SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Bonviva. For information on changes after approval please refer to module 8.

1. Introduction

Postmenopausal osteoporosis (PMO) is a common disorder affecting a large number of women above the age of 50 years. It is currently defined as a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.
World Health Organisation have proposed diagnostic criteria of the disease based on measurements of Bone Mineral Density (BMD) expressed as T-scores, i.e. the number of standard deviations (SD) difference from the mean value of healthy premenopausal women. A BMD T-score below –2.5 is diagnostic for osteoporosis. T-scores between –1 and –2.5 define osteopenia, while a T-score above –1 is considered normal.
Vertebral fractures are the most common osteoporotic fractures and are associated with increased morbidity and deterioration of the quality of life of the patients. In addition, a number of studies have demonstrated an increased mortality in patients with vertebral fractures. About two thirds of vertebral fractures do not come to clinical attention. However, these morphometric vertebral deformities (as opposed to clinical vertebral fractures) adversely affect aspects of the quality of life of the patients and they are strong, independent risk factor for new vertebral, hip and other osteoporotic fractures. Hip fractures, which usually occur in older women, are associated with the highest mortality and long-term disability.
In osteoporosis there is an imbalance between bone formation and bone resorption resulting in bone loss with every bone remodelling cycle. When this is accompanied by an increase in the activation of new bone remodelling units (high bone turnover) more bone will be lost within the same period. In addition, this will adversely affect the structure of the trabeculae and will consequently increase further the risk of fracture. This pathophysiological background provides the rationale for the use of agents that reduce bone resorption and bone turnover in the treatment and prevention of osteoporosis. Such agents include estrogens, calcitonin, raloxifene and the bisphosphonates. Bisphosphonates decrease osteoclastic bone resorption and reduce the rate of bone turnover without a direct effect on bone formation. They are classified into nitrogen-containing (such as alendronate and risedronate) and non-nitrogen containing (such as etidronate) bisphosphonates. The presence of the nitrogen atom in N-bisphosphonates considerably increases their anti-resorptive potency and determines their molecular mechanism of action.

Ibandronate, a nitrogen-containing bisphosphonate, is intended to be used orally in a daily dose of 2.5 mg for the treatment and prevention of osteoporosis in postmenopausal women.
It inhibits osteoclast activity by suppression of farnesyl pyrophosphate synthase, an enzyme of the mevalonate pathway. This leads to a reduced synthesis of the isoprenoid geranylgeranyl pyrophosphate and subsequently of the prenylation of small GTP-binding proteins that are essential for the integrity of the cytoskeleton of the osteoclasts and for intracellular signalling. In long-term studies in relevant animal models, ibandronate was shown to reduce the rate of bone turnover, to increase bone mass and to maintain or increase bone strength with no adverse effects on bone quality or biomechanical competence at doses much higher than those intended for human use.
An intravenous formulation of ibandronate is currently registered in Europe for the treatment of malignancy-associated hypercalcaemia in patients with or without bone metastases and for the prevention of skeletal events in patients with breast cancer and bone metastases.

The treatment and prevention trials were conducted in accordance with the CPMP Note for Guidance on Postmenopausal Osteoporosis in Women (CPMP/EWP/552/95 rev1), both in terms of the characteristics of patients studied and the endpoints used to assess efficacy, with the exception of the BMD inclusion criterion which specified a lumbar spine BMD T-score below – 2.0 in one of the Phase 3 studies. Since this programme was aimed at an approval in the US and Europe, the more conservative inclusion criterion of T-score below –2.0 was chosen for the phase 3 study. The applicant

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has performed a separate analysis of the primary endpoint (incidence of new morphometric vertebral fractures) in those patients with a baseline BMD T-score below -2.5, in line with the current CPMP guideline.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Film-coated tablet containing the active substance in a core formulation which also contains lactose as the chief matrix ingredient together with microcrystalline cellulose, crospovidone, povidone, stearic acid and colloidal silica. The film-coat consists of a conventional Opadry/macrogol 6000 mixture.

Tablets are packed in standard blister packs (PVC covered with a heat-seal coated Aluminium lidding foil).

Active substance

Ibandronic acid INN is present in the tablets as the sodium salt monohydrate. The active substance quality and the batch control test procedures are identical to what have already been approved for the concentrate for solution for infusion (1 mg/1 ml, 2 mg/2 ml and 4 mg/4 ml), which are currently approved in the EU. Similarly, the stability of the active substance has been well demonstrated.

Other ingredients

The other ingredients of the formulation, as listed above, comply with PhEur monographs where relevant. There are no ingredients which give rise to concerns related to TSE.

Product development and finished product

Several oral formulations have been used during the clinical development. A capsule formulation was used in early Phase I and II studies. Film-coated tablets were subsequently used in the remainder of the Phase I/II studies. The tablet formulation used in the pivotal Phase III trials is the same as the tablets intended for marketing. The objective has been to develop a rapidly dissolving tablet, and this has been facilitated by the properties of the active substance. It is used as a fine crystalline powder and is freely soluble in water, so the tablets dissolve very rapidly in aqueous media: Dissolution >90% after 15 minutes. The film-coating has no effect on the dissolution rate.

Two polymorphs of the drug substance have been identified. Both polymorphic forms have similar solubility and intrinsic dissolution properties, therefore no effect of the crystal modification on the in vivo drug release is expected.

The manufacturing processes involve conventional operations: Spray granulation, drying, sieving, blending, tablet compressing and film-coating. The manufacturing processes have been demonstrated to be robust and produce tablets of consistent quality.

Product Specification

The finished product specification at release includes tests for assay, uniformity of content, disintegration, and microbiological aspects. Degradation products are part of the stability-testing program. The control tests comply with Ph. Eur. where relevant, and the specification is in line with ICH Q6A.The limits for degradation products are in accordance with ICH Q3B.

Full details have been provided for 6 batches of the finished product. They all comply with the specifications, and show good uniformity.

Stability of the Product

A total of 6 batches have been studied under ICH conditions (long term and accelerated) originating from the Mannheim production site; (3) and the Basel production site (3); one batch was photostability tested. Parameters investigated included appearance, disintegration, dissolution, assay, related substances and microbiological contamination. Results indicated that the tablets are stable; also they are not sensitive to light. The small variations observed can be attributed to analytical method variations.

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However, arising from a change in production from Mannheim to Basel, only short-term data were available from the Basel site at the time of the CPMP opinion. Furthermore, since there were doubts about the comparability of the two datasets, it was decided to restrict the shelf life until further stability data were available. In general, no significant changes were observed in product quality during storage in the short-term, and the shelf-life as defined in the SPC is justified by the data available at the time of the CPMP opinion.

Discussion on chemical, pharmaceutical and biological aspects

This is a simple standard formulation of a soluble substance resulting in a rapidly dissolving tablet. The purity of the active substance and the control of the manufacturing process and finished product indicate reliable reproducibility of the product and should indicate in turn a reliable performance in the clinic.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Bisphosphonates are stable analogues of naturally occurring pyrophosphates. They are adsorbed onto mineral surfaces in bone and are actively taken up by endocytic osteoclasts. Bisphosphonates with nitrogen-substituted side chains such as pamidronate, alendronate, risedronate and ibandronate, inhibit the biosynthesis of isoprenoid compounds. The latter are essential for the biosynthesis of important signalling proteins, the disruption of which leads to loss of osteoclast activity and induction of apoptosis. Bisphosphonates also reduce osteoclastic activity through an indirect action mediated by osteoblasts. The relative importance of these two mechanisms is unknown. In either case the end result is a reduction in bone resorption and turnover.

- *In vitro* **studies**

In *in vitro* studies, ibandronate was found to be a potent inhibitor of osteoclast activity, with IC50 values in the low nanomolar range. In vitro and single-dose in vivo comparisons indicate that it is 3-10 times as potent as alendronate.

- *In vivo* **studies**

Primary pharmacodynamics has been investigated in vivo in ovariectomised (OVX) or ovario-hysterectomised (OHX) rats, dogs and monkeys, which are well-established models of human post-menopausal osteoporosis. There were a total of four prevention studies, two in rats and one each in dogs and monkeys, as well as a treatment study in rats and dogs. In all three species, ibandronate dose-dependently inhibited or reversed OVX-induced decreases in bone mass and strength in cancellous bone, with less pronounced effects on cortical bone, over an interval ranging from 0.2 to 25 µg/kg/day s.c. The optimum dose was 1 µg/kg/day s.c. in rats, 1.2-4.1 µg/kg/day s.c. in dogs and 30 µg/kg/month i.v. in monkeys, with a trend towards impairment of bone formation in dogs receiving ≥ 4.1 µg/kg/day. In both rats and dogs, s.c. and p.o. bioavailability was ≈ 100% and 1%, respectively. In growing rats, a single s.c. dose of 48 µg/kg inhibited bone resorption by 50% and increased calcium uptake by 10 mg and urinary excretion by 2 mg, with the balance being accounted for by increased bone deposition.
Up to 30 µg/kg/day s.c. had little or no effect on bone mass in very old, intact female rats, whereas in growing rats bone mass and strength were increased by 3-15 mg/kg/day p.o. with no clear dose-relationship. Likewise, 1 µg/kg/day s.c. to 10 mg/kg/day p.o. for 3-12 months had no effect on bone mass or strength in full-grown intact dogs. Thus, ibandronate increases bone mass and calcium balance in growing animals, but not in full-grown, intact adults. There was no adverse effect on the repair of cortical or cancellous bone lesions in dogs exposed to twice the proposed human dose.

- **General and safety pharmacology programme**

Secondary pharmacodynamics has addressed the effect of ibandronate in models of tumour-induced hypercalcaemia, for which the drug substance was approved in 1996. Studies on bone resorption and hypercalcaemia induced by retinoids in thyro-parathyroid-ectomised (TPX) rats demonstrated a linear dose-response relationship over an interval from 0.0015-0.15 mg/kg, which includes the approved maximum human therapeutic dosage of 0.07-0.1 mg/kg by i.v. infusion. In hypercalcaemia and

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hypercalciuria induced by parathyroid hormone-related protein (PTHrP) in TPX rats, ibandronate inhibited osteolysis but had no effect on the PTHrP-induced increase of renal tubular absorption of calcium. As expected, it also prevented the parathyroid-hormone-mediated increase in bone resorption in partially nephrectomised rats. In rodents inoculated with osteolytic neoplastic cells of human or murine origin, ibandronate consistently reduced the number and size of osteolytic bone lesions.

Safety pharmacology studies revealed no adverse effects on the central nervous, cardiovascular, respiratory or gastrointestinal system at exposures well above those anticipated in humans. In rats and dogs administered 5-20 mg/kg p.o., there was a decrease in urinary volume and/or the Na+ /K+ ratio. Further investigation to elucidate adverse effects on the kidney was conducted during the toxicity studies.

Non-clinical pharmacodynamic interaction studies were not conducted.

- **Summary of salient findings**

Although the exact mechanism of action of bisphosphonates is unknown, the final result is a reduction in bone resorption and turnover.
In vitro and in vivo studies in rats, dogs and monkeys demonstrate that ibandronate is a potent inhibitor of osteoclast activity, and inhibits or reverses OVX-induced decreases in bone mass and strength in cancellous bone, with less pronounced effects on cortical bone.
Safety pharmacology studies revealed no adverse effects on the relevant systems.

Pharmacokinetics

Because ibandronate, like other bisphosphonates, is almost exclusively (>98%) taken up by calcified tissue, the pharmacological effects of ibandronate cannot be considered directly related to blood levels. For this reason, it is argued that single and repeat dose pharmacological effects are better assessed by measuring the drug concentrations in bone than in plasma, and that tissue distribution studies are more relevant to the mechanism of action than the plasma profiles.
The methods of analysis used to study tissue distribution are appropriate. Liquid scintillation counting (LSC) of ^{14}C-ibandronate in various tissues was used both at single and repeated administration Autoradiography was used for animals dosed with ^{14}C-ibandronate for 1 and 7 days. An enzyme – linked immunosorbent assay (ELISA) was used to measure ibandronate in serum and urine.

Bioavailability
In rats and dogs, ibandronate was shown to have an oral bioavailability of about 1%. Intake of food and calcium concomitant with oral dosing in rats reduced the bioavailability further, as compared to rats fasted at the time of dosing.
Various in vivo studies in rats and dogs and in vitro studies in rat and human liver microsomes and duodenum preparations all indicate that the drug is not metabolised anywhere in the body except possibly for a very small fraction in the duodenum. Once entered into the circulation, it is rapidly removed by liver and kidney uptake, followed by a relatively slow release and long-term binding to the bone. The binding of ibandronate to plasma proteins and blood cells is rather low, indicating an easy diffusion into the extravascular space.

Tissue distribution and clearance after repeated administration of ibandronate are comparable to those found after single administration.
The lack of calculation of clearance parameters in rats is justified since clearance parameters could not be reliably measured in rats. In dogs given 0.01 mg/kg ibandronate s.c., 41.9 % of the dose was excreted in urine after 24 hours. Volume of distribution was 7.3 l/kg, indicating penetration into a deep compartment (bone, liver and kidney). Excretion is almost exclusively through urine.
Serum kinetics was determined in OVX Cynomolgus monkeys given 10, 30 and 150 µg/kg/month i.v. for 16 months. Exposure was linear in relation to dose, thus clearance mechanisms were not saturated.

Distribution
Tissue distribution following a single i.v. administration was studied in rats. They were given 0.1 mg/kg ^{14}C-ibandronate i.v., 50% of the dose was found in calcified tissue after 2 and 24 hours.

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Radioactivity was 17 to 38 times higher in calcified tissue than in non-calcified tissue. Relative distribution of radioactivity was bone>liver>kidneys>spleen.
Excretion via faeces was low and biliary excretion of ibandronate was very low.
Because of the intended long-term administration of ibandronate, accumulation of the compound was studied in rats treated for 7 days with 0.1 mg/kg ^{14}C-ibandronate and autoradiographed 2 and 24 hours after the last administration. The scans clearly showed that bone tissue is the main target for accumulation. The tissues ranked in order of amount of radioactivity were: bone tissue>>>kidney (renal cortex) >liver, faeces and spleen. There appeared to be a higher radioactivity in the kidney (renal cortex) after repeated dosing than after single dosing.
LSC distribution studies in rats given ^{14}C-ibandronate i.v. for 7 days showed that concentrations increased 4-7 fold in calcified tissues and kidneys during repeated administration. Other organs showed only little (2-fold) or no accumulation.

Ibandronate concentration in bone
Ibandronate concentration in bone was determined in rats after 2 years daily oral dosing of 3,7 or 15-mg/kg ibandronate. The uptake of ibandronate was dose-dependent and linear, and there was no evidence of skeletal saturation. This indicates a normal bone physiology after lifelong administration in doses far in excess of the therapeutic dose.
In aged OVX rats treated for 12 months the concentration of ibandronate in bones was dose-dependent, and uptake of drug by the bone was linear with the dose.
In OVX cynomolgus monkeys treated for 16 months, the ibandronate concentration appeared to be dose-dependent in a non-linear fashion. The non-linearity was explained by the suppression of OVX-induced bone turnover.

Protein binding and drug interactions
Different studies point out that the binding of ibandronate to plasma proteins and blood cells is rather low. This implies an easy diffusion of the product into the extravascular space. Furthermore, this level of binding is unlikely to result in drug interactions.

No enzyme induction took place in the liver of ibandronate treated rats, and ibandronate did not inhibit any of the major cytochrome P450 iso-enzymes in human liver microsomes, suggesting that hepatic drug-drug interaction is unlikely in man.

Other pharmacokinetic studies
Bisphosphonates have a high affinity to the hydroxyapatite crystals in the bones, and therefore investigations on placenta transfer at the time of foetal bone mineralisation are of interest. The results of the placental transfer study indicate a low, however existent foeto-placental transfer of ^{14}C-ibandronate.
The transfer of radioactivity into the milk was studied after a single i.v. administration of 0.08 mg/kg ^{14}C-ibandronate to lactating rats. This study demonstrated the presence of low levels of ibandronic acid in the milk following administration.
Adequate information with regard to these issues has been included in section 4.6 of the SPC. However, given the intended treatment population of post-menopausal women, the information obtained on placental transfer, transfer into milk and also reproduction toxicity (see later) does not create great concern in this application.

Toxicology

The high affinity of bisphosphonates to bone mineral along with their low potential to penetrate soft tissue, due its high molecular polarity, explains their relatively good safety profile. Systemic toxicity is generally considered related to the uptake of bisphosphonate complexes by tissue macrophages. Other toxic specific effects are those related to the pharmacological effect of the bisphosphonates. These include increased trabecular bone mass, decreased serum calcium and phosphorus levels, and reduced bone marrow space leading to haematological changes.
The applicant has performed a comprehensive toxicology programme in mice, rats and dogs.

Single dose toxicity

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These studies have been carried out in mice, rats, and dogs.
Acute toxicity was seen only at high oral doses (LD_{50} in mice=1494 mg/kg, LD_{50} in rats = 811 mg/kg). This is about 600-fold and 300-fold greater than the intended daily maximum oral human dose.

Repeat dose toxicity

Repeated-dose toxicity studies were carried out in rats and dogs.
The primary target organs were kidney, and to a lesser extent, liver, lung and gastrointestinal tract. Findings in these organs were dose and time dependent. Slightly decreased serum calcium and phosphorus values, and decreased red blood cell count due to extension of trabecular bone mass at the expense of bone marrow space were seen at all dose levels, and therefore NOELs could not be established.
This information comes from previously submitted studies. In addition, a toxicokinetic study and long-term studies as would be required to support the osteoporosis indication have been submitted. The duration of these studies rangedbetween 2 weeks and 12 months, as expected for a product intended for chronic use. These studies did not reveal any unexpected findings compared to previously conducted studies.

The main kidney findings were tubular changes, i.e. tubulonephrosis. Kidney lesions appeared to be irreversible at high long-term dosing, whereas some reversibility was seen at lower dose levels in rats and dogs. Liver toxicity was only seen at very high dose levels during long-term administration.
In rats and dogs, gastrointestinal disorders were seen only at the high, lethal dose levels, i.e. well above the nephrotoxic dose level.
Bone alterations and the related secondary alterations in bone marrow and spleen also continued at recovery in both rats and dogs.
In the rat, abnormal respiration was seen at the highest toxic dose levels. In the dog, respiratory disorders were only seen at lethal doses. At lethal chronic doses, other organ toxicity like testicular atrophy and thymus involution were seen in the dog. All these effects were seen at very high and thus irrelevant chronic dose levels.
ECGs were recorded in all repeat dose dog studies. No changes in heart rate, wave form, wave amplitude or wave intervals could be attributed to ibandronate treatment. The risk of QT/QTc interval prolongation is considered unlikely for the recommended dosages of ibandronate for osteoporosis

Toxicokinetics were measured for most chronic toxicity studies, but calculations were hampered by very high variability of blood exposure in animals and humans and analytical limitations. Oral bioavailability, when assessed from the excretion in urine, was 0.9% in dogs and 0.6% in humans. In fasted rats, oral bioavailability was about 1% as assessed from the pharmacodynamics studies on bone. The similarity of oral bioavailability in animals and humans suggest that comparison of oral doses can be a relevant estimate for safety margins in addition to the exposure data based on AUC values.
The calculated safety margins for chronic treatment were based on the no-observed-adverse effect level, NOAEL, defined as the highest dose without liver or kidney findings. These safety margins give no special reason for concern for the human clinical use.

Genotoxicity and carcinogenicity studies

None of the in vitro and in vivo genotoxicity studies indicated any genotoxic potential of ibandronate.
None of the three oral carcinogenicity studies (one in rats and two in mice) indicated any carcinogenic potential of ibandronate.

Reproduction toxicity

In the reproduction toxicity programme, ibandronate was found to reduce sperm concentration in males and, in females, to decrease the number of corpora lutea and increase pre-implantation loss. When given orally, it was foetotoxic, but not teratogenic in rats. However, as foetal effects were limited to variations with a high spontaneous occurrence and there was no foetotoxicity in an i.v. rat study or in the rabbit, ibandronate is considered unlikely to be a direct toxicant. In offspring exposed in utero and through the milk, there were no direct effects on growth, behaviour or reproductive performance. Dystocia in rat dams and teeth abnormalities in their pups could be attributed to disturbances in maternal calcium metabolism. None of these effects are a cause for concern, as they

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occurred at exposures at least 20 times higher than the proposed human dose and as the drug product is intended for use in postmenopausal women.

Local tolerance
Ibandronate was a severe irritant when injected paravenously or s.c. in rats and rabbits and corrosive in an acute skin irritation test in rabbits. Although these routes are irrelevant to oral administration, they indicate a potential to cause irritation or burns to the oesophagus and gastric mucosa. Appropriate warnings to this effect are included in Section 4.4. of the SPC.

Environmental risk assessment
The drug substance was tested for acute toxicity to aquatic organisms, inhibition of activated sludge and biodegradability according to OECD guidelines. It was concluded that exposure levels of concern to the environment are not to be expected.

Discussion on toxico-pharmacological aspects

The pharmacokinetic studies are limited to the measurment of drug concentration in bone and other tissue distribution studies. This approach is considered acceptable since ibandronate is almost exclusively taken up by calcified tissue, and therefore the pharmacological effects are not directly related to blood levels.
The oral bioavailability of ibandronate in rats and dogs is about 1%, and is further reduced by concomitant intake of food and calcium in rats. There is no indication that ibandronate is metabolisedin any species after in vivo administration
The binding of ibandronate to plasma proteins and blood cells is low, and therefore unlikely to result in drug interactions.
In short the pharmacokinetic studies submitted are generally adequate and give an adequate overview.
The toxicology programme identified the kidney, and to a lesser extent liver, lung and gastrointestinal tract as primary target organs. Findings in these organs were dose and time dependent. The calculated safety margins, based on the no-observed-adverse effect level (NOAEL), give no special reason for concern for the human clinical use.
In conclusion for the toxicology package, no unexpected toxic effects have been revealed with the newly performed studies. There is no increased preclinical concern for the given indication.

4. Part IV: Clinical aspects

The applicant, Roche Pharmaceuticals, applied for a marketing authorisation (via the centralised procedure) for ibandronic acid, for the indication "treatment and prevention of osteoporosis in post-menopausal women". Ibandronic acid, under the trade name *Bondronat* is currently marketed in the EU for the treatment of hypercalcaemia related to malignant disease and for the prevention of skeletal events in patients with breast cancer and bone metastases.
In total, 1585 patients were exposed to the recommended dose of 2.5 mg daily. The dose and dosing interval selected for the pivotal studies are based on the two phase 2 studies MF4348, and MF4433. In support of the application of daily treatment with 2.5 mg ibandronate, two main trials were performed, MF 4411 supporting the application for daily orally administered ibandronate for the treatment of postmenopausal osteoporosis and MF4499 supporting the daily administration of 2.5 mg ~~Ibandronate~~ ibandronate for the prevention of postmenopausal osteoporosis. MF4411 was a multi-center, double-blind, placebo-controlled, randomised, phase 3 fracture study carried out in North America and Europe and MF4499 was a multi-center, double-blind, placebo-controlled, randomised, dose finding, phase 2-3 study. Additionally, a supportive phase 3 study, MF4491 for the treatment of postmenopausal osteoporosis with BMD as the primary endpoint was also performed. This study was a multi-center, open-label, randomised study using 2.5 mg ibandronate administered orally with either 30 min or 60 min post-dose fast during 12 months

Clinical pharmacology

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The clinical pharmacology of ibandronate has been studied in healthy male volunteers, in healthy postmenopausal women, in postmenopausal women with osteoporosis, in patients with varying degrees of renal impairment and in patients with metastatic bone disease. A total of about 700 subjects in 24 clinical pharmacology studies, one phase 2 study and from clinical pharmacology assessments within two therapeutic trials, contributed to the clinical pharmacology data.

Pharmacodynamics

Pharmacodynamic parameters related to the efficacy of bisphosphonates are reflected in markers of bone metabolism. A reduction in markers of bone resorption is the earliest effect that can be demonstrated, while effects on markers of bone formation are, by virtue of nature, delayed.

- Mechanism of action

Ibandronic acid is a nitrogen-containing bisphosphonate, which exerts its action by inhibiting the osteoclast activity though inhibition of the enzyme farnesyl pyrophosphate synthase. Subsequently, the prenylation of GTP-binding proteins that are essential to the integrity of the cytoskeleton of the osteoclasts and for intracellular signalling, is inhibited. The net result is a decrease in osteoclastic bone resorption and a reduction in the rate of bone turnover. In vitro and in animal models, ibandronate has been shown to be more potent than other bisphosphonates, such as alendronate and risedronate.

Dynamic studies:

Treatment of postmenopausal osteoporosis
The general pattern observed is to a reasonable degree consistent: a dose dependent inhibition of the parameters of bone resorption a slight and clinically not significant decrease in serum calcium values with a compensatory transient increase in PTH levels. In study MF 4348 urinary CTX, the best predictor of bone resorption, was suppressed dose dependently reaching a minimum about three months after initiation of therapy. This suppression remained consistent throughout therapy and returned to baseline values within 12 months of discontinuation. Serum osteocalcin, the primary marker of bone formation, levels declined dose dependently reaching a level of about 40 per cent of baseline after 6 months of treatment. In study MF 4411 CTX suppression was observed after three months, remaining suppressed throughout treatment and after 36 months of therapy the median reduction was 65 per cent compared to baseline values. Maximal suppression of serum osteocalcin levels was reached after 6 months with a median reduction of 36 per cent that remained constant throughout the study.

Prevention of postmenopausal osteoporosis
In study MF 4499, urinary CTX, was suppressed dose dependently reaching minimum about three months after initiation of therapy. This suppression remained consistent throughout therapy with a median reduction of 41 per cent following 24 months of treatment with 2.5 mg daily compared to baseline. Serum osteocalcin levels declined dose dependently reaching a minimum level about 9 months after therapy was initiated. In patients receiving 2.5 mg daily, a median reduction of 34 per cent of baseline values after 24 months of treatment was found. No studies have specifically been conducted for the investigation of the secondary pharmacology of ibandronate.

In neither the primary dose-finding study MF 4348, the confirming dose-finding study MF 4433 or in the pivotal phase III study MF 4411, no attempt has apparently been made at linking steady state plasma concentrations of ibandronate to the biochemical markers of clinical efficacy or primary endpoints. Given the variability of plasma concentrations present and the size of the effect studied, a statistically significant or clinically meaningful correlation is not likely to materialise.

Pharmacokinetics

- General:

A complete pharmacokinetic documentation has been submitted.

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Ibandronic acid was determined in human plasma and urine by gas chromatography – mass spectrometry (GC-MS) and/or an enzyme linked immunosorbent assay (ELISA). These methods are considered suitable for their purposes and are well validated.
The pharmacokinetics of ibandronate is generally well described. Following oral administration of 2.5 mg ibandronate, the pharmacokinetic profile is consistent and predictable across the target population as well as in other populations studied. No evidence of dose-dependent pharmacokinetics has been found. Time dependency has been demonstrated as accumulation occurs in the target population upon prolonged exposure. A 1.5 to 2-fold increase in AUC following 12 months of oral administration was shown, as were similar changes in maximum plasma concentrations. Considering the very low bioavailability and the huge inter- and intraindividual variability, an accumulation in this order of magnitude is not judged to be of clinical significance.

Absorption
Maximum plasma concentrations of ibandronate are reached within one hour when not administered concomitantly with food. Absolute bioavailability is 0.6 per cent and is further reduced by 90 per cent if ibandronate is administered concomitantly with food.

Distribution
The apparent terminal volume of distribution in man is at least 90 L, but the estimation of this parameter is hampered by the problems associated with the estimations of the terminal slope of the time-concentration curves due to a paucity of data points. Ibandronate is distributed into soft tissue and a substantial proportion of the drug is bound to the bone. Plasma protein binding is about 85 per cent.

Elimination
Ibandronate is not metabolised and is eliminated unchanged in the urine with a renal clearance of about 60 mL/min. Total clearance is about 84-160 mL/min and the residual clearance probably reflects uptake of the drug in the bone.

Pharmacokinetics has not been investigated in subjects below 18 years of age. The pharmacokinetics of ibandronate has not been studied in patients suffering from hepatic impairment but, as ibandronate is not metabolised, no dose reduction in these patients seems necessary.
Studies in patients suffering from varying degrees of renal impairment have demonstrated a linear relationship between renal function and renal clearance of ibandronate. Exposure to ibandronate as assessed by AUC increases about two-fold in subjects with creatinine clearance below 30 mL/min. The mean Cmax increases by 50 per cent with a huge interindividual variation. As the pharmacokinetics of ibandronate was not assessed in patients with end-stage renal disease managed other than by haemodialysis, the pharmacokinetics of ibandronate in these patients is unknown. Due to limited clinical experience in this patient group, ibandronate is not recommended for patients with a creatinine clearance below 30 mL /min.
Appropriate warning of the use under these circumstances is made in the SPC.

- Interaction studies:

In vitro studies do not suggest that ibandronate possess a potential for clinically relevant pharmacokinetic drug-drug interactions related to cytochrome P450. In vivo interaction studies have been performed for concomitant administration of hormone replacement therapy, tamoxifen, melphalan/prednisone and ranitidine. Concomitant administration with ranitidine increased absolute bioavailability by 20 per cent, while no pharmacokinetic interactions were observed for the other drugs. The effect of ranitidine is most likely secondary to gastric pH change, and can be considered of no clinical relevance.

- Bioequivalence studies:

The applicant has used the capsule for some early phase I and II studies, while phase III were conducted with the film-coated tablet. In order to show a reasonable degree of bioequivalence between these formulations, the applicant has provided relative bioavailability calculations of capsule versus film-coated tablet formulations. The resulting point estimate of AUC ratio is 108% with 90% CI confidence limits of 75-157%. For Cmax ratio, the point estimate is 95% with 90% confidence limits

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of 63-145%. While the confidence limits exceed the usual recommended limits, this is deemed justifiable in the present case. Ibandronate has a very low bioavailability and thus comes with inherent large variability that is reflected in the confidence intervals

Clinical efficacy

The applicant is seeking registration of the use of ibandronate in the daily dose of 2.5 mg for the treatment of osteoporosis in postmenopausal women and for the prevention of postmenopausal osteoporosis. The clinical studies providing support for these indications are listed here:

Study No. (Location)	Phase Design Duration	Total No. of Patients	Primary Endpoint	Purpose of the Study
Treatment of postmenopausal osteoporosis				
MF4348 (Denmark)	Phase 2 SC, DB, PC, DF, // 1 year	180	Lumbar spine BMD	Efficacy and safety of daily dosing (placebo, 0.25 mg, 0.5 mg, 1.0 mg. 2.5 mg, 5.0 mg) in women with low forearm BMD (T-score ≤ -1.5). [60 minute post-dose fast].
MF4433 (Denmark)	Phase 2 SC, DB, PC, // with XO 2 years[1]	240	Lumbar spine BMD	Efficacy and safety of 2.5 mg daily and 20 mg intermittent[2] dosing vs. placebo in women with low lumbar spine BMD (T-score ≤ -2.5). [60 minute post-dose fast].
MF4411 (US/Canada/ Europe)	Phase 3 MC, DB, PC, // 3 years	2929	New incident vertebral fractures	Efficacy and safety of 2.5 mg daily and 20 mg intermittent[2] dosing vs. placebo in women with low lumbar spine BMD (T-score -2.0 - -5.0) and 1 – 4 prevalent vertebral fractures. [60 minute post-dose fast].
MF4491 (US/Europe)	Phase 3b MC, O, // 1 year	213	Lumbar spine BMD	Comparison of a 30-minute vs. 60-minutes post-dose fast with daily administration of 2.5 mg in women with low lumbar spine BMD (T-score ≤ -2.5).
Prevention of Postmenopausal Osteoporosis				
MF4499 (US/Canada)	Phase 2/3 MC, DB, PC, DF, // 2 years	653	Lumbar spine BMD	Efficacy and safety of daily dosing (0.5 mg, 1.0 mg, 2.5 mg, placebo) in women at least 1 year postmenopausal and with normal or low lumbar spine BMD (T-score ≥ -2.5). [30 minute post-dose fast].

DB = double-blind, BMD = bone mineral density, DF = dose finding, MC = multicenter, O = open-label, PC = placebo-controlled., SC = single center, // = parallel group, XO = cross over
[1] Placebo-controlled for the first 12 months
[2] 20 mg ibandronate every other day for 12 doses at the start of every 3 month cycle

A GCP inspection of the multicenter, phase III, clinical trial MF4411 was performed. Compliance with the protocol and GCP appeared to be satisfactory and the quality of the data reported was acceptable.

Dose-response studies and main clinical studies

The dose and dosing interval selected for the pivotal studies are based on the two phase 2 studies MF4348, and MF4433. The phase 3 studies MF4411 and MF4499 are the two pivotal studies supporting the indication. The MF4491 was conducted in order to investigate whether reducing the post-dose fasting might increase long-term compliance.

Dose response studies

MF4348, and MF4433 are two phase 2 double-blind, placebo-controlled, randomised studies. The primary endpoint in these trials was the change in lumbar spine BMD in the ITT population.

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Study MF4348 was a 1-year dose-finding study in 180 women with low forearm BMD (T-score ≤ -1.5). The effect of daily oral ibandronate at doses 0.25, 0.5, 1.0, 2.5 and 5.0 mg on BMD was investigated. There were dose-dependent increases in lumbar spine BMD in the ITT population with an apparent plateau at the 2.5 mg after 12 months.
Study MF4433, of two years duration in 240 women with osteoporosis, included the 2.5 mg daily dose selected from study MF4348, and, in addition, investigated an intermittent treatment regimen of 20 mg ibandronate given every other day for 24 days at the start of every 3-month cycle. Based on predefined equivalence margin of 2% for the 95% CI the two regimes were to be equally efficacious as regards effect on BMD. Furthermore, ibandronate 2.5 mg daily increased lumbar spine BMD after one year to levels similar to those seen in study MF4348 indicating consistency of the effect of this dose. Based on the results of MF4348 and MF4433, the 2.5 mg daily dose seems an appropriate choice for the pivotal phase III trials.

Main studies (phase III = therapeutic confirmatory trials)

As mentioned before, in support of the application of daily treatment with 2.5 mg- ibandronate, two main trials were performed, MF4411 supporting the daily oral administration of ibandronate for the treatment of post menopausal osteoporosis and MF4499 supporting the daily oral administration of 2.5 mg ibandronate for the prevention of bone loss.
Additionally, a supportive phase 3 study, MF4491 for the treatment of PMO with BMD as the primary endpoint was also performed.

Study MF4411

1. Description of the study

MF4411 was a multi-center, double-blind, placebo-controlled, randomised, phase 3 fracture study carried out in North America and Europe.
A total of 2929 women, in the age of 55 –80 years, at least 5 years post-menopausal with at least one vertebral fracture and a BMD score below –2.0 in at least one of the vertebrae L1-L4 were randomised into 3 parallel groups and treated as outpatients for three years with either: placebo, 2.5 mg ibandronate, one tablet q.d. or 20 mg ibandronate, intermittent treatment with one dose every other day for 12 doses at the start of each 3 month cycle and were evaluated for efficacy.
The medication was administered orally and the patients were instructed to take the tablets after at least a 6 hours fast immediately after waking in the morning with sufficient water and remain fasting for a minimum of 1 hour after dosing. All patients received daily oral supplements of 400 IU vitamin D and 500 mg calcium.
Patients were randomised in a clinically relevant order. At visit 1 the patients was randomised in blocks of 6 patients into one of the 3 treatment groups. The randomisation was carried out in accordance with a predetermined randomisation list based on block randomisation. Each center was provided with at least one block with 6 numbers
The blinding procedures were performed in a classical and appropriate manner

The exclusion criteria applied to women with more than two lumbar spinal fractures, with a BMD below –5.0, women suffering from diseases (chronic liver and gastrointestinal diseases, cancer, alcoholism, primary hyperparathyroidism, Paget's disease, and active diseases, except thyroid hormone treated hypothyroidism) or treated with drugs (steroids, hormones etc.) known to influence bone metabolism, women previously treated with bisphosphonates, women suffering from renal impairment or women with hypo-or hypercalcaemia, women treated with any investigational drugs within 30 days preceding the first dose of the study drug were given, women treated with aminoglycosides within 4 weeks prior to randomisation and women with aspirin-sensitive asthma in their medical history.

2. Primary endpoints

The objective of the study was to investigate the efficacy and safety of continuous and intermittent oral administration of ibandronate in the long-term treatment of postmenopausal osteoporosis.

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The primary efficacy parameter was the number of patients with new incident vertebral fractures at 3 years of treatment with the study medication in the ITT (intention to treat) population.
Incident vertebral fractures were classified as either new incident fractures (of previously normal vertebrae) or worsening incident fractures (of previously deformed vertebrae). Only new fractures were included as a primary endpoint
An incident vertebral fracture was defined by a reduction of at least 20% in the anterior, medial or posterior height of a vertebral body and an absolute decrease in height by ≥ 4 mm.
Radiographs were taken at the screen visit and annually thereafter. Fractures were based on the radiologists qualitative diagnosis and on morphometrically criteria using digitised images produced from the original lateral X-rays.
Prevalent vertebral fractures were defined as vertebral deformities identified at baseline having a 20% reduction in any height of vertebral bodies between T4 and L4 and required an additional qualitative confirmation by an experienced radiologist.
Clinical fractures were those coming to medical attention, were reported as adverse events and were confirmed by X-rays.

Secondary efficacy parameters include the rate of patients with new vertebral fractures (including clinical fractures), total number of fractures, height, changes in bone mineral density at the lumbar spine and hip, urinary excretion of the C- or N-telopeptides of collagen type I (CTX and NTX), corrected for creatinine as biochemical markers of bone resorption and serum bone specific alkaline phosphatase and osteocalcin as biochemical markers of bone formation.

3. Statistical analysis

The primary efficacy parameter was analysed by a life-table survival method. A confirmatory analysis was done by testing the homogeneity of the time to event. The reduction in the relative risk was performed by using a Cox proportional hazards model that included an interaction between baseline BMD and treatment as a covariate. The analysis of time to event for clinical fractures was done using Kaplan Meier analysis. ANOVA was used to investigate the treatment effect on the relative3-year BMD changes, adjusting for baseline BMD as a covariate. Kruskal Wallis test was used for the comparison of treatment groups based on 3-year data for the relative changes in markers of bone turn over. Differences in the reduction of height were assessed by Wilcoxon test.

RESULTS

4. Study populations/accountability of patients

The intention to treat (ITT) population consists of all patients receiving at least one dose of study medication and where at least one follow-up data point was available. This population was used in all fracture analyses
The per-protocol (PP) population includes all patients in the ITT population except those with major deviation from the study protocol. These subjects were excluded due to the intake of forbidden concomitant medication affecting bone metabolism, the lack of BMD or vertebral fracture assessment at baseline or follow up, insufficient compliance, or the development of a confounding condition affecting bone metabolism. This PP population was defined in order to assess the effect of ibandronate in a cohort fulfilling the ideal study criteria. All analyses of non-fracture endpoints were performed in the PP study group.
A total of 2929 patients were evaluable for ITT analyses and was identical with the safety population.
A total of 2125 patients were evaluable for PP analyses: 706 in the placebo group, 711 in the 2.5 mg group and 708 patients in the group receiving intermittent treatment.

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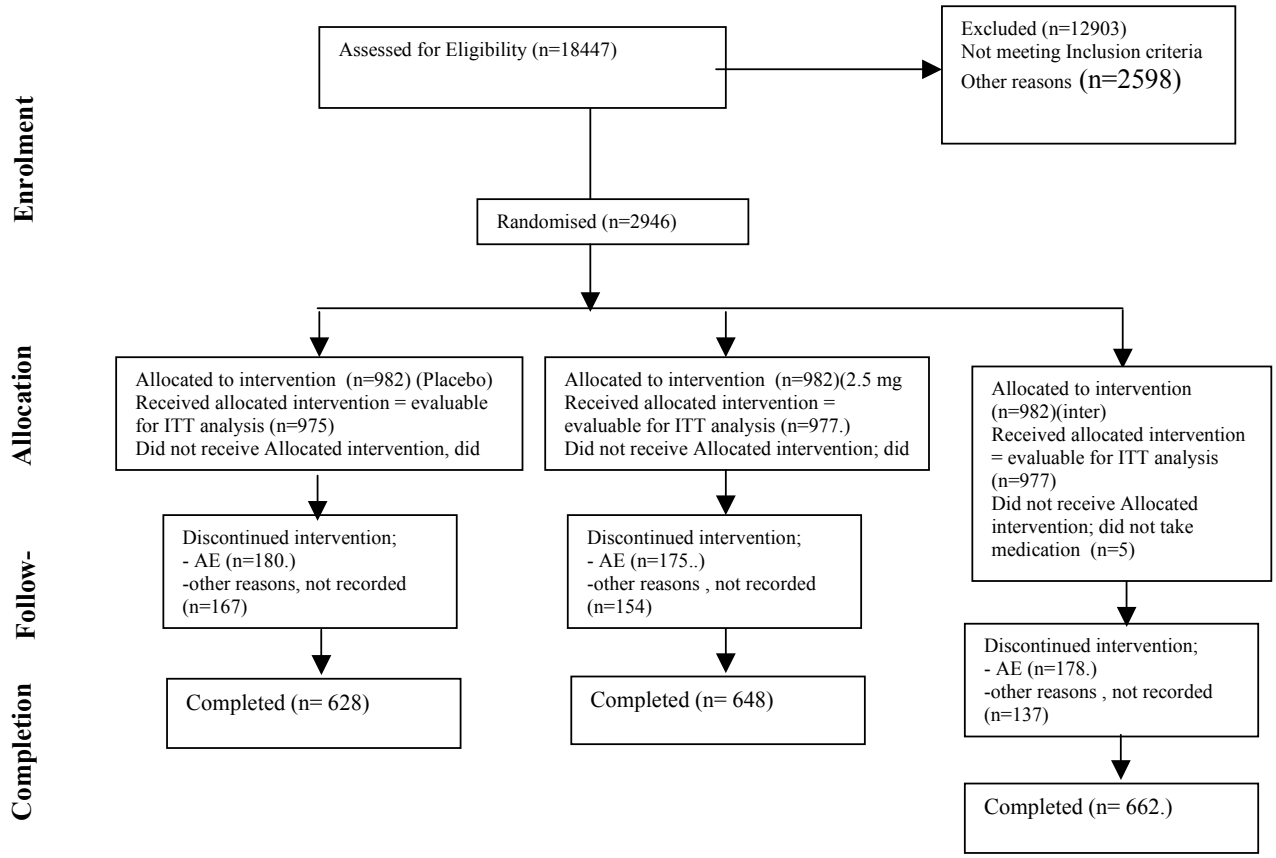

5. Efficacy results

Treatment with 2.5 mg daily oral ibandronate led to a clinically meaningful and highly significant reduction in the incidence of new morphometric vertebral fractures in patients with postmenopausal osteoporosis leading to relative risk reduction of 62% ($p < 0.0001$). This reduction was evident after two years and was maintained over the 3-year period of treatment. Furthermore, this effect was also shown for new and worsening vertebral fractures separately, as well as for clinical vertebral fractures. The magnitude and significance of the anti-fracture efficacy was consistently observed in various subgroups of patients. In particular no geographical differences were observed. Daily ibandronate treatment had no effect on the incidence of non-vertebral fractures, but appeared to be effective in a high-risk subpopulation. The lack of an observable treatment effect on the incidence of nonvertebral fractures in the total patient population was probably due to the low-risk patient population included in the study. Also, a significant reduction in the loss of stature was consistently shown with daily ibandronate therapy. Consistent with the anti-fracture effect, study MF4411 also revealed that daily therapy with 2.5 mg oral ibandronate induces a significant and clinically relevant increase in BMD (lumbar, femoral neck or hip) that was not confined to the first year of treatment but continued throughout the observation period.

<u>Study MF4499</u>

1. Description of the study

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MF4499 was a multi-center, double-blind, placebo-controlled, randomised, dose-finding, phase 2-3 study.
Six hundred patients were to be enrolled, 150 patients in each of the four groups with the purpose of having 112 patients completing two years of treatment. Patients were assigned randomly to one of four parallel groups. Placebo, or ibandronate 0.5 mg, 1.0 mg or 2.5 mg. Inclusion criteria were: women at least one year post menopausal and written informed consent. Exclusion criteria were: mean BMD at lumbar spine < -2.5 SD (T-score), osteoporotic fracture in history, bilateral oophorectorny, diseases known to influence bone metabolism (chronic liver and GI diseases, cancer, alcoholism, primary hyperparathyroidism, Paget disease, histologically documented osteomalacia and active thyroid diseases without treatment) or treatment with drugs (steroids, hormones etc.) within the previous six months known to influence bone metabolism, treatment with bisphosphonates, renal impairment, hypo-or hypercalcaemia, treatment with any investigational drugs within 30 days preceding the first dose of the study drug were given, and -vitamin D deficiency.
The medication was administered in a similar way as for study MF4411. Only the post-dose fasting period differed: 30 minutes in study MF4499 compared to 60 minutes in study MF4411.
Patients were randomised into four parallel groups on the basis of baseline BMD and time since menopause: placebo, or ibandronate 0.5 mg, 1.0 mg or 2.5 mg. The doses were chosen on the basis of a dose finding phase 2 study showing a significant dose-dependent increase in BMD at doses 1.0, 2.5 and 5.0 mg ibandronate compared with placebo.
The blinding procedures were performed in a classical and appropriate manner

2. Primary endpoints

The objective of the study was to investigate the dose-response, efficacy and safety of continuous oral ibandronate administration for the prevention of bone loss in postmenopausal women and to define the optimum dose to prevent bone loss.
The primary efficacy parameter was the change in BMD of the lumbar spine after 2 years of treatment in the ITT population.

Secondary efficacy parameters were relative change from baseline in BMD of the total body, distal forearm and proximal femur and the relative change from baseline and placebo in rate of bone turnover, as assessed by serum C-telopeptide (CTX), PTH and osteocalcin concentrations and urinary CTX excretion (ratio of CTX/creatinine).

3. Statistical analysis

A close test procedure was adopted for the primary efficacy variable, lumbar spine BMD. The primary model was an ANOVA, which took treatment and allocated stratum into account as independent factors. The primary analysis population was the ITT population. Subgroup analysis for the primary efficacy variable was conducted for stratum, weight, calcium compliance, baseline vitamin D status, and time since menopause. A one-way ANOVA model containing only the treatment factor was used. The methods for the secondary variables for the comparison between treatment groups of the relative change in BMD were the same as the one used for the analyses of the primary variable. The Wilcoxon Rank sum test was used for the comparison between treatment groups for the relative change from baseline in markers of bone turnover and PTH.

RESULTS

4. Study populations/accountability of patients

As shown in the figure, 653 patients (of 1484 screened) at 11 study centres in the US and Canada were assigned to one of the 4 strata and randomised into four treatment groups. Five patients did not receive any medication (three in the placebo and one in each of the 0.5 mg and 1.0 mg groups 547 patients completed 2 years of treatment. A total of 101 were prematurely withdrawn with a frequency for each reason equally distributed across treatment groups (27 (17%) in the placebo, 23 (14%) in 0.5 mg, 21 (13%) in the 1.0 mg and 30 (18%) in the 2.5 mg groups). The most frequent reasons were AEs (41%).

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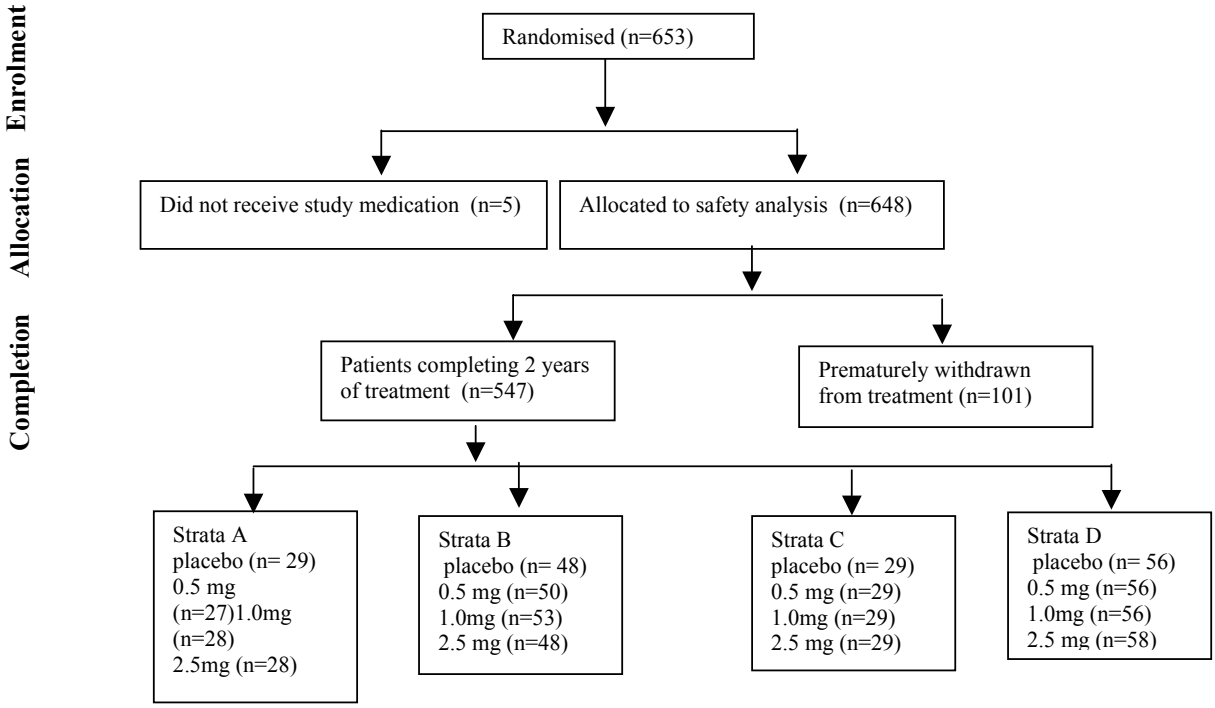
Two analyses sets were performed: ITT (620 patients) and PP. The ITT population included all patients who received study medication and had a evaluable lumbar BMD measurement and at least one follow up visit. The PP group was defined to provide the most controlled efficacy calculation and analyses were considered supplementary. From the randomised population 5 were excluded from the safety analysis, 33 from ITT and 138 from PP analysis. The frequency of patients excluded and thereasons from each analysis population was balanced across the treatment groups



5. *Efficacy results*

Whereas the MF4411 study in osteoporotic patients demonstrated that, treatment with daily ibandronate resulted in BMD increment of 6.5% at the lumbar spine and 3.4% at the total hip after 3 years.In study MF4499 treatment with daily ibandronate resulted in BMD increment of 3.1% at the lumbar spine and 2-3% at the total hip at 2 . These effects on BMD was detected in both early and late postmenopausal women as well as women with normal or low BMD.

Supportive study(ies)

The phase 3 study, MF4491 with BMD as the primary endpoint was performed in support of the indication treatment of post menopausal osteoporosis and with the purpose of investigating whether shortening the post-dose fasting interval from 60 to 30 minutes maintained efficacy, as the applicant considered that reducing this fasting interval may help to improve long-term compliance.
The study was a multi-center, open label, and randomised one on the efficacy and safety of oral ibandronate 2.5 mg daily with either 30 min or 60 min post-dose fast during 12 months in patients with postmenopausal osteoporosis. The objective was to demonstrate comparable efficacy of 2.5 mg oral ibandronate to increase bone mass when the post-dose fast is reduced from 60 min to 30 min. In addition to the treatment with ibandronate, patients received vitamin D and calcium supplements. Two hundred and thirteen subjects were included. Women >= 5 years postmenopausal, age 55-80 years with spine BMD<=-2.5 were included. The primary efficacy parameter was the relative change from baseline to last available value of lumbar BMD within the treatment period. Secondary parameters include relative changes in proximal femur BMD and the rate of bone turnover. Safety parameters were also assessed.
The mean change in lumbar spine BMD from baseline to the end was 3.07% in the 30 min group compared to 4.95% in the 60 min group. As it appears, non-inferiority was not demonstrated as the lower boundary of the 95% CI was < -2%. A non parametric analysis also failed to show non-

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inferiority. This indicates a better clinical benefit with the longer fasting time. This recommendation of administration is included in the SPC.
The mean change for the proximal femur BMD from baseline to the end are similar to those for the lumbar spine BMD.

Discussion on clinical efficacy

Two double-blind, placebo-controlled, randomised studies were performed to determine the most optimal dose to be used in Phase III trials. Based on these studies, 2.5 mg daily seems an appropriate choice for the pivotal studies.
In general, accelerated postmenopausal bone turnover was reduced by ibandronate, with 2.5 mg daily ibandronate significantly suppressing markers of bone resorption and formation compared to placebo in patients with postmenopausal osteoporosis or at risk of developing osteoporosis. The response to treatment of markers of bone turnover was rapid and the effect was sustained throughout the period of treatment.
In conclusion the applicant has submitted data that demonstrates substantial evidence of efficacy for daily administration of 2.5 mg oral ibandronate in reducing the risk of vertebral fractures in patients with postmenopausal osteoporosis. In addition, the applicant has demonstrated that in patients with osteopenia, daily oral administration of 2.5 mg ibandronate significantly increases BMD, supporting the prevention claim.

Clinical safety

Safety parameters are based on data from four studies MF 4411, MF4348, MF 4433, and MF 4499, including 1251 patients treated with the requested regimen of 2.5 mg daily ibandronate, 1245 patients treated with placebo, 1055 treated with the 20 mg intermittent ibandronate regimen and 446 patients treated with other daily regimens of ibandronate. The majority of patients in these four trials (2929/3997 or 73%) were enrolled in the 3-year placebo controlled treatment study MF 4411. This study thus represents the main demonstration of safety in support of the requested 2.5 mg once daily ibandronate regimen in this indication. The main safety parameters assessed in the oral post menopausal osteoporosis studies consisted of adverse events and clinical laboratory tests. In study MF 4411, histomorphometric assessments were performed on fully evaluable bone biopsy cores from selected study centres in Europe and North America in order to investigate the effects of ibandronate on the quality of newly formed bone and bone remodelling.

Patient exposure

In MF 4411 patients in both the daily and intermittent arms were exposed to 78% of the planned total dose. With regard to study MF –4499, patients in each of the ibandronate treatment arms received a mean exposure of approximately 90% of the planned dose.

Adverse events and serious adverse event/deaths and discontinuation due to adverse events

The frequency of adverse events in MF 4411, MF4348, MF 4433, and MF 4499 are listed in the table below. In general the adverse event profile of ibandronate in study MF 4411was representative of that in the other placebo-controlled studies. The most frequent types of adverse event in these studies were those of the respiratory system, body as a whole, digestive system, musculoskeletal system, nervous system, and cardiovascular system. Overall rates for these body systems were generally comparable for placebo and ibandronate groups.

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	MF 4411 PMO Treatment 3 years		MF 4348 PMO Treatment 1 year		MF 4433[a] PMO Treatment 1 year		MF 4499 PMO Prevention 2 years	
	Plac N=975 (%)	Iban 2.5 mg N=977 (%)	Plac N=30 (%)	Iban 2.5 mg N=30 (%)	Plac N=81 (%)	Iban 2.5 mg N=81 (%)	Plac N=159 (%)	Iban 2.5 mg N=163 (%)
Total patients with at least one AE	88.9	90.9	76.7	80.0	91.4	88.9	93.1	97.5
RESPIRATORY SYSTEM	46.3	45.5	23.3	16.7	42.0	33.3	59.1	57.7
Upper respiratory inf.	30.9	31.7	13.3	6.7	28.4	21.0	47.8	45.4
Bronchitis	6.9	10.8	-	10.0	4.9	3.7	6.3	4.9
Sinusitis	6.4	5.8	-	-	3.7	1.2	11.3	11.0
Pneumonia	4.7	6.1	3.3	3.3	3.7	4.9	1.9	4.3
BODY AS A WHOLE	42.6	43.9	20.0	30.0	30.9	34.6	44.0	42.3
Accidental injury	16.4	14.9	6.7	6.7	7.4	4.9	15.1	6.1
Back pain	12.5	14.2	6.7	10.0	7.4	4.9	10.1	9.2
Pain in extremity	6.2	7.6	-	-	4.9	3.7	8.2	9.2
Abdominal pain	5.5	4.6	3.3	-	1.2	-	1.9	4.9
Infection	3.6	4.2	-	3.3	9.9	17.3	2.5	4.9
Asthenia	2.5	3.0	3.3	3.3	-	1.2	1.3	6.7
Allergic Reaction	1.6	1.9	-	-	1.2	1.2	3.1	6.1
Flu syndrome	1.3	1.3	-	-	-	-	7.5	4.3
DIGESTIVE SYSTEM	42.3	39.9	40.0	20.0	35.8	40.7	51.6	52.1
Dyspepsia	9.1	11.4	3.3	-	-	1.2	13.8	15.3
Diarrhea	5.3	7.0	6.7	6.7	1.2	11.1	3.1	6.1
Constipation	6.3	4.9	3.3	10.0	-	6.2	6.9	8.0
Gastroenteritis	5.5	5.5	3.3	-	2.5	3.7	6.3	4.9
Flatulence	2.9	2.6	6.7	3.3	1.2	1.2	3.8	4.3
Tooth disorder	2.4	2.9	3.3	-	2.5	-	1.9	7.4
Sore Throat	1.6	1.5	-	-	-	2.5	5.0	3.1
Nausea	6.3	4.2	3.3	-	11.1	3.7	3.1	3.7
Gastrointestinal Disorder	0.6	0.8	3.3	-	6.2	_-	2.5	-
MUSCULOSKELETAL SYSTEM	39.2	39.8	16.7	10.0	23.5	23.5	37.7	41.7
Arthralgia	13.5	13.5	6.7	10.0	7.4	11.1	13.8	12.9
Osteoporosis fracture	11.2	9.8	-	-	4.9	4.9	5.0	4.9
Arthrosis	6.7	5.3	-	-	1.2	1.2	2.5	1.2
Myalgia	5.1	5.0	-	-	3.7	6.2	5.0	9.8
Joint disorder	2.7	3.0	-	-	1.2	1.2	6.9	7.4
Arthritis	2.4	3.3	-	-	-	-	5.0	3.1
Tenosynovitis	3.3	2.7	-	-	-	1.2	1.9	5.5
NERVOUS SYSTEM	21.0	23.5	16.7	16.7	19.8	23.5	32.1	30.1
Headache	5.0	5.9	3.3	-	7.4	13.6	10.7	9.8
CARDIOVASCULAR SYSTEM	20.4	22.6	6.7	20.0	9.9	9.9	13.8	14.7
Hypertension	7.8	7.7	3.3	10.0	4.9	4.9	6.9	4.9
Periph. vascular dis.	0.1	0.8	-	6.7	-	-	-	1.2
UROGENITAL SYSTEM	15.9	19.1	13.3	23.3	12.3	7.4	19.5	17.2
Cystitis	6.4	6.6	6.7	20.0	9.9	7.4	4.4	2.5
Urinary tract infection	4.0	5.6	-	-	-	-	5.7	4.9
METABOLIC AND NUTRITIONAL DISORDERS	11.3	13.2	6.7	6.7	1.2	1.2	14.5	14.7
Hypercholesterolemia	3.9	4.4	-	-	-	-	6.3	7.4
SPECIAL SENSES	15.0	13.5	-	-	4.9	7.4	13.8	11.0
Cataract	5.7	4.9	-	-	1.2	1.2	3.8	3.1

[a] Data from first year of study, (second year was not placebo-controlled

In study MF 4411, the proportion of patients that experienced an AE with a possible or probable relationship to trial treatment was slightly higher in the 2.5 mg daily ibandronate group (19.8%) than

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in the placebo group (17.9%). Treatment-related adverse events reported at a frequency of greater than 1%, more frequently associated with administration of ibandronate 2.5 mg once daily than with placebo, were dyspepsia, diarrhoea and myalgia. These were, in most cases, not serious in nature and did not lead to premature withdrawal from treatment. In the prevention study MF 4499, the nature and frequency of related adverse events were comparable for placebo (11.9%) and ibandronate 2.5 mg daily (9.2%).

The most frequent types of SAEs in the four studies were those of the cardiovascular system, musculoskeletal system, and the digestive system. The overall proportion of patients reporting SAEs was higher in all groups in study MF 4411 compared with the other three studies, which might reflect the longer duration of this study and differences in the patient population compared with prevention study MF 4499.
Most SAEs (> 99%) were assessed as unrelated to trial treatment for study MF 4411. In study MF 4499, all SAEs were assessed as unrelated to trial treatment.
A total of 14 deaths occurred in the 2.5 mg daily ibandronate treatment groups, and 13 in the placebo groups. All deaths were assessed as unrelated to trial treatment.

In conclusion, there were no differences between the placebo and active treatment groups in the frequency or nature of SAEs assessed as possibly related to treatment. Furthermore, the nature and frequency of adverse events leading to death was similar for the ibandronate and placebo groups in the four placebo-controlled oral studies using ibandronate 2.5 mg daily.

Laboratory findings

There were no differences in laboratory safety test results between placebo treated patients and those receiving ibandronate 2.5 mg daily, with the exception of alkaline phosphatase, which was reduced in ibandronate treated patients, consistent with the known pharmacological action of the drug. In particular, there was no increase in the ibandronate 2.5 mg daily groups of abnormalities indicative of hepatic or renal dysfunction, hypocalcaemia or hypophosphataemia.

Histomorphometric analyses of transiliac bone biopsy cores support the bone safety after 3 years of oral administration of ibandronate

Safety in special populations

A subgroup analysis of adverse events by baseline creatinine clearance was performed for study MF 4411. In the majority of patients (approximately 94%), baseline creatinine clearance was in the range 30-90 mL/min, with equal distribution between the subgroups 30-60 mL/min and >60-90 mL/min. There was no consistent effect of renal function, i.e. patients with creatinine clearance of 30-60 mL/min did not have a higher rate of AEs than those in the range >60-90 mL/min.
A subgroup analysis of adverse events in patients with a history of gastrointestinal tract disorders was also performed for study MF 4411.Approximately 30% of patients had a history of the selected GI disorders. Oral ibandronate did not increase the overall risk of digestive system AEs in patients with a relevant medical history of gastrointestinal disorders. Patients with a relevant history of gastrointestinal disorders showed higher incidence rates of digestive system AEs in all 3 treatment groups compared to patients without such a history. The magnitude of difference between subgroups was similar across groups.
A subgroup analysis of adverse events by NSAID use was performed for study MF 4411. In patients receiving concomitant NSAIDs, in all groups there was a higher rate of episodic or acute AEs involving pain or discomfort requiring symptomatic relief, and for which it is likely that the NSAID was the treatment, not the cause. Considering the known side effects of NSAID this analysis seems relevant. Although there were no difference in the frequency of AEs at the whole body level between patients receiving both NSAID and ibandronate and patients receiving placebo and ibandronate it seems that the former group exhibit a higher frequency of dyspepsia and diarrhoea indicating that the GI toxic effects of NSAID and ibandronate could be additive.The SPC includes an appropriate warning about this.

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Discussion on clinical safety

Overall the data indicate that treatment with oral ibandronate at the dose of 2.5 mg is safe with an acceptable tolerability in the treatment and prevention of postmenopausal osteoporosis. There were no notable differences in the safety profile between the placebo and ibandronate 2.5 mg group in terms of adverse events, deaths, serious adverse events, and adverse events leading to premature withdrawal from treatment. Neither were there any differences between active treatments and placebo with respect to any kind of AE in subgroups of patients stratified on renal function or among patients with or without a history of GI disorders. The overall rate of treatment related adverse events was higher in the ibandronate group compared with the placebo group in study MF 4411 as a result of the higher rates for dyspepsia, diarrhoea, rash and myalgia in the treatment group. However, these events were not serious in nature and did not lead to premature withdrawal from treatment. Furthermore patients receiving both NSAID and ibandronate have a higher frequency of dyspepsia and diarrhoea indicating that the GI toxicity of these compounds could be additive, which is a point to be emphasised. Administration of ibandronate was not associated with serious or treatment-limiting digestive system AEs, adverse renal or hepatic effects, defects of bone mineralisation, or hypocalcaemia.

5. Overall conclusions and benefit/risk assessment

Quality

The important quality characteristics of ibandronic acid are well defined and controlled, and the tabletted product is formulated, manufactured and controlled in a way that is satisfactory. The specifications and batch analytical results indicate a consistent product with uniform clinical performance from batch to batch. There are no outstanding quality issues, which have a negative impact on the benefit/risk balance.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that ibandronate inhibits or reverses the decrease in both bone mass and strength. Safety pharmacology studies revealed no adverse effects on the central nervous, cardiovascular, respiratory or gastrointestinal system at exposures well above those anticipated in humans

From the pharmacokinetic point of view, mice, rats and dogs were the most relevant species for preclinical efficacy and safety studies. The studies submitted are generally fulfilling and give an adequate overview.

Overall, the toxicology programme showed the kidney, and to a lesser extent liver, lung and gastrointestinal tract as primary target organs. According to the studies performed it can be concluded that there is no special concern for the human clinical use.

All this information has been included in the SPC.

Efficacy

Two dose response studies determined that 2.5 mg daily is the optimal choice for the pivotal studies.

Two main trials were performed to support the daily oral administration of 2.5 mg of ibandronate for the treatment and prevention of osteoporosis in postmenopausal women. In addition a supportive phase III study for the treatment of osteoporosis in postmenopausal women with BMD as primary endpoint was performed

The data obtained demonstrates that the daily administration of 2.5 mg of ibandronate reduces the risk of vertebral fractures in patients with postmenopausal osteoporosis, and , significantly increases BMD in patients with osteopenia, supporting the prevention claim

Safety

Data submitted with regard to the safety profile of ibandronate reveals that the treatment with oral ibandronate at the dose of 2.5 mg is safe with an acceptable tolerability in the treatment and prevention of postmenopausal osteoporosis. There were no notable differences in the safety profile between the placebo and ibandronate 2.5 mg group in terms of adverse events, deaths, serious adverse events, and adverse events leading to premature withdrawal from treatment.

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Benefit/risk assessment

The studies submitted demonstrate the efficacy for daily administration of 2.5 mg of ibandronate for treatment and prevention of osteoporosis in postmenopausal women. In addition, the data submitted indicates that oral treatment at the indicated dose is safe and has an acceptable margin of tolerability. Taking this into account, it can be concluded that the benefit/risk for this product is positive.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Bonviva was favourable in the treatment and prevention of osteoporosis in postmenopausal women was favourable and therefore recommended the granting of the marketing authorisation.

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