with their medication after 1 year.[41] Therefore, the recent US Surgeon General's report[42] highlighted the urgent need to improve adherence in postmenopausal osteoporosis and address suboptimal therapeutic outcomes. Interestingly, the report recommends simplified dosage as one of the strategies for improving adherence, and recent findings in a study of women's medication preferences suggest that the majority of women (63%) with postmenopausal osteoporosis would prefer a monthly treatment to their current weekly regimen, if the option were available.[43] In this study, the most commonly cited reasons for a monthly preference were 'less frequent administration' (73%) and 'fits better with lifestyle' (49%), indicating the level of inconvenience patients perceive with current bisphosphonate dosage regimens.

Osteoporosis is more common in the elderly, and consequently there is an increased likelihood of concurrent diseases requiring concomitant medication, which can worsen the level of non-adherence.[44] In addition, such polypharmacy also exposes individuals to a higher risk of treatment-related adverse events and drug interactions,[45] which themselves have been identified as a cause of discontinuation with therapy.[36,37] The prevalence of concomitant therapy in the elderly has been surveyed in 1197 community-dwelling people aged ≥64 years,[46] where it was found that 78% used prescription drugs and 25% received more than five concomitant medications (mean number of medications per person: 3.8). Preliminary data from the analysis of US prescriptions for more than 250 000 women with postmenopausal osteoporosis suggest similarly high numbers of concomitant medications,[47] with approximately 35% taking four or more other prescription drugs as well as their bisphosphonate. Strategies for reducing medication complexity and burden would appear to be much needed for patients with osteoporosis.

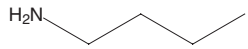
## 2. Oral Ibandronate

### 2.1 Development of a Monthly Bisphosphonate to Improve Adherence

Ibandronate is a nitrogen-containing bisphosphonate with particular structural features (figure 1) and characteristics that enable administration with extended between-dose intervals: (i) high potency;[48] and (ii) favourable skeletal binding.[49,50] These characteristics were selected to provide the basis for




Alendronate has an alternative $R_2$ chain, with a primary nitrogen atom:




Risedronate also has a different $R_2$ chain, with a tertiary nitrogen atom:

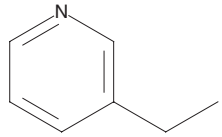



**Fig. 1.** Chemical structure of ibandronate, demonstrating the unique structure of the $R_2$ side chain with the tertiary N atom, compared with the well known examples of alendronate and risedronate (alendronate, risedronate and ibandronate all have an hydroxyl group as the $R_1$ substituent).

less frequent oral and intravenous dosage regimens[50] than are currently available. The ability of ibandronate to be given with reduced frequency was first demonstrated in preclinical studies involving a wide range of appropriate animal models of osteoporosis.[49]

Antiresorptive potency is measured by *in vivo* and *in vitro* models that assess the quantity of bisphosphonate necessary for clinical efficacy. Ibandronate has been the subject of a rigorous preclinical programme, closely following the WHO recommendations for using animal models of osteoporosis.[51] In rats,[52,53] dogs[54,55] and monkeys,[56] long-term administration of extended-interval ibandronate (for up to 16 months) provided similar improvements in various indices of bone mass to those achieved with daily administration.

Preclinical experience with other bisphosphonates has raised potential safety issues regarding bone quality[57] and upper gastrointestinal tolerability.[58] In preclinical trials, even when ibandronate was administered at >5000 times the therapeutic dose in rats, it was associated with the formation of new, normal-quality bone, with no evidence of impaired mineralisation.[48] Extended-interval ibandronate has a low potential for upper gastrointestinal toxicity[51] and is predicted to minimise oesophageal irritation, given the diminished tablet-esophagus contact as a result of reduced administration frequency. In a phase III, double-blind, placebo-controlled study, the incidence of upper gastrointestinal adverse events with intermittent (20mg every other day for 12 doses every 3 months) ibandronate was comparable to placebo, despite the lack of upper gastrointestinal exclusion criteria.[27] Almost one-third of patients in this study had a history of upper gastrointestinal disorders; however, this group showed no increase in risk of upper digestive system adverse events when treated with oral ibandronate.

The feasibility of administering oral ibandronate continuously or intermittently was initially demonstrated in a randomised, double-blind, placebo-controlled, phase II study.[59] Daily or intermittent oral ibandronate regimens that provided equivalent cumulative doses were shown to be similarly effective in increasing BMD and decreasing bone turnover in women with postmenopausal osteoporosis. Ibandronate therapy was also well tolerated, with a safety profile similar to placebo.

These positive initial findings led to the further clinical development of ibandronate, with the ultimate goal of generating a simple, once-monthly, orally administered bisphosphonate.

The BONE (oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe) study demonstrated that daily and intermittent (>2-month dose-free interval) ibandronate produce significant increases in bone density compared with placebo at the lumbar spine (6.5% and 5.7%, respectively) after 36 months ($p < 0.0001$).[27] Comparisons with BMD changes in the literature following bisphosphonate administration suggest that values obtained in BONE were broadly comparable to those from across the nitrogen-containing bisphosphonate class (table II).[19,25,26,60]

BMD scores are generally accepted as surrogate markers of bone strength, although some have debated the degree of correspondence between treatment-related improvements in BMD scores and changes in fracture risk.[62-66] Decreases in resorption marker levels are significantly and independently associated with fracture risk reduction.[62,67,68] Given this relationship, it is not surprising that ibandronate was efficacious versus placebo in reducing vertebral fracture rates. In BONE, the incidence of new vertebral fractures over 3 years was significantly and substantially reduced with both oral daily and intermittent ibandronate compared with placebo, with relative risk reductions versus placebo of 52% and 50% for the daily and intermittent groups, respectively.[27]

As the first prospectively designed trial powered to assess fracture reduction with a nitrogen-containing bisphosphonate administered less frequently than daily (no weekly formulation has been similarly evaluated in a prospective fracture trial), the BONE study provides proof of the potential antifracture efficacy of extended-interval ibandronate administration. Although cross-study comparisons have limitations, these fracture risk reductions are comparable to those reported for other daily bisphosphonates (relative risk reduction vs placebo: alendronate 0.53, risedronate 0.51).[25,26]

The incidence of nonvertebral fractures did not differ between the placebo, daily and intermittent

**Table II.** Bone mineral density (BMD) [lumbar spine, total hip, femoral neck, trochanter] change versus baseline for alendronate, risedronate and ibandronate at 12 and 36 months

| Drug | BMD (%) at 12 months | | | | BMD (%) at 36 months | | | |
|---|---|---|---|---|---|---|---|---|
| | lumbar spine | total hip | femoral neck | trochanter | lumbar spine | total hip | femoral neck | trochanter |
| Alendronate (daily) | 5.4[a] | 3.1[a] | 2.9[a] | 4.4[a] | 6.2[b]* | 4.7[b]* | 4.1[b]* | 6.1[b]* |
| Alendronate (weekly)[a] | 5.1 | 2.9 | 2.3 | 3.9 | NE | NE | NE | NE |
| Risedronate (daily) | 4.0[c] | 2.5[c] | 2.1[c] | 3.3[c] | 5.9[d]* | NE | 3.1[d]* | 6.4[d]* |
| Risedronate (weekly)[c] | 3.9 | 2.4 | 1.9 | 3.0 | NE | NE | NE | NE |
| Ibandronate (daily)[e] | 4.7 | 2.6* | 2.1* | 3.7* | 6.5 | 3.4 | 2.8 | 5.5 |
| Ibandronate (extended-interval)[e] | 4.0 | 2.3* | 2.0* | 3.6* | 5.7 | 2.9 | 2.4 | 5.2 |
| Ibandronate (monthly)[f] | 4.9 | 3.1 | 2.2 | 4.6 | NE | NE | NE | NE |

a Schnitzer et al.[60] (2000).

b FIT (Fractyre Intervention Trial) 1, Black et al.[26] (1996).

c Brown et al.[19] (2002).

d VERT (Vertebral Efficacy with Risedronate Therapy) study, Reginster et al.[25] (2000).

e Chesnut et al.[27] (2004).

f MOBILE (Monthly Oral iBandronate In LadiEs) study, Miller et al.[61] (2005).

**NE** = not evaluated; * BMD change vs placebo.

ibandronate groups in BONE.[27] The population of the BONE study had a relatively high mean femoral neck BMD T-score at baseline (less than one-third of patients had a femoral neck BMD T-score of −2.5 or lower; mean femoral neck BMD T-score = −2.0) and their total hip BMD T-score was even higher, being −1.7 in all three groups. This might suggest a lower relative risk for new hip and nonvertebral fractures, a hypothesis supported by the low fracture rates in the BONE placebo group.

Evidence of nonvertebral antifracture efficacy was demonstrated in a *post hoc* subgroup analysis of the daily oral ibandronate regimen in higher risk patients, who were identified by a significant interaction found between treatment effect on nonvertebral fractures and femoral neck baseline BMD above and below a T-score of −3.0 ($p = 0.0027$). Using this criterion, a relative risk reduction of nonvertebral fractures with oral daily and intermittent oral ibandronate (69%, $p = 0.013$ and 37%, $p = 0.22$, respectively) was demonstrated in patients with a baseline femoral neck BMD T-score less than −3.0.[27]

Having demonstrated the antifracture efficacy of oral ibandronate with an extended interval dosage, it was important to generate a simple, convenient administration regimen to encourage greater patient adherence. The MOBILE (Monthly Oral iBandronate In LadiEs) study showed the efficacy (defined by BMD increase) and safety of three monthly oral ibandronate regimens in a multinational, phase III, non-inferiority trial.[61] After 1 year, lumbar spine BMD increased by 4.3%, 4.1% and 4.9% in the 50/50mg (50mg dose given for 2 consecutive days), 100mg and 150mg monthly groups. All monthly regimens were non-inferior to the proven 2.5mg daily regimen (3.9% lumbar spine BMD increase), and subsequent, prospective statistical analyses demonstrated the superiority of the 150mg monthly regimen to the 2.5mg daily regimen ($p = 0.002$). These increases in BMD with monthly ibandronate were expected given the positive BMD and antifracture results of the pivotal BONE study.

Within the MOBILE study, the BMD increases noted at 1 year were associated with a pronounced decrease in a resorption marker (serum C-telopep-

tide of the α-chain of type I collagen [sCTX]).[61] After 3 months, similar decreases in sCTX were observed in all treatment arms and maintained throughout the study period. After 1 year, median sCTX levels were decreased by 62.8%, 66.7% and 75.8% in the 50/50mg, 100mg and 150mg monthly arms, respectively, compared with 67.3% in the daily arm. Comparable findings were reported in the BONE study, with urinary CTX and NTX (N-telopeptides of the α-chain of type I collagen) reductions maintained throughout the study period ($p < 0.0001$). In addition, both ibandronate groups showed a marked, significant reduction in serum osteocalcin at all timepoints compared with placebo ($p < 0.0001$ for both ibandronate groups vs placebo).[27]

### 2.2 Safety Profile of Oral Ibandronate

Nitrogen-containing bisphosphonates have been used for up to 10 years, with generally favourable safety profiles.[69,70] A common concern with bisphosphonates is the occurrence of upper gastrointestinal adverse events. Early post-marketing safety data for alendronate introduced the risk of upper gastrointestinal ulcerations, related to the fact that patients were not adhering to the administration guidelines, and thus leading to a class labelling for oral bisphosphonates. These data show that patients are more likely to experience uncomfortable upper gastrointestinal adverse events when bisphosphonates are not taken as directed,[71-74] and that patients receiving alendronate and concomitant NSAIDs can experience an increase in the occurrence of upper gastrointestinal adverse events,[75,76] due to synergistic, ulcerogenic effects.[77-79]

In the MOBILE study,[61] the incidence of upper gastrointestinal adverse events was comparable across the monthly and daily treatment arms and, as expected, was increased in patients with a history of upper gastrointestinal disorders versus those without. Equally, the frequency of upper gastrointestinal adverse events was similar across all three treatment arms of the BONE study, even though one-third of the patients had a history of upper gastrointestinal disorders and were not excluded from the trial. Within this study, 62% of patients were receiving concomitant NSAIDs and 14% of participants were receiving gastroprotective medications (predominantly histamine $H_2$ antagonists and proton-pump inhibitors).[80] These data suggest a favourable upper gastrointestinal tolerability profile for ibandronate.

The safety profile of oral ibandronate in postmenopausal osteoporosis management has been assessed in numerous treatment[27,59,81-83] and prevention studies.[84,85] In these studies, oral ibandronate was well tolerated, with a safety profile similar to placebo,[27,84,85] and a comparable, balanced, incidence of drug-related and/or unrelated adverse events across treatment groups.[27,59,81-83]

## 3. Practical Implications for Primary Care

The US Surgeon General's report estimated that 10 million Americans currently have osteoporosis, with a further 34 million having low bone mass, which puts them at increased risk for osteoporosis and associated fractures.[42] The low priority given to preventing bone disease, combined with the increasing age of the US population,[86] means the number of hip fractures could triple by the year 2020.[42] Given this ever-increasing proportion of elderly in the population, effective treatment of osteoporosis is essential and lies with primary healthcare teams, as they are the only ones appropriately placed to screen for the treatment and prevention of osteoporosis before fractures occur.[87] Effectively managing prevention and treatment of osteoporosis requires action at the population level if it is to have an impact on the resource-sapping effects of osteoporotic fractures.[88]

Effective treatments exist,[89] but their use is hampered by suboptimal screening and low implementation,[87] as well as poor patient compliance with treatment.[29,76] To improve treatment, physicians need to be better informed about osteoporosis and its treatment guidelines,[90] and information about the disease needs to be effectively shared with patients to improve their adherence to treatment.[91] In this respect, it is valuable to recognise the benefits provided by nurse monitoring and feedback to patients regarding treatment effectiveness (via bone turnover marker measurements).[92]

As well as implementing better education, healthcare teams can consider other barriers to adherence, including concomitant medication burden

and dose administration convenience. One of the recommendations of the Surgeon General's report is the development of simplified dose administration regimens to encourage patient adherence. The recent availability of once-monthly ibandronate will allow physicians and patients the opportunity to decrease the administration frequency to once monthly. As data concerning vertebral fractures and BMD improvements suggest that the efficacy of ibandronate may be similar to that of alendronate and risedronate, it is reasonable to consider ibandronate as a favoured option for patients who could benefit from this unique dose-administration regimen. This, along with patient education and monitoring, will hopefully improve patient adherence to bisphosphonates and consequently the outcomes for osteoporotic patients.

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