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Ibandronate

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Contents

Abstract

▲ Ibandronate (ibandronic acid) is a third generation bisphosphonate which inhibits bone resorption in human and animal studies. It also inhibits bone formation only at high doses (10 μg/kg/day) in animal studies.

▲ In animal models, ibandronate was more potent than etidronate, clodronate, pamidronate and alendronate and equivalent in potency or more potent than risedronate in inhibiting induced hypercalcaemia and bone resorption.

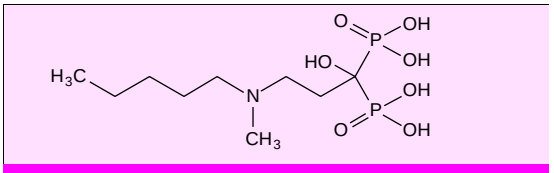
▲ In clinical studies, single-dose ibandronate (0.2 to 6mg intravenously) significantly reduced albumin-corrected serum calcium levels and urinary markers of bone resorption in patients with hypercalcaemia of malignancy, and in those with bone metastases. Serum calcium levels were normalised in 50 and 67% of ibandronate 2mg recipients and in about 76% of 4mg recipients.

▲ In postmenopausal women with osteoporosis or osteopenia, ibandronate (0.5 to 5 mg/day orally or 0.5 to 2mg every 3 months intravenously) dose-dependently increased bone mineral density, with parallel reductions in the biochemical markers of bone turnover.

▲ In preliminary studies in patients with Paget's disease a single intravenous ibandronate dose (2mg) decreased serum alkaline phosphatase levels and urinary markers of bone turnover.

▲ Adverse events associated with the use of ibandronate in the management of hypercalcaemia of malignancy include increased body temperature, hypocalcaemia and hypophosphataemia. Less commonly, flu-like symptoms and gastrointestinal intolerance may occur.

Features and properties of ibandronate (BM 210955, RPR 102289A, ibandronic acid)	
Indications	
Tumour-induced hypercalcaemia	Launched
Bone metastases, osteoporosis, Paget's disease	Clinical trials
Mechanism of action	
Bisphosphonate	Inhibits bone resorption by directly or indirectly inhibiting osteoclast activity
Dosage and administration (hypercalcaemia of malignancy)	
Recommended dosage	2 to 4mg
Route of administration	Intravenous infusion
Frequency of administration	Single dose which may be repeated if required
Pharmacokinetic profile (2 to 6mg)	
Peak plasma concentration	89 to 337 μg/L
Area under the plasma concentration-time curve	318 to 960 μg/L • h
Clearance	7.2 to 7.8 L/h
Elimination half-life	10 to 16h
Adverse events	
Most frequent	Increase in body temperature, hypocalcaemia, hypophosphataemia
Serious events	Not established



Ibandronic acid

1. Pharmacodynamic Profile

Effects on Bone Metabolism

Studies in Animal Models

• Ibandronate (ibandronic acid) [subcutaneous or oral for 4 days] inhibited 1,25-dihydroxyvitamin D-induced hypercalcaemia in thyroparathyroidectomised rats. Oral ibandronate was approximately >31-, >19-, 14- and 2-fold more potent, respectively, than oral etidronate, clodronate, pamidronate and alendronate, and subcutaneous ibandronate was >14,000-, 857-, 43- and 6-fold more potent than the same comparator drugs administered subcutaneously (statistical significance not given). However, ibandronate was comparable in potency to risedronate.[1]

• In a study of the inhibition of arotinoid-stimulated bone resorption in thyroparathyroidectomised rats, ibandronate (subcutaneous or intravenous 0.0003 to 0.1 mg/kg for 3 doses) was compared with clodronate (0.1 to 10 mg/kg), pamidronate (0.01 to 1 mg/kg) and alendronate (0.001 to 0.1 mg/kg). At the dose producing 100% inhibition, ibandronate was 500, 50, 10-fold more potent, respectively, than comparator agents. In a separate experiment, ibandronate was 2-fold more potent than risedronate (further experimental details not provided).[2]

• Subcutaneous ibandronate (0.1, 1 and 10 μg/kg/day) administered to healthy female rats for 11 days inhibited bone resorption ($p < 0.01$ to 0.001 *vs* controls), calculated by deducting calcium retention from bone formation. Furthermore, ibandronate 1 and 10 μg/kg/day also significantly increased intestinal calcium absorption and calcium balance. Only the highest dose also decreased bone formation (calculated by measuring the disappearance of radiolabelled calcium from plasma over 72 hours) and increased urinary calcium excretion ($p < 0.05$ to 0.01 *vs* controls).[3]

• In addition, the duration of effect of ibandronate was examined in the previous study. Single-dose ibandronate was administered 3 days (10 μg/kg) or 30 days (10 and 100 μg/kg) before calcium kinetic measurements. The effect of ibandronate 100, but not 10, μg/kg on calcium kinetics was still apparent 30 days after administration ($p < 0.01$ *vs* controls): net intestinal absorption, urinary calcium excretion and calcium balance increased, and bone resorption decreased. The effect of the 10 μg/kg dose was apparent 3 days after administration.[3]

• Ibandronate (subcutaneous 0.1, 0.3, 1, 10 and 100 μg/kg/day for 1 month), administered to ovariohysterectomised dogs, prevented the bone loss (at doses of ≥1 μg/kg/day), the increase in bone erosion depth (≥ 3 μg/kg/day) and osteoid volume and surface (≥ 0.1 μg/kg/day) and the decrease in serum 1,25-dihydroxyvitamin D levels (≥0.3 μg/kg/day) observed in placebo-treated dogs. Mineralising surfaces were significantly reduced only by ibandronate 10 and 100 μg/kg/day ($p < 0.01$). No significant changes were observed in osteoclast surface or numbers, or serum levels of calcium, phosphorus, parathyroid hormone or osteocalcin, and no signs of osteomalacia were found.[4]

• In murine models, osteolytic bone lesions were induced by breast cancer cell lines producing matrix metalloproteinases (MMPs; commonly secreted by breast tumours and involved in the development of metastases). Relative to the untreated group, ibandronate (subcutaneous 4μg for 12 days) limited the increase in size of bone metastases (about 380 *vs* 20%, respectively; $p < 0.01$), and the formation of new lesions was prevented to a greater extent by ibandronate given for 3 weeks before inoculation with breast cancer cells (about 2 *vs* 0.5 mm^2/mouse, respectively; $p < 0.005$).[5]

Studies in Humans

• A single intravenous bolus dose of ibandronate 1 or 2mg significantly increased lumbar spine bone mineral density by 2 and 3%, respectively, in 12

healthy men and 5 postmenopausal women. Trochanter bone mineral density increased significantly (2%) in men only. No significant increases were observed in femoral neck densities.[6]

• In the above study,[6] urinary excretion of the C-terminal portions of the collagen cross-linking molecules (CTX; crosslaps) in men was reduced by more than 200% (1mg dose; $p < 0.01$ *vs* baseline) and 300% (2mg dose; $p < 0.01$ *vs* baseline) at day 14 and continued to decrease at day 30. In women a less marked reduction was observed [150% at day 7 to 30 after ibandronate 1mg ($p < 0.01$ *vs* baseline)]. A reduction in urinary calcium excretion occurred in all patients on days 7 and 14 and a transient reduction in serum calcium was observed at day 7 to 14 in men only (numerical data not given; $p < 0.05$ *vs* baseline).[6]

• Serum parathyroid hormone levels increased at day 7 and 14 in both men and women after the 2mg dose in the same study. Serum alkaline phosphatase levels decreased from day 90 (1mg) and day 30 (2mg) in men only. In general, most biochemical markers returned to basal levels after 30 to 150 days.[6]

Effects on Renal Function

• Ibandronate was administered to rats to determine its effects on renal function in comparison with other bisphosphonates. All drugs were administered subcutaneously at a dose of 1 mg/kg/day for 9 days. The total amount of malate dehydrogenase (an early marker of renal toxicity) excreted in the urine was 22.7 units after ibandronate and 13.4, 18.5, 18.9, 22.8 and 27.9 units, respectively, after pamidronate, etidronate, alendronate, risedronate and clodronate and was generally within the range observed in control animals (4.9 to 24.2 units).[7]

• In the above study,[7] the therapeutic ratio, comparing nephrotoxic potential with antiresorptive effect, was determined by using the antiresorptive ED_{50} values from a previous study (ED_{50} = the dose of drug needed to lower the 1,25-dihydroxyvitamin D-induced hypercalcaemia by 50%).[1] The therapeutic ratio for ibandronate was approximately 2, 6, 45, 1300 and 13 000 times greater than that for risedronate, alendronate, pamidronate, clodronate and etidronate, respectively. However, no significant correlation was found between antiresorptive potency and renal toxicity for any agent.[7]

• In thyroparathyroidectomised rats in which bone resorption was stimulated by parathyroid hormone-related protein (PTHrP), ibandronate (subcutaneous 0.001, 0.003 or 0.01 mg/kg for 4 to 6 days) did not affect the renal tubular reabsorption of calcium as shown by its lack of effect on the relationship between urinary calcium excretion and plasma calcium levels.[8]

2. Pharmacokinetic Profile

In general, published data on the pharmacokinetic parameters of ibandronate are not available. Thus, unpublished data, obtained after a single intravenous ibandronate injection of 0.5, 1 or 2mg to healthy volunteers and a single intravenous infusion of 2, 4 or 6mg to postmenopausal women, are presented in this section.[9] However, 1 small trial, published as an abstract, gives the pharmacokinetic parameters of an intravenous infusion of ibandronate 6mg in patients with multiple myeloma.[10]

• In healthy volunteers and postmenopausal women, the area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of ibandronate were linearly related to dosage after the 2, 4 and 6mg infusions and ranged from 318 to 960 μg/L · h and 89 to 328 μg/L, respectively. The highest C_{max} achieved after the 2mg injection was 246 μg/L.[9]

• Distribution and elimination parameters of ibandronate were independent of dose. The apparent volume of distribution (Vd) was 150L and the drug was 99% bound to plasma protein.[9] The binding to erythrocytes and platelets was low: approximately 10% of ibandronate (when tested at concentrations of 5 to 5000 μg/L) binds to blood cells and the blood to plasma ratio is approximately 0.7.[11] The elimination half-life ($t_{½}$) of ibandronate was 10 to 16 hours and total body clearance (CL) was 7.8 L/h. Ibandronate was excreted mainly unchanged in the urine; renal clearance (CL_R) was

5.3 L/h and about 60% of the dose was recovered in the urine.[9]

- In 24 patients with multiple myeloma, the C_{max} of an intravenous infusion of ibandronate 6mg was 337 μg/L and was achieved in 1 hour (time to reach C_{max}; t_{max}). The AUC was about 866 μg/L · h. CL and $t_{½}$ values were generally similar to those observed in healthy volunteers or postmenopausal women (7.2 L/h and 9.8 hours, respectively) but the Vd and CL_R were slightly lower (about 101L and 3.5 L/h, respectively). In these patients, about 46% of the drug was excreted in the urine.[10]

3. Therapeutic Trials

Hypercalcaemia of Malignancy

- Ibandronate was administered as a single intravenous infusion to patients with hypercalcaemia of malignancy (albumin-corrected serum calcium levels >2.65 mmol/L,[12] ≥3.0 mmol/L[13] or >2.7 mmol/L[14]). Doses studied ranged from 0.2 to 2mg (n = 30),[12] 2 to 6mg (n = 125),[13] or 0.6 to 2mg (n = 151 patients).[14]

- Ibandronate reduced albumin-corrected serum calcium levels in all patients.[12-14] A reduction in serum calcium levels was observed from day 2 and the nadir was reached approximately 5 days after the start of treatment.[12,13]

- However, in a further study the reduction in serum calcium levels after single-dose ibandronate (intravenous 0.2 to 1.6mg) in 10 patients with hypercalcaemia of malignancy was not statistically significant. Furthermore, serum levels of PTHrP (released by tumours and involved in the development of hypercalcaemia) were not altered after ibandronate therapy. Serum calcium levels decreased to a lesser extent in 6 patients with initially high PTHrP levels than in those with normal levels at baseline (16 *vs* 27%; $p < 0.05$). Six days after treatment 5 patients with high PTHrP and 1 with normal PTHrP levels were still hypercalcaemic.[15]

- The calcium lowering response to ibandronate was dose-related in 2 of the 3 studies in which this was reported.[13,14] Normalisation of calcium levels (≤2.7 mmol/L[13,14] and a decrease of 0.3 mmol/L from baseline levels,[14]) was achieved by 50, 75.6 and 77.5% of patients after 2, 4 and 6mg, respectively, ($p < 0.05$; 4 and 6mg *vs* 2mg)[13] [fig. 1] and 44, 52 and 67% of patients after 0.6, 1.1 and 2mg, respectively, ($p = 0.0276$; 2 *vs* 0.6mg)[14] [fig. 1]. In the study in which response was not dose related, 53.3% of patients treated with ibandronate 0.2 to 2mg achieved normal calcium levels (2.10 to 2.65 mmol/L).[12]

- In the study in which patients received ibandronate 2, 4 or 6mg, the median time spent within the normal serum calcium range was 11 to 12 days and more than 25% of patients from each dosage group were within this range at the end of the 36-day observation period.[13] The duration of response did not significantly differ between doses in 2 relevant studies; median time to relapse was 18 and 26 days in ibandronate 4 and 6mg recipients, respectively,[13] and 11, 17 and 12 days in patients receiving ibandronate 0.6, 1.1 and 2mg, respectively.[14] In 1 study the time to relapse among ibandronate 2mg recipients was not specified, but more than 50% of these patients were still normocalcaemic at the end of the study (36 days).[13]

- A significantly better response rate was observed in patients with breast and haematological tumours than in those with other tumour types (details of tumour types not given) in 1[13] of 2 studies in which this was assessed. Furthermore, patients with moderate hypercalcaemia (3 to 3.5[13] or ≤3.5[14] mmol/L) responded significantly better to ibandronate (0.6 and 1.1mg,[14] and 2 to 6mg[13]) than those with severe hypercalcaemia (>3.5 mmol/L[13,14]). In 1 of these studies, the correlation of response to initial serum calcium levels was not observed in 2mg recipients.[14]

- The urinary markers of bone resorption, calcium, pyridinoline (PD) and deoxypyridinoline (DPD) [expressed as a ratio to creatinine] decreased only in ibandronate 1.1 and 2mg recipients ($p < 0.0011$ to 0.0001) and not in 0.6mg recipients.[14]

- In another study, a significant reduction in serum calcium levels (from 3.2 to 2.5 nmol/L at

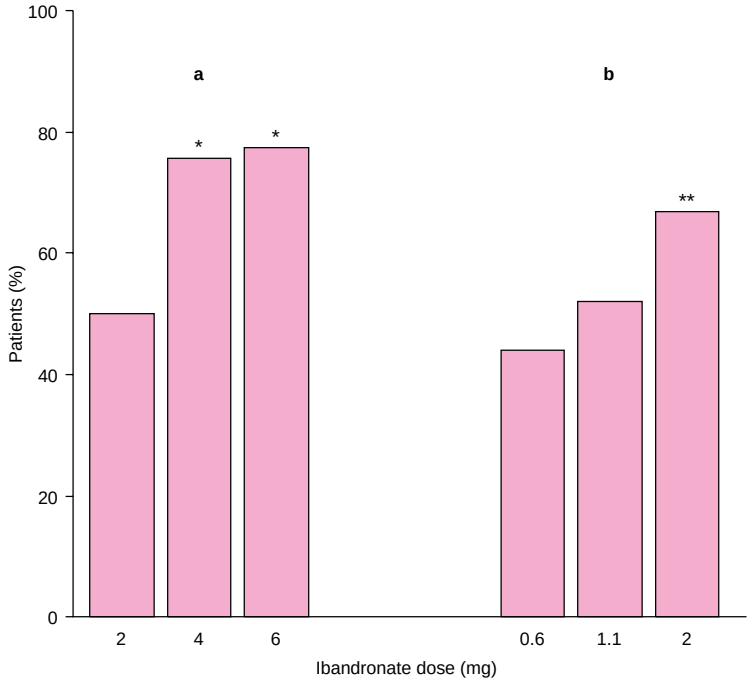


Fig. 1. Efficacy of ibandronate in hypercalcaemia of malignancy. Percentage of patients showing a response (decrease in serum calcium by ≥0.3mmol/L compared with baseline levels and /or serum calcium level ≤2.7mmol/L): results from 2 studies presented (**a**) Ralston et al.[12] and (**b**) Pecherstorfer et al.[13] * $p < 0.05$ *vs* 2mg; ** $p = 0.0276$ *vs* 0.6mg.

day 7) was observed after single-dose intravenous ibandronate (4mg) in 5 patients with hypercalcaemia of malignancy and osteolytic bone lesions (this study may have misquoted the units for serum calcium since normal serum calcium levels range from about 2.1 to 2.6 mmol/L). Furthermore, urinary calcium excretion [expressed as a ratio to creatinine (CR)] also significantly decreased from 14 mmol/10mmol$_{CR}$ (initial) to 6.9 mmol/10mmol$_{CR}$. No significant differences were noted in serum intact parathyroid hormone levels.[16]

Bone Metastases

Clinical studies examining the efficacy of ibandronate in patients with bone metastases did not include end-points such as effect on bone pain, skeletal complications or quality of life parameters. However, they examined the influence of ibandronate on the markers of bone resorption and these results are provided in this section.

- A single intravenous bolus dose of ibandronate (3mg) in 15 normocalcaemic women with breast cancer and bone metastases led to decreased bone resorption, as indicated by significant reductions in urinary excretion of calcium, PD and DPD. In addition, a decrease in albumin-corrected serum calcium levels (2.20 to 2.16 mmol/L on day 21; $p < 0.05$) and phosphate levels (1.10 to 0.97 mmol/L on day 21; $p < 0.05$) and subsequent increases in serum parathyroid hormone and 1,25-dihydroxyvitamin D levels were observed. Reductions in serum calcium levels were maintained for 21 days, and decreases in urinary calcium excretion for 28 days, after the dose.[17]

- In a second study, treatment with oral ibandronate (5, 10, 20 or 50mg, frequency of dose not pro-

vided) for 4 months also resulted in a decrease in urinary excretion of the biochemical markers of bone resorption, PD, DPD and N-terminal portions of the collagen crosslinking molecules (NTX) and CTX by 10, 21, 37 and 42%, respectively, in 101 patients with bone metastases. Symptomatic improvement led to 20 patients requesting continuation of treatment after 4 months.[18]

Osteoporosis

The studies in this section involved postmenopausal women, all of whom were receiving daily calcium supplements (1000mg).[19,20]

- Ibandronate (0.25, 0.5, 1 or 2mg) administered as an intravenous bolus dose every 3 months for 1 year resulted in increases in bone mineral densities at the spine (2.4 to 5.2%) [fig. 2], total hip (1.19 to 2.9%) and trochanter (2.6 to 4.2%), but not the femoral neck, in 105 postmenopausal women with osteoporosis (defined as bone mineral density at the lumbar spine of ≥2.5 standard deviations below the mean for young normal women). However, only the 2mg dose produced significant changes at all sites versus placebo ($p < 0.05$ or 0.01).[19]
- Furthermore, reductions in the urinary excretion of PD (16 to 26.2%), DPD (21.6 to 38.1%), CTX (32.8 to 66.1%) and NTX (30.6 to 66.9%) and serum total alkaline phosphatase (1.4 to 9.9%) and osteocalcin levels (2.5 to 6%) and an increase in serum parathyroid hormone levels (9.1 to 21.4%) were observed after 1 month, indicating a reduction in bone turnover. In general, these changes were significant for ibandronate 0.5, 1 and 2mg versus placebo. The decreases in serum osteocalcin levels and in the urinary excretion of NTX and CTX were dose-dependent.[19]
- Similar results were observed after administration of oral ibandronate (0.25, 0.5, 1, 2.5 or 5mg once daily) for 12 months in 141 postmenopausal women with osteopenia (defined as bone mineral

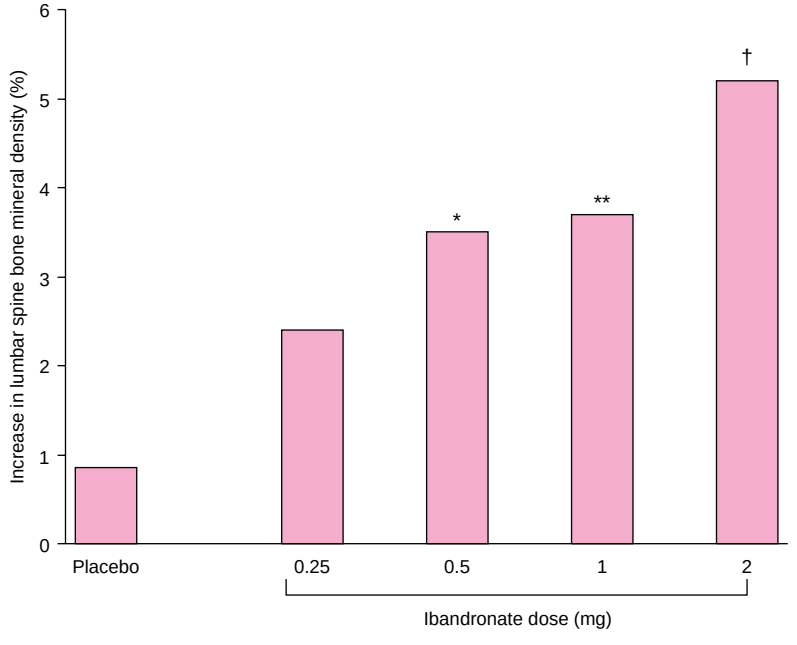


Fig. 2. Efficacy of ibandronate in the treatment of osteoporosis. Improvements in lumbar spine bone mineral density after 12 months' treatment with intravenous ibandronate or placebo once every 3 months in 105 postmenopausal women with osteoporosis (bone mineral density of ≥2.5 standard deviation below the mean of young normal women at the lumbar spine).[18] * $p < 0.06$ *vs* placebo; ** $p < 0.004$ *vs* placebo; † $p < 0.001$ *vs* placebo.

density of ≥1.5 standard deviations below the premenopausal mean value for healthy white women). A significant increase in bone mineral density occurred at the spine, total proximal femur, trochanteric region, intertrochanteric region, femoral neck and Ward's triangle with all doses ($p < 0.05$ *vs* placebo) except the lowest. Increases in bone densities were similar between patients receiving ibandronate 2.5 and 5mg.[20]

• In addition, significant dose-dependent reductions were observed in the biochemical markers of bone turnover after 3 months ($p < 0.001$) in all but the 0.25mg recipients. Serum osteocalcin levels were reduced by 16 to 35%, urinary excretion of CTX by 44 to 88%, serum total alkaline phosphatase levels by 11 to 23% and serum bone-specific alkaline phosphatase levels by 16 to 37% in ibandronate 0.5 to 5mg recipients. However, the differences between ibandronate and placebo recipients were not statistically significant[20]

Paget's Disease

• In 5 patients with active mono- or polyostotic Paget's disease, intravenous ibandronate 2mg (bolus or infusion) led to a 31.2 and 34.7% reduction in urinary PD and DPD excretion, respectively, after 7 days and a 45% reduction in serum alkaline phosphatase levels after 90 days.[21]

• Intravenous ibandronate (2mg as a bolus or infusion) resulted in a decrease in mean serum alkaline phosphatase levels from 516 to 217 U/L at 3 months in 20 patients with active mono- or polyostotic Paget's disease. Alkaline phosphatase levels normalised in 9 patients initially, but only 4 patients had levels ≤170 U/L 12 months after treatment. After this point, relapse of disease was evident in all patients as indicated by a 25% increase in serum alkaline phosphatase levels from their nadir.[22]

4. Tolerability

Data on the incidence of adverse events associated with ibandronate in patients with hypercalcaemia of malignancy, bone metastases or osteoporosis have been obtained from published clinical studies.[13,17,19,20] Manufacturer's prescribing information has been used to provide supplementary data on the incidence of adverse events in patients with malignancy-associated hypercalcaemia.[23]

• The most common adverse event associated with intravenous ibandronate in patients with hypercalcaemia of malignancy is an increase in body temperature. In addition, the reduction in serum calcium levels may result in hypocalcaemia. Serum phosphate levels may also fall.[23] In a clinical study involving 125 patients with hypercalcaemia of malignancy receiving intravenous ibandronate (2 to 6mg), 70% of patients developed asymptomatic hypophosphataemia.[13] Less commonly, flu-like symptoms such as fever, chills and bone and/or muscle pain may occur, and gastrointestinal intolerance has been reported in rare cases. Although not reported with ibandronate to date, bronchoconstriction has been observed with other bisphosphonates in aspirin-sensitive asthmatic patients.[23]

• In a clinical study in normocalcaemic patients with bone metastases, non-serious adverse events associated with intravenous ibandronate (3mg) included asymptomatic hypocalcaemia (10 patients) and hypophosphataemia (8 patients), bone pain (2 patients) and proteinuria (7 patients). No changes were observed in body temperature.[17]

• In placebo-controlled studies in patients with postmenopausal osteoporosis[19] or osteopenia[20] the incidence of gastrointestinal events was similar between placebo and ibandronate (0.25 to 2mg intravenously every 3 months or 0.25 to 5 mg/day orally) recipients[19,20] with the exception of diarrhoea, which was more common in patients receiving ibandronate 5mg.[20] Gastrointestinal events included diarrhoea, constipation, nausea, vomiting, heartburn, flatulence, abdominal pain and gastroenteritis.

• Although patients with osteoporosis receiving intravenous ibandronate (0.25 to 2mg every 3 months) tended to have a higher incidence of musculoskeletal pain, fever and flu-like symptoms

than placebo recipients, this did not achieve statistical significance.[19]

- In patients with osteoporosis,[19] osteopenia[20] or bone metastases,[17] no significant changes were observed in laboratory parameters, haematological parameters, or liver and kidney function in ibandronate (0.25 to 2mg intravenously every 3 months or 3mg single dose, or 0.25 to 5 mg/day orally) recipients.[17,19,20]

- Adverse events experienced by patients with osteoporosis (n = 126 or 180) or bone metastases (n = 15) receiving oral (0.25 to 5 mg/day) or intravenous (3mg single dose or 0.25 to 2mg every 3 months) ibandronate and considered to be serious included leg cramps, carcinoma, cystorhinostomia, vomiting, pulmonary infection, deterioration of pre-existing impaired glucose tolerance, infection, breast cancer, tachycardia, death from suspected myocardial infarction and stenosis of the iliac artery.[17,19,20] However, the authors stated that these events did not appear to be related to ibandronate.[20]

5. Ibandronate: Current Status

Ibandronate is a third generation bisphosphonate which has been launched in Austria and Germany for the management of hypercalcaemia of malignancy. Ibandronate is also in late phase clinical trials worldwide for the management of metastatic bone disease and osteoporosis and in the European Union for the treatment of Paget's disease.

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