Drugs Aging (2016) 33:295–303
DOI 10.1007/s40266-016-0360-7

ADIS DRUG EVALUATION

Ibandronate: A Review in Japanese Patients with Osteoporosis

Gillian M. Keating[1]

Published online: 25 February 2016

Abstract Once-monthly intravenous (IV) ibandronate (Bonviva®) 1 mg and once-monthly oral ibandronate 100 mg are approved in Japan for the treatment of osteoporosis. In two well-designed trials in Japanese patients with primary osteoporosis, IV ibandronate 1 mg once monthly was noninferior to oral risedronate 2.5 mg once daily in terms of the cumulative incidence of new or worsening vertebral fractures at 3 years (MOVER trial) and oral ibandronate 100 mg once monthly was noninferior to IV ibandronate 1 mg once monthly in terms of the increase from baseline in lumbar spine bone mineral density at 12 months (MOVEST trial). Once-monthly IV and oral ibandronate were generally well tolerated in patients with osteoporosis. In conclusion, once-monthly IV and oral ibandronate are useful options for the treatment of Japanese patients with osteoporosis.

Ibandronate in Japanese patients with osteoporosis: a summary

Nitrogen-containing bisphosphonate with potent antiresorptive activity

Once-monthly IV ibandronate 1 mg is noninferior to once-daily oral risedronate 2.5 mg in terms of the cumulative incidence of new or worsening vertebral fractures at 3 years

Once-monthly oral ibandronate 100 mg is noninferior to once-monthly IV ibandronate 1 mg in terms of the increase in lumbar spine bone mineral density at 12 months

Generally well tolerated

1 Introduction

Osteoporosis is characterized by decreased bone strength, which predisposes affected patients to an increased risk of fractures [1]. Bone mineral density (BMD) accounts for almost 70 % of bone strength, with bone quality accounting for the remaining 30 % [1]. It is estimated that approximately 17 million women and men aged ≥40 years in Japan have osteoporosis at the lumbar spine or femoral neck [2]. Osteoporosis-related fractures are associated with impaired mobility and health-related quality of life, and increased mortality [1]. The goals of treatment in osteoporosis are to maintain good skeletal health and prevent fractures [1].

Osteoporosis occurs in both women and men, although it is seen most commonly in postmenopausal women [1].

The manuscript was reviewed by: ***J. Iwamoto***, Institute for Integrated Sports Medicine, Keio University School of Medicine, Tokyo, Japan; ***H. Kaji***, Department of Physiology and Regenerative Medicine, Kinki University Faculty of Medicine, Osaka, Japan; ***J. Takada***, Department of Orthopedic Surgery, Sapporo Medical University, Sapporo, Japan.

✉ Gillian M. Keating
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

Estrogen depletion during and following menopause leads to an imbalance in which osteoclast-mediated bone resorption exceeds osteoblast-mediated bone formation [1]. Bisphosphonates are antiresorptive agents that redress this imbalance [3]. The nitrogen-containing bisphosphonate ibandronate is approved in various countries for the treatment of osteoporosis, although there are differences between countries in terms of approved formulations and dosage regimens. In Japan, a once-monthly intravenous (IV) formulation of ibandronate (Bonviva®) and a once-monthly oral formulation of ibandronate are approved for the treatment of osteoporosis [4, 5]. This narrative review discusses the efficacy and tolerability of once-monthly IV ibandronate 1 mg and once-monthly oral ibandronate 100 mg in the treatment of Japanese patients with osteoporosis, as well as briefly summarizing the pharmacology of ibandronate.

2 Pharmacodynamic Properties of Ibandronate

Ibandronate is a potent antiresorptive agent, which acts selectively on bone tissue and inhibits osteoclast activity at sites of active resorption without directly affecting bone formation [6, 7]. In postmenopausal women, ibandronate reduces elevated bone turnover towards premenopausal levels, resulting in progressive net gains in bone mass and a reduced risk of fractures [7].

In terms of binding affinity for hydroxyapatite, the rank order (highest to lowest) of bisphosphonates is zoledronate > alendronate > ibandronate > risedronate [8–10]. Bisphosphonates such as ibandronate that bind less avidly to the bone surface have greater penetration into the bone surface and distribute more widely in bone, which may help prevent proximal femoral fractures [8–10].

A number of preclinical studies in animal models of osteoporosis showed that intermittent ibandronate regimens reduced bone turnover and increased BMD [11]. A recent study in ovariectomized rats demonstrated that combination therapy with once-monthly subcutaneous ibandronate and once-daily oral eldecalcitol (an active vitamin D_3 derivative) had a synergistic inhibitory effect on bone resorption, without supressing bone formation [12].

The bone turnover marker urinary cross-linked C-telopeptide of type 1 collagen (uCTX) is produced by osteoclast-mediated bone resorption and is a sensitive biomarker of pharmacodynamic response to ibandronate [13, 14]. Dose-dependent reductions in creatinine-corrected uCTX were seen in postmenopausal Japanese women with osteopenia receiving two doses (13 weeks apart) of IV ibandronate 0.5, 1 or 2 mg, with a negligible change seen in those receiving IV ibandronate 0.25 mg [15]. A rapid reduction in uCTX levels was seen up to day 8, after which uCTX levels gradually increased. Dose-dependent reductions in creatinine-corrected uCTX were also seen in healthy postmenopausal Japanese women receiving a single dose of oral ibandronate 20, 50, 100 or 150 mg and in postmenopausal Japanese women with primary osteoporosis receiving four doses of oral ibandronate 20, 50, 100 or 150 mg at monthly intervals. Although suppression of uCTX was negligible with the 20 mg dose, greater suppression was seen with higher doses. In patients with primary osteoporosis, uCTX levels decreased immediately after ibandronate administration and reached a nadir at day 8. Although a gradual increase in uCTX levels was subsequently seen, uCTX levels remained numerically lower in patients receiving ibandronate 50–150 mg than in patients receiving placebo at 1 month after administration [15].

Changes in bone turnover markers in patients with osteoporosis receiving IV or oral ibandronate in the pivotal MOVER [16] and MOVEST [17] trials are discussed in Sect. 4.

3 Pharmacokinetic Properties of Ibandronate

In vitro, ibandronate was 90 % protein bound in human serum at a concentration of 5 ng/mL [4].

No metabolites were identified when ibandronate was incubated with hepatic microsomes in vitro [4]. Moreover, ibandronate did not inhibit the cytochrome P450 (CYP) enzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in vitro [4]. Ibandronate is eliminated from the blood via distribution to the bone followed by gradual release and via renal excretion [15].

Ibandronate has a low risk of metabolic interaction with other drugs, reflecting its lack of hepatic metabolism and its lack of inhibition or induction of CYP enzymes [7]. The oral bioavailability of ibandronate is reduced by the presence of food (particularly products containing calcium), and calcium supplements, antacids and some oral medicines containing multivalent cations may interfere with the absorption of ibandronate [7].

Compared with healthy adults [creatinine clearance (CL_{CR}) >90 mL/min], patients with CL_{CR} of 40–70 and <30 mL/min had 1.30- and 2.44-fold higher maximum plasma concentration (C_{max}) and 1.55- and 2.97-fold higher area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) values following IV administration of ibandronate 0.5 mg [4]. Ibandronate should be administered with care to patients with severe renal dysfunction, as data are limited in this patient population [4].

Population pharmacokinetic analysis using data from healthy Caucasian and Japanese men, postmenopausal Caucasian women without osteopenia and postmenopausal Japanese women with osteopenia suggested that ethnicity

is unlikely to affect the pharmacokinetics of ibandronate [3]. Thus, any differences between Caucasian and Japanese subjects in ibandronate pharmacokinetics may reflect differences in patient demographics (e.g. disease status, gender, bodyweight and CL_{CR}) [3].

Dose-proportional increases in AUC_{∞} were seen following administration of single doses of IV ibandronate 0.125, 0.25 or 0.5 mg to healthy men or IV ibandronate 0.25, 0.5, 1 or 2 mg to postmenopausal Japanese women with osteopenia [4, 15].

In Japanese subjects, the bioavailability of ibandronate was 0.91 % with oral versus IV administration [15]. In healthy postmenopausal Japanese women receiving single oral doses of ibandronate 20, 50, 100 or 150 mg and in postmenopausal Japanese women with primary osteoporosis receiving four once-monthly doses of oral ibandronate 20, 50, 100 or 150 mg, C_{max} and AUC_{∞} values increased dose-proportionally up to 100 mg, with greater than dose-proportional increases seen with the 150 mg dose [15]. Mean C_{max} was reached in ≈1–1.2 h with single-dose administration in healthy women and in ≈0.8–1.1 h with multiple-dose administration in women with osteoporosis [15].

In the 72 h following IV administration of ibandronate 0.25–2 mg to postmenopausal Japanese women with osteopenia, 55.4–64.6 % of the administered dose was excreted in the urine [15]. In the 48 h following administration of oral ibandronate 20–150 mg to postmenopausal Japanese women with primary osteoporosis, 0.407–1.08 % of the administered dose was excreted in the urine [15]. The elimination half-life ($t_{½}$) was independent of dose, with a mean $t_{½}$ of 18.5 h reported in postmenopausal Japanese women with osteopenia receiving IV ibandronate 1 mg and a mean $t_{½}$ of 16.1 h reported in postmenopausal Japanese women with primary osteoporosis receiving four doses of oral ibandronate 100 mg [15]. The mean total clearance of ibandronate was 70.1 mL/min and the mean renal clearance was 43.9 mL/min with IV ibandronate 1 mg, and mean renal clearance was 36.0 mL/min with oral ibandronate 100 mg [15].

Ibandronate exposure was similar after administration of IV ibandronate 1 mg or oral ibandronate 100 mg, with mean AUC_{∞} values of 240 and 219 ng·h/mL and mean AUC from time zero to 48 h values of 230 and 209 ng·h/mL [15].

The relative bioavailability of a single dose of oral ibandronate was reduced when it was administered 30 min, compared with 60 min, before a standard meal [18]. In healthy postmenopausal Japanese women, the mean AUC from time zero to the time of the last measurable concentration (AUC_{last}) was 1.40 ng·h/mL when ibandronate 2.5 mg was administered 60 min before a meal, 1.12 ng·h/mL when ibandronate 2.5 mg was administered 30 min before a meal and 1.96 ng·h/mL when ibandronate 5 mg was administered 30 min before a meal. In healthy Caucasian and Asian men and postmenopausal women, the mean AUC_{last} was 16.0 ng·h/mL when ibandronate 50 mg was administered 60 min before a meal and 11.1 ng·h/mL when ibandronate 50 mg was administered 30 min before a meal. Thus, food and drink (other than water) should be avoided for ≥60 min after taking ibandronate [18].

4 Therapeutic Efficacy of Ibandronate

Results of two earlier trials (available as abstracts) demonstrated the therapeutic potential of once-monthly regimens of IV and oral ibandronate in Japanese women with osteoporosis [19, 20]. This section focuses on the results of the pivotal, randomized, double-blind, multicentre MOVER [16] and MOVEST [17] trials, which were conducted in Japan and included patients aged ≥55 [17] or ≥60 [16] years with primary osteoporosis, which was defined according to Japanese diagnostic criteria (i.e. no disease causing low BMD other than osteoporosis, no secondary osteoporosis and bone assessment criteria fulfilled) [21].

4.1 The MOVER Trial

The MOVER trial examined the noninferiority of IV ibandronate versus oral risedronate in the prevention of vertebral fractures in Japanese patients with primary osteoporosis [16]. Patients had a fragility fracture (defined as nontraumatic osteoporotic fracture that occurred by slight external force combined with low BMD), lumbar spine or proximal femur BMD of <80 % of the young adult mean, and one to five radiologically confirmed vertebral fractures in the thoracic/lumbar spine (T4–L4) [16].

In MOVER, patients received IV ibandronate 0.5 or 1 mg once monthly or oral risedronate 2.5 mg once daily for 3 years [16]. Supplementary calcium 305 mg/day and vitamin D 200 IU/day were also administered to all patients. Across the three treatment groups, women accounted for 91.2–94.7 % of patients and mean patient age was 72.2–73.0 years. At baseline across the three treatment groups, one, two or at least three prevalent vertebral fractures were present in 48.2–49.5 %, 25.3–27.7 % and 24.1–26.1 % of patients, respectively [16].

The primary endpoint was the incidence of nontraumatic morphometric vertebral fractures at 3 years, including both new vertebral fractures and worsening of prevalent vertebral fractures [16]. The primary analysis compared IV ibandronate with oral risedronate; analyses comparing IV ibandronate 0.5 mg with IV ibandronate 1 mg should be considered exploratory [16].

Table 1 Efficacy of once-monthly intravenous or oral ibandronate in Japanese patients with osteoporosis: results of the MOVER and MOVEST trials

Treatment	No. of pts[a]	Cumulative incidence of vertebral fractures[b]		Mean relative increase from baseline in BMD (%) [mean baseline T score]		
		% of pts	HR (95 % CI)	Lumbar spine (L2–L4)	Total hip	Femoral neck
MOVER trial results at 3 years [16]						
IV IBN 0.5 mg/month	376	19.9[c]	1.09 (0.77–1.54)[d]	7.7 [−2,71]	2.2 [−2.17]	2.1 [−2.48]
IV IBN 1 mg/month	382	16.1[c]	0.88 (0.61–1.27)[d]	9.0*† [−2.68]	3.1*†† [−2.09]	3.1 [−2.41]
Oral RIS 2.5 mg/day	376	17.6[c]		7.6 [−2.59]	2.0 [−2.18]	2.2 [−2.53]
MOVEST trial results at 12 months [17]						
Oral IBN 100 mg/month	183	1.1		5.22[c,e] [−3.09]	2.41 [−2.41]	2.58 [−2.98]
IV IBN 1 mg/month	189	0.5		5.34[c] [−3.14]	2.76 [−2.47]	2.64 [−2.99]

BMD bone mineral density, *HR* hazard ratio, *IBN* ibandronate, *IV* intravenous, *pts* patients, *RIS* risedronate

* $p \leq 0.01$ vs. IV IBN 0.5 mg/month

† $p < 0.01$, †† $p < 0.001$ vs. oral RIS 2.5 mg/day

[a] No. of pts in the per-protocol population (primary efficacy analysis)

[b] Nontraumatic morphometric new or worsening [16] or new [17] vertebral fractures

[c] Primary endpoint

[d] Noninferior to oral RIS

[e] Noninferior to IV IBN

Once-monthly IV ibandronate 1 mg was noninferior to once-daily oral risedronate 2.5 mg in terms of the cumulative incidence of new or worsening vertebral fractures at 3 years, with a hazard ratio (HR) of 0.88 (95 % CI 0.61–1.27) (Table 1) [16]. When only women were considered, the HR for new or worsening vertebral fractures with IV ibandronate 1 mg versus oral risedronate was 0.95 (95 % CI 0.66–1.39) at 3 years [16].

The cumulative incidence of new vertebral fractures was 11.6 % in patients receiving IV ibandronate 1 mg versus 13.2 % in patients receiving oral risedronate (HR 0.87; 95 % CI 0.57–1.33) [16]. No significant differences were seen between patients receiving IV ibandronate 1 mg and those receiving oral risedronate in the cumulative incidence of osteoporotic nonvertebral fractures (7.2 vs. 8.4 %; $p = 0.605$) or nonvertebral fractures at six major sites (femur, forearm, humerus, clavicle, tibia/fibula, pelvis) (4.6 vs. 6.3 %; $p = 0.449$). The cumulative incidence of new vertebral fractures (16.8 vs. 11.6 %), osteoporotic nonvertebral fractures (9.0 vs. 7.2 %) or nonvertebral fractures at six major sites (5.3 vs. 4.6 %) did not appear to differ significantly between patients receiving IV ibandronate 0.5 mg and patients receiving IV ibandronate 1 mg [16].

At 3 years, the mean relative increases from baseline in lumbar spine BMD and total hip BMD were significantly greater with IV ibandronate 1 mg than with oral risedronate or IV ibandronate 0.5 mg (Table 1) [16].

At 1 year, the BMD responder rate (defined as an increase in BMD above baseline) was significantly higher with IV ibandronate 1 mg than with oral risedronate for femoral neck BMD (72.0 vs. 59.8 %; $p < 0.001$) and for total hip and trochanter BMD (both $p < 0.05$), with no significant between-group difference for lumbar spine BMD (92.2 vs. 90.7 %) [22]. At 3 years, significantly more patients receiving IV ibandronate 1 mg versus oral risedronate had an increase above baseline of ≥6 % for lumbar spine BMD (67.2 vs. 56.3 %; $p < 0.01$) and an increase above baseline of ≥3 % for femoral neck BMD (50.7 vs. 40.5 %; $p < 0.01$), total hip BMD (55.8 vs. 38.2 %; $p < 0.0001$) and trochanter BMD (65.4 vs. 50.4 %; $p < 0.0001$) [22].

With IV ibandronate 1 mg, mean relative reductions from baseline to 6 months in creatinine-corrected uCTX and urinary cross-linked N-telopeptide of type 1 collagen (uNTX) were 67 and 53 %; similar relative reductions were reported in patients receiving oral risedronate [16]. Mean relative reductions from baseline to 6 months in serum bone-specific alkaline phosphatase (BALP) and serum osteocalcin (OC) levels were 41 and 35 % in patients receiving IV ibandronate 1 mg. Significantly ($p < 0.005$) greater mean relative reductions from baseline in creatinine-corrected uCTX, creatinine-corrected uNTX, serum BALP and serum OC were seen with IV ibandronate 1 mg than with IV ibandronate 0.5 mg [16].

Results of a subgroup analysis were generally consistent with overall study findings [23]. In patients receiving IV ibandronate 1 mg or oral risedronate, the 3-year incidence of vertebral fractures was 11.2 versus 12.6 % in patients with one prevalent fracture at baseline, 20.4 versus 22.1 % in patients with at least two prevalent fractures at baseline

and 25.2 versus 31.3 % in patients with at least three prevalent fractures at baseline. In patients receiving IV ibandronate 1 mg or oral risedronate, the 3-year incidence of vertebral fractures was 13.7 versus 17.3 % in patients with a baseline femoral neck BMD T-score of ≥−2.5, 16.4 versus 19.1 % in patients with a baseline femoral neck BMD T-score of <−2.5, and 21.4 versus 22.2 % in patients with a baseline femoral neck BMD T-score of <−3.0 [23].

In addition, the 3-year incidence of osteoporotic nonvertebral fractures in patients receiving IV ibandronate 1 mg versus oral risedronate was 6.8 versus 7.2 % in patients with one prevalent fracture at baseline (HR 0.92; 95 % CI 0.41–2.10), 7.6 versus 9.5 % in patients with at least two prevalent fractures at baseline (HR 0.84; 95 % CI 0.41–1.73) and 7.4 versus 10.1 % in patients with at least three prevalent fractures at baseline (HR 0.83; 95 % CI 0.29–2.38) [23]. In patients receiving IV ibandronate 1 mg versus oral risedronate, the 3-year incidence of osteoporotic nonvertebral fractures was 7.9 versus 7.1 % in patients with a baseline femoral neck BMD T-score of ≥−2.5 (HR 1.08; 95 % CI 0.49–2.35), 7.6 versus 9.4 % in patients with a baseline femoral neck BMD T-score of <−2.5 (HR 0.87; 95 % CI 0.39–1.94), and 8.5 versus 12.4 % in patients with a baseline femoral neck BMD T-score of <−3.0 (HR 0.74; 95 % CI 0.27–2.03) [23].

4.2 The MOVEST Trial

The MOVEST trial examined the noninferiority of oral versus IV ibandronate in Japanese patients with osteoporosis [17]. Patients had lumbar spine BMD of <70 % of the young adult mean or <80 % of the young adult mean with fragile bone fracture. Across both treatment groups, women accounted for 96.7–98.4 % of patients in the MOVEST trial and mean patient age was 68.8–69.3 years. At baseline across both treatment groups, zero, one or at least two prevalent vertebral fractures were present in 67.8–68.8 %, 18.0–18.6 % and 13.2–13.7 % of patients, respectively [17].

Patients received oral ibandronate 100 mg once monthly or IV ibandronate 1 mg once monthly [17]. Patients were instructed to take oral ibandronate 60 min before their first food or drink of the day. Supplementary calcium 610 mg/day and vitamin D 400 IU/day was also administered to all patients [17]. The primary endpoint was the relative percentage change from baseline in lumbar spine (L2–L4) BMD at 12 months [17].

Once-monthly oral ibandronate 100 mg was noninferior to once-monthly IV ibandronate 1 mg in terms of the mean relative increase from baseline in lumbar spine BMD at 12 months (Table 1) [17]. Mean relative increases from baseline in total hip and femoral neck BMD at 12 months are shown in Table 1 [17].

At 12 months, the BMD responder rate (defined as an increase in BMD above baseline) was 91.8 % with oral ibandronate and 92.1 % with IV ibandronate for lumbar spine BMD, 86.2 and 91.5 % for total hip BMD and 71.3 and 74.1 % for femoral neck BMD [17]. When defined as a ≥3 % increase from baseline in BMD, the responder rate was 71.6 % with oral ibandronate and 75.7 % with IV ibandronate for lumbar spine BMD, 39.2 and 43.4 % for total hip BMD and 43.1 and 41.8 % for femoral neck BMD [17].

Mean relative reductions from baseline to 12 months in bone turnover markers were 62.80 % with oral ibandronate and 59.51 % with IV ibandronate for creatinine-corrected uCTX levels, 46.42 and 44.65 % for serum tartrate-resistant acid phosphatase (TRAP) 5b levels, 68.98 and 66.66 % for serum N-terminal propeptide of type 1 collagen (P1NP) levels, and 47.28 and 43.35 % for serum BALP levels [17].

The cumulative incidence of new vertebral fractures over 12 months is shown in Table 1 [17]. The cumulative incidence of new nonvertebral fractures was 1.1 % in patients receiving oral ibandronate and 2.6 % in patients receiving IV ibandronate [17].

5 Tolerability of Ibandronate

5.1 General Adverse Event Profile

Once-monthly IV and oral ibandronate were generally well tolerated in Japanese patients with osteoporosis [16, 17]. During 3 years of follow-up in MOVER, the incidence of adverse events was 98.8 % with IV ibandronate 0.5 mg, 97.6 % with IV ibandronate 1 mg and 96.8 % with oral risedronate, with adverse events leading to withdrawal occurring in 8.3, 10.2 and 9.4 % of patients, respectively [16]. During 12 months of follow-up in MOVEST, adverse events occurred in 85.4 % of patients receiving oral ibandronate and 87.2 % of patients receiving IV ibandronate, drug-related adverse events occurred in 22.9 and 18.7 % of patients and adverse events leading to withdrawal occurred in 2.0 and 2.0 % of patients [17].

Among patients receiving IV ibandronate 0.5 mg, IV ibandronate 1 mg and oral risedronate in MOVER, the most commonly reported adverse events included nasopharyngitis (45.7, 50.9 and 49.5 %), contusion (24.1, 21.7 and 24.4 %), osteoarthritis (18.2, 15.3 and 12.6 %), back pain (12.9, 19.5 and 13.5 %), arthralgia (13.1, 11.4 and 9.4 %) and constipation (10.5, 10.5 and 13.5 %) [16]. Among patients receiving oral and IV ibandronate in MOVEST, the most commonly reported adverse events included nasopharyngitis (23.4 and 30.5 %), back pain (10.7 and 11.8 %), contusion (8.3 and 6.4 %), osteoarthritis (5.9 and 2.0 %) and muscle pain (2.0 and 5.4 %) [17].

The incidence of serious adverse events was 24.6 % with IV ibandronate 0.5 mg, 24.8 % with IV ibandronate 1 mg and 32.5 % with oral risedronate in MOVER [16], and 4.4 % with oral ibandronate and 3.0 % with IV ibandronate in MOVEST [17]. In MOVER, adverse events leading to death occurred in 1.2 % of patients receiving IV ibandronate 0.5 mg, 0.7 % of patients receiving IV ibandronate 1 mg and 1.5 % of patients receiving oral risedronate [16]. No adverse events leading to death occurred in the MOVEST trial [17].

5.2 Adverse Events of Special Interest

Acute phase reaction (APR)-related adverse events occurred in 9.0 % of patients receiving IV ibandronate 0.5 mg, 11.2 % of patients receiving IV ibandronate 1 mg and 4.9 % of patients receiving oral risedronate in MOVER [16] and in 11.2 % of patients receiving oral ibandronate and 11.8 % of patients receiving IV ibandronate in MOVEST [17]. Most APR-related adverse events were transient and mild [16, 17]; they were usually associated with the first administration of study drug and decreased with each subsequent dose [16, 17].

No differences in gastrointestinal (GI)-related adverse events were seen between the treatment groups in MOVER [16]. GI-related adverse events occurred in 27.5 % of patients receiving IV ibandronate 0.5 mg, 29.2 % of patients receiving IV ibandronate 1 mg and 26.6 % of patients receiving oral risedronate, with serious GI-related adverse events occurring in 1.2, 0.5 and 2.2 % of patients, respectively [16]. GI-related adverse events occurred in 12.2 % of patients receiving oral ibandronate and 9.9 % of patients receiving IV ibandronate in MOVEST, with oesophageal irritation occurring in 1.0 and 2.5 % of patients in the corresponding treatment groups [17].

Renal function-related adverse events (most commonly increased serum creatinine levels and proteinuria) occurred in 2.9 % of patients receiving IV ibandronate 0.5 mg, 2.7 % of patients receiving IV ibandronate 1 mg and 2.0 % of patients receiving oral risedronate in MOVER; all of these adverse events were of mild severity [16]. No renal function-related adverse events were reported in MOVEST [17].

There were no reports of hypocalcaemia, osteonecrosis of the jaw or atypical femoral fracture in either trial [16, 17].

6 Dosage and Administration of Ibandronate

IV and oral ibandronate are approved in Japan for the treatment of osteoporosis (as specified in Japanese Society for Bone and Mineral Research guidelines) [4, 5]. The approved dosage of IV ibandronate is 1 mg once monthly and the approved dosage of oral ibandronate is 100 mg once monthly. Oral ibandronate should be administered with water upon waking, and food and drink (other than water) should be avoided for ≥60 min after taking oral ibandronate [5]. IV and oral ibandronate are contraindicated in patients with a history of hypersensitivity to the ingredients of ibandronate or other bisphosphonates, in patients with hypocalcaemia and in women who are, or may be, pregnant [4, 5]. Local prescribing information should be consulted for further information on contraindications and precautions relating to ibandronate.

7 Place of Ibandronate in the Management of Japanese Patients with Osteoporosis

The efficacy of ibandronate in osteoporosis is well established, with well-designed trials (e.g. BONE [24], MOBILE [25], DIVA [26]) demonstrating the ability of various intermittent IV and oral ibandronate regimens to increase BMD and/or reduce fracture risk in postmenopausal women with osteoporosis. Improvements in BMD were maintained after 5 years' follow-up [27, 28], and time to fracture was significantly ($p < 0.05$ vs. placebo) delayed in patients with an annual cumulative ibandronate exposure of ≥10.8 mg [29].

In Japan, an IV ibandronate dosage of 1 mg once monthly was approved based on the results of the MOVER trial [16]. In MOVER, once-monthly IV ibandronate 1 mg was noninferior to once-daily oral risedronate in reducing the risk of new or worsening vertebral fractures after 3 years' follow-up (Sect. 4.1). Exploratory analyses suggested dose-dependent advantages with IV ibandronate 1 mg over IV ibandronate 0.5 mg in terms of preventing vertebral fractures and improving BMD and bone turnover markers.

Results of the MOVER trial have been incorporated into the updated 2015 Japanese guidelines for the prevention and treatment of osteoporosis [30]. In terms of evaluation of efficacy, the guidelines state that ibandronate had a positive effect on bone density and a preventive effect on vertebral fractures. Other agents classified as having a positive effect on bone density and a preventive effect on vertebral fractures include the bisphosphonates minodronate, alendronate and risedronate; the selective estrogen receptor modulators raloxifene and bazedoxifene; the active vitamin D_3 product eldecalcitol; conjugated estrogen; the parathyroid hormone teriparatide; and the monoclonal antibody targeting the receptor activator of nuclear factor-κB ligand denosumab [30]. The guidelines also state that ibandronate is reported to have a preventive effect on nonvertebral fractures [30]. MOVER was not primarily designed to examine the effect of ibandronate on nonvertebral fractures; however, several other analyses (including a meta-analysis [31], a pooled analysis [32] and a post hoc analysis of the DIVA study

[33]) indicate that intermittent regimens of oral and/or IV ibandronate have a significant preventive effect on nonvertebral fractures. The guidelines state that no positive effect on hip fractures was reported with ibandronate [30], although results of the US VIBE database fracture study suggest that patients receiving oral ibandronate once monthly had a low risk of hip fracture [34].

Taking into account effects on uCTX levels (Sect. 2), ibandronate exposure (Sect. 3), results of a dose-finding trial [20] and results of MOVEST [17], an oral ibandronate dosage of 100 mg once monthly appears optimal in Japanese patients, whereas the approved dosage of oral ibandronate in the EU [7] and the US [35] is 150 mg once monthly. This difference in optimal dosage most likely reflects the different bioavailabilities of oral ibandronate in Japanese versus Western subjects (0.91 vs. 0.63 %) [15]. The mechanism underlying this ethnic difference in the bioavailability of ibandronate is unclear [15]. In the MOVEST trial, once-monthly oral ibandronate 100 mg was noninferior to once-monthly IV ibandronate 1 mg in terms of the increase in lumbar spine BMD at 12 months (Sect. 4.2); longer-term data are needed regarding the effect of oral ibandronate 100 mg on fracture incidence.

Active vitamin D_3 products (e.g. eldecalcitol, alfacalcidol, calcitriol) are recommended for use in patients with osteoporosis [1]. Combination therapy with intermittent ibandronate and daily eldecalcitol had a synergistic effect on the inhibition of bone resorption, without affecting bone formation, in an experimental animal model of osteoporosis (Sect. 2), suggesting that combination therapy with ibandronate and active vitamin D_3 products would be beneficial in clinical practice.

Once-monthly IV ibandronate 1 mg and oral ibandronate 100 mg were generally well tolerated in Japanese patients with osteoporosis (Sect. 5). No unexpected adverse events were reported in patients receiving ibandronate in the MOVER and MOVEST trials, and the tolerability profiles were consistent with those seen with intermittent ibandronate regimens in other trials [17].

Hypocalcaemia has been reported in patients receiving bisphosphonates [4]. Although hypocalcaemia was not reported in MOVER or MOVEST (Sect. 5), patients receiving ibandronate should be monitored carefully [4].

Osteonecrosis of the jaw has also been reported in patients receiving bisphosphonates, although it appears to occur more commonly in patients with cancer receiving high-dose bisphosphonate therapy than in those with osteoporosis [9]. The risk of osteonecrosis of the jaw also appears higher in patients receiving bisphosphonates with a higher binding affinity for hydroxyapatite (e.g zoledronate) than in those receiving bisphosphonates with a lower binding affinity for hydroxyapatite (e.g. ibandronate) [9, 36]. Although there were no cases reported in MOVER or MOVEST (Sect. 5), patients receiving bisphosphonates (including ibandronate) should be carefully monitored for osteonecrosis of the jaw [4].

A lack of data means that ibandronate should be administered with care to patients with severe renal dysfunction [4]. In general, IV and oral bisphosphonates are not associated with a long-term decline in renal function when administered in accordance with local prescribing information to patients with various degrees of renal impairment [37].

Adherence to treatment is an issue in patients receiving anti-osteoporosis agents [38]. Factors affecting adherence include efficacy, tolerability, route of administration and dosing frequency. For example, patients may find once-monthly administration of ibandronate more convenient than bisphosphonates requiring daily or weekly administration. GI-related adverse events may occur more commonly with oral bisphosphonates than with IV bisphosphonates, meaning that some patients may prefer IV ibandronate because of tolerability issues, whereas other patients may wish to avoid an IV infusion and so prefer oral ibandronate [38].

In conclusion, once-monthly IV ibandronate 1 mg and once-monthly oral ibandronate 100 mg are useful options for the treatment of Japanese patients with osteoporosis. IV ibandronate 1 mg once monthly is noninferior to oral risedronate 2.5 mg once-daily in terms of the cumulative incidence of new or worsening vertebral fractures at 3 years, and once-monthly oral ibandronate 100 mg is noninferior to once-monthly IV ibandronate 1 mg in terms of the increase in lumbar spine BMD at 12 months. Once-monthly IV and oral ibandronate are both generally well tolerated in Japanese patients with osteoporosis. In addition, with its once-monthly administration regimen, ibandronate may be more convenient than bisphosphonates requiring more frequent administration.

Data selection sources: Relevant medical literature (including published and unpublished data) on ibandronate was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 8 February 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Ibandronate, ibandronic, osteoporosis, osteoporoses, Japan.
Study selection: Studies in patients with osteoporosis who received ibandronate. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Acknowledgments During the peer review process, the manufacturer of ibandronate was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflicts of interest Gillian Keating is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

References

1. Orimo H, Nakamura T, Hosoi T, et al. Japanese 2011 guidelines for prevention and treatment of osteoporosis: executive summary. Arch Osteoporos. 2012;7:3–20.
2. Yoshimura N, Muraki S, Oka H, et al. Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab. 2009;27(5):620–8.
3. Pillai G, Gieschke R, Goggin T, et al. Population pharmacokinetics of ibandronate in Caucasian and Japanese healthy males and postmenopausal females. Int J Clin Pharmacol Ther. 2006;44(12):655–67.
4. Chugai Pharmaceutical Co Ltd. Bonviva® IV injection (ibandronate sodium hydrate injection): Japanese prescribing information; 2013.
5. Chugai Pharmaceutical Co Ltd. Bonviva® tablets (ibandronate sodium hydrate): Japanese prescribing information; 2016.
6. Barrett J, Worth E, Bauss F, et al. Ibandronate: a clinical pharmacological and pharmacokinetic update. J Clin Pharmacol. 2004;44(9):951–65.
7. European Medicines Agency. Bonviva (ibandronic acid): EU summary of product characteristics. 2014. http://www.ema.europa.eu. Accessed 7 Jul 2015.
8. Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone. 2006;38(5):617–27.
9. Inderjeeth CA, Glendenning P, Ratnagobal S, et al. Long-term efficacy, safety, and patient acceptability of ibandronate in the treatment of postmenopausal osteoporosis. Int J Womens Health. 2015;7:7–17.
10. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab. 2010;95(4):1555–65.
11. Bauss F, Russell RGG. Ibandronate in osteoporosis: preclinical data and rationale for intermittent dosing. Osteoporos Int. 2004;15(6):423–33.
12. Sakai S, Takeda S, Sugimoto M, et al. Treatment with the combination of ibandronate plus eldecalcitol has a synergistic effect on inhibition of bone resorption without suppressing bone formation in ovariectomised rats. Bone. 2015;81:449–58.
13. Pillai G, Gieschke R, Goggin T, et al. A semimechanistic and mechanistic population PK–PD model for biomarker response to ibandronate, a new bisphosphonate for the treatment of osteoporosis. Br J Clin Pharmacol. 2004;58(6):618–31.
14. Reginster J-Y, Gieschke R. Clinical utility of a pharmacostatistical model for ibandronate in postmenopausal osteoporosis. Curr Drug Metab. 2006;7(7):827–36.
15. Nakai K, Tobinai M, Hashimoto J, et al. The optimal oral dose selection of ibandronate in Japanese patients with osteoporosis based on pharmacokinetic and pharmacodynamic properties. Eur J Drug Metab Pharmacokinet. 2014. doi:10.1007/s13318-014-0242-5.
16. Nakamura T, Nakano T, Ito M, et al. Clinical efficacy on fracture risk and safety of 0.5 mg or 1 mg/month intravenous ibandronate versus 2.5 mg/day oral risedronate in patients with primary osteoporosis. Calcif Tissue Int. 2013;93(2):137–46.
17. Nakamura T, Ito M, Hashimoto J, et al. Clinical efficacy and safety of monthly oral ibandronate 100 mg versus monthly intravenous ibandronate 1 mg in Japanese patients with primary osteoporosis. Osteoporos Int. 2015;26(11):2685–93.
18. Nakai K. The effect of fasting interval on oral bioavailability of ibandronate [in Japanese]. Jpn Pharmacol Ther. 2015;43(11):1553–60.
19. Nakamura T, Mizunuma H, Itabashi A, et al. Intravenous injections of ibandronate for six months increases bone mass in Japanese osteoporotic subjects [abstract no. SA355]. J Bone Miner Res. 2006;21(Suppl 1):S182.
20. Nakamura T, Mizunuma H, Itabashi A, et al. Monthly oral ibandronate is well tolerated and efficacious in Japanese osteoporotic subject [abstract no. T405]. J Bone Miner Res. 2007;22(Suppl 1):S333.
21. Orimo H, Hayashi Y, Fukunaga M, et al. Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab. 2001;19(6):331–7.
22. Nakano T, Yamamoto M, Hashimoto J, et al. Higher response with bone mineral density increase with monthly injectable ibandronate 1 mg compared with oral risedronate in the MOVER study. J Bone Miner Metab. 2015. doi:10.1007/s00774-015-0717-8.
23. Ito M, Tobinai M, Yoshida S, et al. Effect of monthly intravenous ibandronate injections on vertebral or non-vertebral fracture risk in Japanese patients with high-risk osteoporosis in the MOVER study. J Bone Miner Metab. 2015. doi:10.1007/s00774-015-0723-x.
24. Chesnut C, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19(8):1241–9.
25. Reginster J-Y, Adami S, Lakatos P, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis. 2006;65(5):654–61.
26. Delmas PD, Adami S, Strugala C, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. Arthritis Rheum. 2006;54(6):1838–46.
27. Miller PD, Recker RR, Reginster J-Y, et al. Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study. Osteoporos Int. 2012;23(6):1747–56.
28. Bianchi G, Czerwinski E, Kenwright A, et al. Long-term administration of quarterly IV ibandronate is effective and well tolerated in postmenopausal osteoporosis: 5-year data from the DIVA study long-term extension. Osteoporos Int. 2012;23(6):1769–78.
29. Miller PD, Recker RR, Harris S, et al. Long-term fracture rates seen with continued ibandronate treatment: pooled analysis of DIVA and MOBILE long-term extension studies. Osteoporos Int. 2014;25(1):349–57.
30. 2015 guideline for prevention and treatment of osteoporosis [in Japanese]. Orimo H, editor. The Committee for Developing Guidelines for Prevention and Treatment of Osteoporosis: Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation. Life Science Publishing, Tokyo. ISBN 978-4-89775-339-3 C3407.
31. Harris ST, Blumentals WA, Miller PD. Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Curr Med Res Opin. 2008;24(1):237–45.
32. Cranney A, Wells GA, Yetisir E, et al. Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. Osteoporos Int. 2009;20(2):291–7.

33. Sambrook P, Cranney A, Adachi JD. Risk reduction of non-vertebral fractures with intravenous ibandronate: post-hoc analysis from DIVA. Curr Med Res Opin. 2010;26(3):599–604.
34. Harris ST, Reginster JY, Harley C, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the eValuation of IBandronate Efficacy (VIBE) database fracture study. Bone. 2009;44(5):758–65.
35. Genentech USA Inc. Boniva® (ibandronate sodium) tablets: US prescribing information. 2015. http://www.gene.com. Accessed 7 Jul 2015.
36. Kos M. Incidence and risk predictors for osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. Arch Med Sci. 2015;11(2):319–24.
37. Miller PD, Jamal SA, Evenepoel P, et al. Renal safety in patients treated with bisphosphonates for osteoporosis: a review. J Bone Miner Res. 2013;28(10):2049–59.
38. Lee S, Glendenning P, Inderjeeth CA. Efficacy, side effects and route of administration are more important than frequency of dosing of anti-osteoporosis treatments in determining patient adherence: a critical review of published articles from 1970 to 2009. Osteoporos Int. 2011;22(3):741–53.