European Medicines Agency

EMEA/104761/2007

Bonviva

International Nonproprietary Name:

Ibandronic acid

Following the procedure

EMEA/H/C/501/X/03

1 SCIENTIFIC DISCUSSION

1.1 Introduction and rationale

The applicant Roche Registration Limited submitted on 28 April 2005 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Bonviva 3mg/3ml solution for injection as a 3-monthly dosing regimen of ibandronate only for the indication of *"treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures"* under Annex II, point 2 iii, iv, v to Commission Regulation (EC) No 1085/2003.

The rationale for this being the inconvenience associated with dosing of oral bisphosphonates since, particularly for patients with existing GI tract disease or intolerance to oral bisphosphonates, it could be convenient to administer drug parenterally.

Osteoporosis as a consequence of the menopause is characterized by decreased bone mass and strength resulting from a compromise of bone density and/or bone architecture, leading to increased fragility and fracture risk. The morphologic characteristics of this process are a reduction in the number of trabeculae, thinning of the trabeculae and loss of trabecular connectivity. The main reason for this process is the oestrogen deficiency after menopause, which in all mammals increases bone turnover and results in an imbalance between bone resorption and bone formation. An imbalance favouring bone resorption over formation leads to a decrease in bone mass and microarchitecture (connectivity) of bone tissue thereby reducing bone strength, which will consequently increase the risk of fracture.

Vertebral fractures are the most common osteoporotic fractures and are associated with increased morbidity and deterioration of the quality of life of the patients. Many vertebral fractures are occult and asymptomatic, however they are associated with an increased mortality. Hip fractures, which usually occur in older women, are associated with a high mortality and long-term disability. The mortality rate is 20% higher on average within 1 year of hip fracture.

The ultimate goal of pharmacological treatment of women with postmenopausal osteoporosis is to reduce the risk of fractures by increasing the bone mass of normal quality. There are several agents currently available for the treatment and/or prevention of post-menopausal osteoporosis including calcitonin, bisphosphonates, 17-beta-estradiol, selective oestrogen-receptor modulators, PTH, strontium ranelate and fluoride.

Bisphosphonates are an important class of drugs used as inhibitors of bone resorption in the treatment of bone diseases. Several bisphosphonates are established as effective treatments in clinical disorders such as Paget's disease of bone, myeloma, and bone metastases. Up to now alendronate, risedronate and ibandronate have become established as effective agents for the prevention and treatment of osteoporosis. Their basis for approval has been the demonstration of anti-fracture efficacy over a 3-4 years treatment period. Anti-fracture efficacy of alendronate and risedronate has been shown for vertebral and hip fractures and that of ibandronate only for vertebral fractures.

In February 2004, the European Commission approved a 2.5 mg daily oral tablet formulation of ibandronate for the prevention and treatment of postmenopausal osteoporosis, and in September 2005 the 150 mg once monthly oral tablet only for indication of the treatment of the osteoporosis.

1.2 The development programme

This submission is primarily based on a single pivotal, Phase 3, non-inferiority trial comparing the efficacy and safety of intermittent i.v. ibandronate to that of daily oral ibandronate given at the approved dose of 2.5 mg (BM16550 – DIVA study).

No new pre-clinical pharmacodynamic and pharmacokinetic studies have been performed in addition to those included in the previous submission for ibandronate 2.5 mg film-coated tablets and 150 mg film-coated tablets. The Applicant's argument for not performing additional pharmacological studies in animals was, that in the previously performed studies in oestrogen depleted animal models the intermittent

treatment was equally effective when compared to daily treatment provided the total cumulative dose was the same.

In support of the clinical efficacy and safety of the 3-monthly i.v. regimen a single pivotal study in 1395 women with postmenopausal osteoporosis was performed, with the change of lumbar BMD from baseline as the primary efficacy endpoint (BM16550[1], DIVA Study). An efficacy analysis is available from the required two years of treatment.

Quality aspects

Introduction

Composition
Bonviva is presented as 3 mg / 3 ml Solution for Injection in a pre-filled syringe (PFS) containing ibandronic acid as the active substance.
Other ingredients include Sodium Chloride, Glacial Acetic Acid, Sodium Acetate and Water for injections.

The syringe is made of colourless glass (type I), closed with a plunger stopper, which serves as piston, and sealed with a tip cap, both made from fluoro-resin laminated butyl rubber. The product contact materials are the plunger stopper, glass barrel and tip cap. These primary packaging components, along with the drug product solution, are terminally sterilised.

The plunger rod is made of food-grade plastic and is not in contact with the injection solution. The commercial package contains the pre-filled syringe(s), with injection needle(s).

Active Substance
The active ingredient has recently been assessed within the procedure EMEA/H/C/501 concerning Bonviva 2.5 mg film-coated tablets. It can best be described as monohydrate with a theoretical water content of 5.01%. It is freely soluble in water and practically insoluble in organic solvents. The information on the drug substance presented earlier is considered acceptable.

Medicinal Product

Pharmaceutical Development

In general the pharmaceutical development is in accordance with the EU guidelines on Pharmaceutical development and is adequately described.

The aim of the development studies was to produce a stable i.v. formulation by a terminal sterilisation process. Parenteral formulations providing the same concentration on a mg/ml basis have been approved in the EU under the trade name Bondronat respectively (1 mg / 1 ml, 2 mg / 2 ml and 6 mg / 6 ml). They are manufactured by virtually the same method and are packed in vials, which have the same glass quality as the syringes. Therefore, most of the pharmaceutical development data are derived from these previous applications.

Different pH values were tested for stability and the one that demonstrated to assure a more stable formulation regarding pH shift and degradation during the sterilisation process and during stability studies was retained. Particle size distribution and polymorphism (both polymorphic forms provide comparable solubility) are not relevant for the preparation of injection solutions. The stability studies have proven that the active ingredient is a very stable compound.

Acetic acid and sodium acetate trihydrate are used as buffer system to maintain the pH at the desired levels and sodium chloride is added to obtain an isotonic solution. All excipients are of Eur Ph quality.

[1] Sherry CL, Kinberg J, Ward P. Randomized, double-blind, parallel groups, multicenter study to compare the efficacy and safety of two IV ibandronate dose regimens (2 m q 2 months and 3 mg q 3 mo) with 2.5 mg daily oral ibandronate in postmenopausal osteoporosis: Year 1 Results (BM16550-DIVA). Research Report 1016092. November 5, 2004.

Manufacture of the Product

The manufacturing process involves conventional operations such as dissolving the active ingredient and excipients in water for injections, filtering and filling into the syringes. Tip caps and plunger stoppers are placed automatically and the syringes are terminally sterilised.

All critical process parameters have been identified and are controlled by appropriate in process controls. The manufacturing process has been validated in accordance with the CHMP guidelines on Manufacture of the finished dosage form and Process validation.
Product Specification

The following specifications are set: identity testing, Assay (HPLC), Purity (TLC). All other tests (appearance, clarity, color, pH, particulate matter, extractable volume, bacterial endotoxins and sterility) are performed according to Ph. Eur. The description and validation of the analytical methods are acceptable.

Stability of the Product

In general the formulation is very stable. Studies have been carried out according to relevant EU/ICH stability guidelines. As packaging material during stability studies pre-filled syringes are used (as applied). Three production batches have been stored for up to 12 months at ICH conditions. No changes are observed in the investigated parameters. Supportive studies have been performed on seven batches for up to 5 years. As the data indicates the medicinal product is very stable an extrapolation of the shelf-life to 2 years with no specific storage conditions is acceptable. Photostability studies revealed that the medicinal product is not sensitive to light.
Results have been generated by validated, stability indicating methods and show satisfactory stability. These results support the shelf life of 2 years without any specific precautions for storage. The proposed shelf-life and storage conditions are reflected in the proposed SPC.

Discussion on chemical, pharmaceutical and biological aspects.

This is a simple i.v. formulation of a soluble substance in a pre-filled syringe. The active substance is very stable well characterised and documented. The excipients are commonly used and comply with Ph. Eur. requirements. The packaging material is well documented. The manufacturing process of the finished product is a well-validated process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

Non-clinical aspects

No new non-clinical data has been submitted for this application. Summary and overview of the studies previously submitted in the applications for 2.5 and 150 mg film-coated tablets are provided in the application.

Pharmacology

The previously submitted non-clinical primary pharmacology data (with daily and intermittently applied ibandronate) demonstrated that the intermittently and daily administered ibandronate were similarly effective in the treatment studies in the OVX rats and OHX dogs, if the total (cumulative) applied dose of ibandronate was about the same. These data suggest that the total (cumulative) dose of ibandronate administered is more important for efficacy than the treatment schedule itself.

The duration of action of intermittently applied ibandronate appears to depend on the combination of dose, dosing frequency and underlying bone turnover rate, but it is currently not known whether the dosing interval depends on the bone remodeling time or on the real drug exposure.

The safety pharmacology program previously submitted supports an intermittent dosing regimen, since a 3-monthly dosing regimen is regarded as being a single dose rather than repeated doses.

Pharmacokinetics

Pharmacokinetic studies, performed in the rat, dog and monkey, have been submitted in the MAA for the 2.5 mg film-coated tablets. The non-clinical pharmacokinetic studies with ibandronate showed the known characteristics of aminobisphosphonates: A very low absorption rate from the GI tract, a high affinity to bone (approximately 40-50% of the dose is found in bone with half-life's of 300-500 days, and <3% in all non-calcified tissues), no biotransformation of the drug and a predominantly renal excretion of the unmetabolised drug.

It was shown in OVX rats that the concentration of ibandronate in vertebrae (L1) and tibia was dose-dependent and linear. Importantly, subcutaneous ibandronate dosing once daily or cyclical intermittent every 25 days resulted in similar concentrations of ibandronate in vertebrae and tibia, if the applied total (cumulative) dose was about the same. These findings provide the basis for the similar primary pharmaco-dynamic effects observed with daily or intermittently applied ibandronate in rats.

Toxicology

The previously submitted toxicology program characterized extensively the toxicity of ibandronate and supported the daily administration of 2.5 mg ibandronic acid for the treatment of postmenopausal women.

In support of the monthly oral regimen with 150 mg ibandronic acid for the treatment of postmenopausal osteoporosis three new single dose toxicity studies and two new repeat-dose toxicity studies (with ibandronate administered by the intravenous route) were submitted.

Nephrotoxicity at daily i.v. administration of ibandronate

The 2-week rat i.v. toxicity study with a daily i.v. administration of 1 or 3 mg/kg ibandronate showed the known toxicology profile of ibandronate as well as the pharmacological effects of ibandronate. It confirmed that the kidney is the primary and the liver the secondary target of ibandronate toxicity. The severity of renal damage (serum creatinine and urea, urinalysis, creatinine clearance, histopathological changes, such as tubular basophilia, tubular dilatation and cast formation, and acute tubular necrosis) was dependent on both the dose and the peak plasma concentration of ibandronate. The severity of findings which are directly related to the kidney damage (serum creatinine and urea, urinary ratios, histopathological findings) were influenced by the speed of intravenous administration. This was also true for the liver enzymes and the secondary effects on body weight and food consumption. In contrast, peak plasma concentration has no impact on the severity of findings that are related to the pharmacological activity of ibandronate.
The nephrotoxicity observed in the 2-week rat i.v. toxicity study (1-3 mg/kg/day ibandronate i.v.) is in agreement with the previous 4 week rat toxicity study, where the highest dose of ibandronate (1 mg/kg/day i.v.) caused a moderate renal tubulonephrosis with proteinuria and a decrease in serum albumin, and with the previous 4 week toxicity study in dogs, where ibandronate at 0.3 and 0.9 mg/kg/day increased kidney weights and caused a dose dependent focal tubulonephrosis and necroses.

Nephrotoxicity at intermittent i.v. administration of ibandronate (single and repeat-dose i.v. application).

NOELs or NOAELs in the single dose studies and the 6-month intermittent repeat-dose study were not determined. The aim was to determine the minimum nephrotoxic dose/effect in rats, particularly after repeated dosing. 1mg/kg ibandronate i.v. was found to be the lowest observed effect level (LOEL) in rats inducing nephrotoxicity, which was subclinical in severity. Histopathological examination revealed a degeneration/necrosis of proximal convoluted tubular (PCT) epithelial cells, which occurred at similar incidence and severity in rats treated once or repeatedly. These effects were not related to the ibandronate plasma concentrations. 'Subclinical' was defined as nephrotoxic histopathological changes without any corresponding findings in haematology, clinical biochemistry or urine analysis parameters.
Hypertrophy/hyperplasia of distal tubules and collecting ducts were only observed after repeat-dose with ibandronate, but not after a single dose.

The nephrotoxicity of the new 6-month rat i.v. toxicity study in rats with 3-weekly intermittently applied ibandronate was similar as in the previously performed 6-month i.v. toxicity study in rats with weekly

applied ibandronate (ibandronate at 0.9 mg/kg/wk caused increased kidney weights and a dose-related epithelial hypertrophy/hyperplasia) and in the second 6-month i.v. toxicity study in rats with twice monthly applied ibandronate (0.3 mg/kg/every 2 weeks iv.) or (0.15 mg/kg/week i.v.); both studies caused no renal toxicity, but NOAELs mainly due to pharmacological effects in both studies were not determined. In the 6-month study in dogs with weekly applied ibandronate i.v. (up to 2.7 mg/kg/week i.v.) the highest dose caused a mild to severe dose-related kidney damage, associated with a mild to severe increase in BUN.

Safety margins

The exposure in animal studies with twice monthly intermittent i.v. treatment over 6 month in the rat and dog was used for the comparison with the exposure in humans. The animal dose of reference was 0.3 mg/kg which represents the renal NOAEL for twice monthly intermittent i.v. treatment.
C_{max} and AUC of human exposure at 3 mg ibandronic acid i.v. are interpolated values (C_{max}: 582 ng/ml; AUC: 808.5 ng.h/ml) and compared to exposure data in rats (C_{max}: 1113 ng/ml, AUC: 1069 ng/h/ml, 0.3 mg/kg/i.v. 2-monthly) and dogs (C_{max}: 1187 ng/ml, AUC: 1352 ng/h/ml, 0.3 mg/kg/i.v. 2-monthly). The safety margins of 1.3 (AUC) and 1.9 (C_{max}) in rats and 1.7 (AUC) and 2.0 (C_{max}) in dogs are small.
Safety margins calculated with the renal LOEL in rats (1 mg/kg/3 wk; 6-month) revealed an about 3-fold greater safety margin of 4.1 (AUC = 3406 ng.h/ml) than calculated using the renal NOAEL in the twice - monthly intermittent study.

Liver toxicity at intermittent ibandronate administration

In contrast to the daily i.v. ibandronate administration of 1and 3 mg/kg/day for 2 weeks no increases in liver enzymes were observed, when ibandronate was given 3-weekly at 1 or 3 mg/kg over 6 months. This observation agrees with the results of the pivotal clinical study BM16549. These findings are also in agreement with previous findings in rats and dogs.
Rat: In the 4-weeks rat i.v. study ibandronate administered daily had no effect on the liver in doses up to 0.9 mg/kg/day and both 6-months studies with intermittently administered ibandronate showed no effects on liver enzymes and histopathology (except increased hematopoiesis).
Dog: In the 4-week dog i.v. study 0.3 and 1 mg/kg/day increased liver enzymes (ASAT, ALAT; females) and liver weights; 1 mg/kg/day caused in two animals severe disseminated fatty liver degeneration, icterus, centrilubular necrosis (F) and focal liver cell necrosis (M).
In the 6-month dog study with weekly i.v. applied ibandronate, the highest dose of 2.7 mg/kg/week i.v. caused only sporadically and transient increases in ASAT (1 male) or ALAT (one female).

Gastrointestinal tract tolerance at intermittent ibandronate administration

The potential for an increased risk of gastrointestinal tract intolerance was not further evaluated in non-clinical studies since - as stated by the Applicant - it was closely monitored in clinical trails. This reasoning is not acceptable. However, previous oral studies in rats and dogs with daily oral doses, exceeding the intended monthly human dose, are available. Gastrointestinal changes in rats and dogs were only observed in the toxic lethal dose range.
Rat: In the rat, ibandronate at doses up to 10 mg/kg/day p.o. given for 12 months was well tolerated. In the 6-month p.o. study in rats with restricted feeding the animals of the high lethal toxic dose range (34.3 mg/kg/day) showed macroscopically an irregular surface of the stomach and haemorrhage of the stomach, and microscopically a hydropic degeneration and inflammatory infiltration in the stomach muscular wall.
Dog: In the dog, oral doses up to 9 mg/kg/day over 4 weeks and 5 mg/kg/day up to 12 months had no effect on the gastrointestinal tract. In the 6-month dog study the toxic high dose (13 mg/kg/day) caused an ulcerative esophagitis. Doses in the toxic-lethal range for dogs induced irritation of the gastrointestinal tract (13 mg/kg/day in a 6-month study; 10 mg/kg/day in a 12-month study).

Discussion Non-clinical aspects

The available non-clinical pharmacology data with daily or intermittently administered ibandronate (previously submitted in support of the MAA for ibandronate 2.5 mg film-coated tablets and 150 mg film-coated tablets) also support the intended intravenous intermittent dosing in the treatment of postmenopausal osteoporosis with 3 mg ibandronic acid i.v. every three months.

No new non-clinical pharmacokinetic studies have been performed regarding absorption, distribution, metabolism and excretion in addition to those included in previous submissions.
It is agreed that new non-clinical pharmacokinetic studies are not required.

A comparison of subcutaneous (s.c.) versus i.v. administration resulted in similar bioavailability and mean concentrations of ibandronate in bone. It is agreed that the s.c. route is an appropriate surrogate for intravenous dosing when assessing the pharmacodynamic effects of ibandronate.

Toxicity with the intermittently applied ibandronate depends on the dose and duration of dose-free intervals, similarly as described for the primary pharmacodynamic effects.

The evaluation of toxicity of ibandronate in toxicity studies supporting the 3-monthly administration of ibandronate in humans has been restricted to the evaluation of nephrotoxicity (the primary target of ibandronate toxicity or toxicity of other nitrogen containing bisphosphonates). The previous assumption that safety margins can be evaluated by a primary assessment of renal safety, which is apparently supported from the available toxicity data, has been already accepted for the MAA of the 2.5 mg film-coated tablets and 150 mg film-coated tablets.

Safety margins from animal/human exposure data regarding nephrotoxicity ranged from 1.3 to 1.7, but they are most probably underestimated since the animal renal NOAEL of 0.3 mg/kg is based on a 2-week dosing interval while humans are dosed at 3-monthly interval, equivalent to a single dose regimen. Regarding liver toxicity there were no observable toxic effects on the liver with 1 or 3 mg/kg applied 3 weekly over 6 months. Gastrointestinal tract toxicity in rats and dogs with orally applied daily ibandronate was only observed in the toxic lethal dose range.

It is agreed with the Applicant, that other safety aspects (including potential of genotoxicity, carcinogenicity, local tolerance, skin irritation and sensitization, the risk of QT/QTc interval prolongation and all pharmacodynamic related effects) are considered to remain unaffected by the change of the treatment regimen from daily to 3-monthly intervals. New reproduction and developmental toxicity studies were not performed, which is no major issue since ibandronate is exclusively applied to postmenopausal women.
It is agreed with the Applicant that based upon the non-clinical safety studies performed, the risk of relevant toxic effects in humans can be considered to be low under the proposed conditions of clinical use.
A new ecotoxicity/environmental risk assessment was carried out according to OECD guidelines. It was concluded that no exposure levels of concern to the environment are to be expected.

Toxicology studies with an i.v. formulation of ibandronate were a part of both the 2.5 and 150 mg film-coated tablet applications both as single-dose and repeat-dose studies. The results support the dosing regimen applied in this submission.

Clinical aspects

Clinical Pharmacology

No new clinical pharmacology studies have been performed to support this application. A comprehensive PK/PD evaluation of ibandronate has already been performed as part of the MAA for Bonviva 2.5 mg tablets as well as 150 mg once monthly. Furthermore, the MAA for Bonviva 2.5 mg tablets also contained data generated from studies performed on the intravenous formulation, although approval of the intravenous formulation and intravenous dosing regimen was not sought at that time. In addition, information from a phase II safety and efficacy study of intravenously administered ibandronate in breast cancer patients with metastatic bone disease, previously not included in applications to support the postmenopausal osteoporosis indication, is included in this MAA.

Pharmacokinetics

Generally, the studies show linear dose proportionality. As the pharmacokinetics of intravenous ibandronate is linear over the dose range 0.125 mg - 6.0 mg the exposure following an intermediate dose of

3 mg every 3 month was estimated by interpolation. Extrapolation of exposure data (C_{max} and AUC) was performed from study MF 9853 after a 2 mg injection (30 seconds) to Japanese osteopenic postmenopausal women. The age of the study population were similar to that in the pivotal phase III clinical study BM 16550.

The predicted peak plasma concentrations and area under the curve in women with postmenopausal osteoporosis after administration of a 3 mg injection (30 seconds) of ibandronate are 582 ± 108 ng/ml and 808.5 ± 143 h•ng/ml respectively.

The decline of serum ibandronate concentrations is multi-exponential; the terminal half-lives showed a considerable variation.

Total clearance is low and between 89 to 138 ml/min after a single i.v. injection; the renal clearance after a single i.v. injection was 64% to 74% of the total clearance. As renal clearance of ibandronate is directly correlated with creatinine clearance and thus inversely correlated with age, and renal clearance accounts for a substantial component of total clearance then it follows that diminishing renal function largely explains age as a covariate for total clearance.

- **Distribution**

Ibandronate was about 87% (range 84-93%) protein bound (determined *in vitro* by ultrafiltration at 5 ng/ml) and about 85% (range 83-87%) protein bound (determined by equilibrium dialysis at 1000 ng/ml).
Systemically available ibandronate (after i.v., s.c. or oral application) is cleared mainly by uptake into bone and excretion via the renal route. After i.v. injection of single doses of ibandronate (≤ 1 mg) in male volunteers and female postmenopausal volunteers the renal clearance was 60% to 74% of the total clearance. On the other hand after i.v. infusion of 2-6 mg ibandronate the percentage of renal clearance was up to 55% of the total clearance. About 40-50% of the orally absorbed ibandronate is distributed into bones and the reminder is eliminated unchanged by the kidney.

- **Elimination**

Preclinical studies in rats and dogs, studies with human liver preparations, and a mass balance study using radiolabeled oral and intravenous doses of ibandronate in human subjects have demonstrated that ibandronate is not metabolised, as also shown in rats and dogs, and is eliminated as unchanged drug in the urine. The plasma profiles of ibandronate are multiphasic and terminal concentrations are low, sustained, and variable. Early plasma levels fall quite quickly, reaching 10% of peak values within 3 hours after intravenous administration. This is followed by a slower elimination phase as ibandronate redistributes back into the blood from bone. The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but are generally in the range of 10 -72 hours. The true terminal half-life is likely to be substantially longer, in common with other bisphosphonates.

Total clearance of ibandronate is low with average values in the range 84 -160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal females) accounts for 50 - 60% of total clearance and is directly related to creatinine clearance. Ibandronate renal clearance is therefore dependent upon renal function. The difference between the apparent total and renal clearances is considered to reflect the uptake in bone.

Pharmacokinetics in special populations

- **Impaired renal function**

Patients with severe renal impairment (creatinine clearance < 30 ml/min) have a 2-3-fold higher exposure to ibandronate compared to subjects with normal kidney function. The decrease in renal clearance was linearly related to the decrease in creatinine clearance. After a single dose of 0.5 mg ibandronate i.v., the total and renal clearance decreased by 66% and 67 % in patients with CL_{CR} <30ml/min. After oral application of 10 mg ibandronate over 21 days the renal clearance of ibandronate was reduced by 77%.
Clinical data in patients with renal impairment at the recommended dosage for the treatment of metastatic breast cancer (6 mg ibandronate i.v. and 50 mg ibandronate p.o, 3-4 weekly) or postmenopausal osteoporosis (150 mg/month p.o., 3 mg/3 month i.v.) are not available. A dose reduction in patients with severe renal impairment is considered as necessary.

In patients with end-stage renal failure it was shown that ibandronate is readily dialyzable (36.4% of the administered i.v. dose within 4 h of dialysis).

- **Impaired hepatic function**

In vitro and *in vivo* data indicate that ibandronate is not metabolised and is excreted in urine. Therefore, the pharmacokinetics of ibandronate is unlikely to be affected in patients with liver disease and dose adjustment is not necessary.

- **Elderly**

Since ibandronate is not known to be metabolised, the only difference in ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function. No dose adjustment is necessary for elderly patients with normal aged-adjusted renal function.

- **Gender**

The age of women treated with ibandronate for postmenopausal osteoporosis may be variable. Since the excretion of ibandronate depends in the renal function, a deterioration of renal function with age may influence the ibandronate disposition.

There appears to be no difference in male/female exposure, judged from pharmacokinetic data in healthy volunteers in Phase I studies.

- **Race**

In male volunteers there was a statistically significant lower central volume of distribution in Japanese subjects compared to Caucasians**.** These inter-ethnic differences are unlikely to be of clinical relevance.

- **Interactions**

No new studies have been performed in addition to those included in the MAA for Bonviva 2.5mg tablets. From a more theoretical point the likelihood for drug-drug interactions with ibandronate is limited since ibandronate is not metabolized through cytochrome P450 or any other drug-metabolising enzymes nor is ibandronate excreted through the acidic or basic transport systems of the kidney in rats.

Pharmacodynamics

As in their MAA for Bonviva 150 mg tablets for once monthly administration the applicant has used a well-described PK/PD-model for aid in dose selection as well as for investigating the potential impact of non-compliance on the efficacy of i.v. therapy.

The primary clinical pharmacodynamic effects of ibandronate on bone were investigated previously at single or repeated doses of oral ibandronate in male healthy volunteers. The ibandronate doses used were 4-20-fold higher than the intended clinical dose for the treatment of postmenopausal osteoporosis with 2.5 mg/day. The pharmacodynamic effects on bone resorption/formation were demonstrated by changes in the pattern of surrogate markers of bone resorption/formation in urine or serum, and the associated transient changes in calcium, PTH and 1,25-Dihydroxyvitamin D_3 serum levels. The magnitude of the observed effects varied and was dependent on the applied ibandronate dose(s) and/or the duration of treatment. The transient increase in PTH and 1,25-Dihydroxy vitamin D_3 serum levels are most probably secondary due to alterations in serum calcium. A large intra- and inter-subject variability in the determination of bone markers was observed.

The effects on markers of bone resorption were observed earlier and were more pronounced than the effects on markers on bone formation. The inhibition of bone turnover by intravenously applied ibandronate has been investigated in the i.v. study as well as in the pivotal i.v. study BM16550.

Additionally secondary pharmacodynamic studies are not required.

Discussion Clinical Pharmacology

Overall, the PK of ibandronate for intravenous administration has been adequately described from studies provided in previous MAAs. Although the dose intended for marketing (3 mg/3 ml) has not been used in any of the PK-studies this is fully acceptable since this formulation does not deviate substantially in its

composition compared to the already studied formulations and knowledge of PK allows extrapolation with regard to exposure and other relevant PK-parameters.

The PD of ibandronate for intravenous administration is well characterised based on data previously submitted by the applicant. The fact that the dose intended for marketing has not been investigated in PD studies or clinical dose-finding studies is fully acceptable. The use of a well described PK/PD-model for reassurance of selected dose is appreciated, as is its use for investigating possible clinical consequences of non-compliance.

Clinical efficacy

- **Introduction**

This submission is primarily based on a single pivotal, Phase III, non-inferiority trial comparing the efficacy and safety of 2 different intermittent i.v. treatment regimens of ibandronate to that of daily oral ibandronate given at the approved dose of 2.5 mg (BM16550 – DIVA study). At the time of submission only 1 year data were available, but 2-year data has been provided during the procedure.

The i.v. dose regimens used in BM16550 were selected based on an assessment of the BMD improvements noted from previous i.v. studies compared to the BMD improvements noted in the successful fracture study MF4411. This assessment predicted that an annual dose of 12 mg i.v. provided as an intermittent i.v. injection of 2 mg every 2 months or 3 mg every 3 months would provide a BMD increase over 12 months of at least the same magnitude as the approved oral daily dose regimen.

The application also contains data from several smaller randomised studies and several open label studies in which intermittent i.v. ibandronate was used for the treatment of osteoporosis. Also, a single small study, MF4488, investigating the efficacy and safety of i.v. ibandronate in the prevention of osteoporosis was submitted. However, the sponsor does not intend to pursue a prevention claim for the i.v. product.

- **Dose finding**

The dose selection was based on theoretical considerations from comparisons across studies. In study MF4470 it was demonstrated that 2 mg every 3 months i.v. administered for 12 months, was associated with a BMD improvement superior to that observed using 1 mg every 3 months i.v. regimen tested in the fracture study MF4380.
Exploring the absolute BMD differences to placebo and baseline, respectively, as a function of dose, from a variety of studies, the absolute BMD differences to placebo were quite consistent across studies, and the data suggested a log-linear dose response curve in the studied dose range. However, as the 2 mg every 3 months result in study MF4470 appeared to be higher than in other studies the absolute BMD changes from baseline were evaluated.
Extrapolation of the dose-response curve indicated that a moderate dose increase, to 3 mg every 3 months i.v., should be at least comparable to 2.5 mg daily oral regimen. Also, it was possible that the top of the dose-response curve could be reached with a 2 mg unit dose and a reduction of the dosing interval may be necessary. Therefore, the sponsor decided to also study a 2 mg every 2 months i.v. regimen as well as the 3 mg every 3 months i.v. regimen in study BM16550 compared to 2.5 mg daily oral regimen.
Based on the results of the pivotal study showing at least comparable clinical efficacy and safety of 2 mg every 2nd month and 3 mg every 3rd month, the applicant has chosen the later dosing regime based on patients satisfaction and convenience.

Main study

The study enrolled 1395 postmenopausal women (94% were Caucasian) between the age of 54 and 80 years who had osteoporosis as indicated by a lumbar spine (L2 – L4) BMD T-score of <-2.5. The mean baseline lumbar spine (L2 – L4) BMD values ranged from 0.745 to 0.747 g/cm^2, and the mean T-scores ranged from –3.254 to –3.269. The mean BMD values for the total hip at baseline were similar in all treatment groups (0.734 to 0.744 g/cm^2).

Patients were randomly allocated in a double-blind manner to one of three treatment groups: 2.5 mg ibandronic acid daily p.o. (n=470), 2 mg i.v. every 2 month (n=454), and 3 mg i.v. every 3 month (n=471). In addition, all patients received plain vitamin D 400 IU/d and elemental calcium 500 mg/d (except in Canada: 1000 mg/d) as a dietary supplement for the full duration of the study. Concomitant treatment with substances/drugs potentially affecting bone metabolism was balanced across the treatment groups (8%-10%); the most frequently received medications were steroids (3% to 4%) and sex hormones (2% to 4%).

To ensure blinding a double-dummy technique was used giving placebo p.o. and i.v. Stratification was performed in order to ensure that across all treatment groups, the distribution of baseline BMD was comparable. Due to the large number of centres (n=58) in this study, patients were also stratified by centre. There were three baseline BMD strata defined as follows: BMD of lumbar spine (L2 – L4) with baseline T-score < -2.5 and ≥ -3.0, BMD of lumbar spine (L2 – L4) with baseline T-score < -3.0 and ≥ -3.5 and BMD of lumbar spine (L2 – L4) with baseline T-score < -3.5 and ≥ -5.0.
42-44% of patients had osteoporotic fractures, predominantly peripheral fractures, at baseline.

Study BM16550 included women with a mean lumbar spine (L2 - L4) BMD T-score below -2.5 but not lower than -5.0, which differed from that in the fracture efficacy trial MF 4411 where patients with a lumbar spine BMD T-score between -2 and -5 at one vertebra were included. The BMD inclusion criteria used in study BM16550 are in agreement the WHO definition and with the current CPMP *Note for Guidance on Postmenopausal Osteoporosis in Women* (CPMP/EWP/552/95, rev 1). A significant risk reduction for new vertebral fractures with 2.5 mg ibandronate daily was demonstrated in patients with a BMD T-score $\leq$ -2.0 SD and in the subgroup of patients with a BMD T-score $\leq$ -2.5 SD in the pivotal fracture study MF4411, thus regarding the study population there is no relevant difference between study MF4411 and BM16550.

Bone mineral density measurements by dual-energy X-ray absorptiometry (DXA) were analyzed at a central reading site. CTX measurements were performed at a central laboratory. Both the investigators and the sponsor were blinded to the results of the BMD and CTX analyses during the study.

Results

Consistent with the 1-year results, the 2-year data demonstrated that the three-monthly treatment of women with postmenopausal osteoporosis with 3 mg ibandronic acid (3 mg q 3 months IV) was non-inferior and also increased BMD significantly relative to the approved oral daily dose regimen (Table 1).

Table 1: Mean Relative Change from Baseline in BMD at the Lumbar Spine and Proximal Femur After One and Two Years of Treatment (Per-protocol Population)

	BM 16550 Ibandronate Year 1			BM 16550 Ibandronate Year 2		
	2.5 mg/d n = 364-368	**2mg q 2mo n = 343-350**	**3mg q 3mo n = 357-359**	**2.5 mg/d n = 330-334**	**2mg q 2 mo n = 316-320**	**3mg q 3mo n = 333-334**
Lumbar spine BMD % increase from baseline	3.82%	5.09%*	4.82%*	4.84%	6.40%*	6.28%*
Total hip BMD % increase from baseline	1.79%	2.52%*	2.36%*	2.20%	3.37%*	3.13%*
Femoral neck BMD % increase from baseline	1.61%	1.97%	2.31%*	2.25%	2.74%	2.78%
Trochanter BMD % increase from baseline	2.97%	4.03%*	3.81%*	3.47%	5.04%*	4.92%*

- $p < 0.05$ vs. 2.5 mg daily

The primary efficacy analysis of this trial was the mean relative increase from baseline BMD in the lumbar spine after one year. Both IV ibandronate treatment groups, 2 mg every 2 months and 3 mg every 3 months, achieved a mean increase in lumbar spine BMD compared to daily treatment with oral ibandronate 2.5 mg, that was both non-inferior and superior, in the primary analysis population (per-protocol) as well as in the intent-to-treat analysis population.

During the second year of the study, mean relative increase from baseline in lumbar spine BMD increased further, and as seen after one year, the 2-year increase in the 3 mg every 3 months IV group, as well as in the 2mg every 2 months IV group, was shown to be non-inferior and superior ($p<0.001$) to that in the 2.5 mg daily group in both the per protocol and intent-to-treat populations. There was no statistical difference between the two IV dose regimens with regard to effects on lumbar spine BMD improvements at either the one or two year time points.

After two years of treatment, mean BMD in the total hip, femoral neck, and trochanter had increased further, and the increase from baseline in BMD at all proximal femur sites in both IV treatment groups after one and two years of treatment was greater than that seen in the 2.5 mg daily oral treatment group. For the total hip and trochanter, this increase in BMD for both IV treatment groups was shown to be superior to that in the 2.5 mg daily treatment group after one and two years of treatment, and for the 3mg q 3months IV group, it was shown to be superior after one year at the femoral neck.

The statistical method is appropriate regarding the sequential testing for non-inferiority and the 1% margin of the CI for the changes in BMD used for equivalence in the non-inferiority testing, i.e. the non-inferior margin has been chosen so that at least 70% of the treatment effect of the active comparator (vs. placebo) should be retained by the test-treatment. This seems to be a safe margin.

The proportion of patients who responded to treatment (defined as those with mean BMD increases ≥ baseline at the lumbar spine and/or proximal femur sites) and the proportion of patients whose lumbar spine BMD increased by ≥ 6% or total hip BMD increased by ≥ 3% from baseline were greater in both IV

treatment groups than in the 2.5 mg daily oral treatment group after one and two years of treatment (Table 2).

Table 2: BMD Responders (%) at the Lumbar Spine and Proximal Femur After One and Two Years of Treatment (Per-protocol Population)

	BM 16550 Ibandronate Year 1			BM 16550 Ibandronate Year 2		
	2.5 mg/d n = 364-368	**2mg q 2mo n = 343-350**	**3mg q 3mo n = 357-359**	**2.5 mg/d n = 330-334**	**2mg q 2mo n = 316-320**	**3mg q 3mo n = 333-334**
Lumbar spine BMD ≥ baseline	85.1	92.3*	91.6*	84.7	92.8*	92.8*
Total hip ≥ baseline	74.5	86.0*	82.6*	77.0	88.6*	85.6*
Lumbar spine and Total hip BMD ≥ baseline	66.9	80.5*	76.3*	68.8	83.1*	80.1*
Lumbar spine BMD ≥ 6% from baseline	25.8	38.3*	36.8*	37.7	53.1*	49.4*
Total hip ≥ 3% from baseline	32.7	41.4*	37.5	40.3	56.3*	49.8*

* $p < 0.05$ vs. 2.5 mg daily

Effect on bone markers. Following oral daily and IV dosing with ibandronate, there was a rapid and pronounced reduction in median serum CTX seen during the first 6 months of treatment, and values in all treatment groups had fallen by ≥ 50% from baseline. In all treatment groups, CTX values appeared to reach a steady state between 6 months and one year of treatment, and the reductions were maintained over the course of the 2-year study.

In the responder analysis, more than 50% of patients in all treatment groups had a trough serum CTX decrease from baseline of 50%, representing the least significant change, after one and two years of treatment, and 20% to 40% of patients had a trough serum CTX decrease from baseline of 70%, the threshold that is correlated to non-vertebral fracture risk reduction by Hochberg in his meta-analysis.

Samples for serum CTX measurements were collected from patients immediately prior to their IV dosing, i.e., at the end of the 3-month IV dosing interval for patients in the 3 mg IV treatment group, and at the end of the 2-month IV dosing interval for patients in the 2 mg IV treatment group. The values reported represent trough or residual levels of serum CTX measured at a single time point. Therefore, the inhibition of bone turnover is only partially reflected by the value of serum CTX at the end of the dosing interval in the two IV treatment groups.

Histomorphometry:

Although the bone histomorphometry analysis was requested for safety purposes, it additionally provided evidence of a reduction in remodeling in all three ibandronate treatment regimens. Activation frequency, the probability that a new remodeling cycle will be initiated at any point on the trabecular bone surface, is the most important histomorphometric variable demonstrating the effect of bisphosphonates on remodeling. All bisphosphonates reduce activation frequency, and ibandronate is no exception, with all treatment values being within the reference database of healthy premenopausal women.

Clinical safety

The clinical safety of ibandronate i.v. is mainly based on the pivotal study BM16550 and includes the analysis of the full two year study period. After one and two years of treatment, 1382 (approximately 99%) patients were included in the safety analysis, and 1358 (approximately 97%) patients in the intent-to-treat analysis of efficacy. The distribution of patients between the treatment groups differed by one patient [N = 458 (1-year) vs. N = 457 (2-year) in the 2.5 mg group and N = 458 (1-year) vs. N = 459 (2-year) in the 3 mg q 3 months IV group]. This difference was due to a randomization number correction on the database during the course of the second year.

The safety population of the year 1 analysis includes 465 patients in the 2.5 mg/d p.o. group, 448 patients in the 2 mg/2 months i.v. group and 469 patients in the 3 mg/3 months i.v. group.

Exposure
The median duration of treatment over the two years of the study was similar in all four groups and ranged from 23.98 to 24.05 months.

Adverse events

The two-year cumulative results of study BM16550 are described in the clinical study report. The 2-year data confirm that the proposed IV ibandronate dose regimen (3mg every 3 months) is an effective treatment with a positive benefit/ risk profile in the treatment of postmenopausal osteoporosis.

Table 3 below, provides a brief overview of the proportion of patients in each dose group reporting adverse events, serious adverse events, including those with a fatal outcome, the proportion of patients that died and the proportion of patients that withdrew from treatment because of adverse events. Over the two years of the study, the overall percentage of patients with adverse events (AEs) was comparable across the treatment groups, and so was the nature of the AEs, and there were no differences of note with regard to deaths, serious adverse events, or early withdrawals for adverse events. In general, musculoskeletal AEs were reported more often by the patients receiving ibandronate intravenously, and they were more likely to be considered drug-related.

Table 3: Overview of the 2-year safety in BM 16550 (safety population)

Patients: n (%)	**2.5 mg/d n = 465**	**2 mg/2 months n = 448**	**3 mg/3 months n = 469**
Any Adverse Event (AE)	408 (87.7)	397 (88.6)	400 (85.3)
Any Drug-Related AE	171 (36.8)	208 (46.4)	197 (42.0)
Any Serious AE (SAE)	67 (14.4)	73 (16.3)	62 (13.2)
Any Drug-Related SAE	4 (0.9)	5 (1.1)	2 (0.4)
Any AE leading to Withdrawal (WD)	49 (10.5)	44 (9.8)	55 (11.7)
Any Drug-Related AE leading to WD	28 (6.0)	29 (6.5)	36 (7.7)
Any Drug-Related SAE leading to WD	2 (0.4)	3 (0.7)	-
Deaths (all unrelated)	3 (0.6)	3 (0.7)	2 (0.4)

Renal toxicity had been described with intra-venous bisphosphonates. The good renal safety profile established during the first year of the study continued into the second year. Over the entire two year treatment period, the proportion of patients with adverse events attributable to the renal and urinary disorders was similar in all three treatment groups (18 patients [3.9%] in the 2.5 mg daily oral dose, 20 patients [4.5%] in the 2 mg q 2 months IV group, and 15 patients [3.2%] in the 3 mg q 3 months IV group).

Renal function was additionally evaluated by assessment of change from baseline in serum creatinine and creatinine clearance estimations. There were no differences among the groups with respect to mean or median change from baseline serum creatinine. In the few patients that displayed such changes, other confounding factors were present, and in most cases there was a more probable cause for the creatinine elevations observed. Importantly, the frequency of such changes within the population studied is comparable to the incidence (0.8%) noted in the placebo treated patients included in the previous fracture trials (Table 4).

(a) Baseline <1.4mg/dL And Increased By >=0.5mg/dL	15 (0.8%)	12 (0.8%)	6 (1.3%)	3 (0.6%)
(b) Baseline >=1.4mg/dL And Increased By >=1.0mg/dL	0	0	0	0
(c) Increased 2 X Baseline	1 (0.1%)	5 (0.3%)	2 (0.4%)	0
Total Pts in (a), (b) or (c)	15 (0.8%)	12 (0.8%)	6 (1.3%)	3 (0.6%)

	MF4411/MF 4380 Placebo N=1924	BM 16550/MF 4411 Ibandronate 2.5mg daily N=1442	BM 16550 Ibandronate 2mg q 2 mo IV N=448	BM 16550 Ibandronate 3mg q 3 mo IV N=469
(a) Baseline <1.4mg/dL And Increased By >=0.5mg/dL	15 (0.8%)	12 (0.8%)	6 (1.3%)	3 (0.6%)
(b) Baseline >=1.4mg/dL And Increased By >=1.0mg/dL	0	0	0	0
(c) Increased 2 X Baseline	1 (0.1%)	5 (0.3%)	2 (0.4%)	0
Total Pts in (a), (b) or (c)	15 (0.8%)	12 (0.8%)	6 (1.3%)	3 (0.6%)

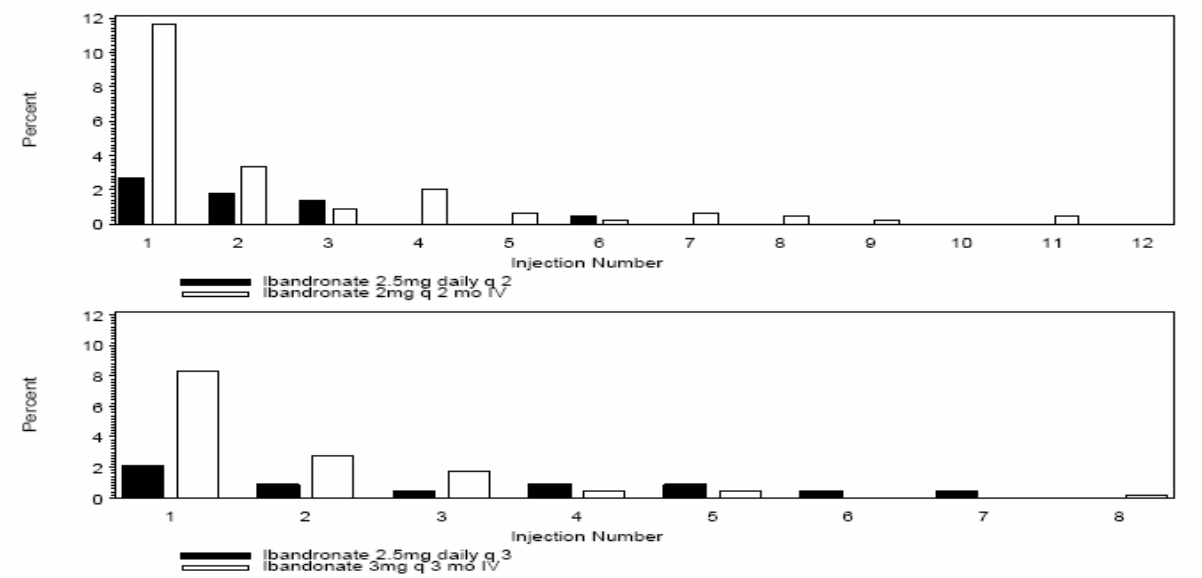
To further investigate the potential for changes in renal function over time, creatinine clearance values were estimated at each time-point for which a serum creatinine value was measured, using the Cockcroft-Gault equation. The incidence of patients with any decrease in creatinine clearance category during the 2-year study was 94 of 453 patients (21%) in the 2.5 mg oral daily group, 90 of 434 patients (21%) in the 2 mg q 2 months IV group, and 104 of 456 patients (23%) in the 3 mg q 3 months IV group, again showing no difference among the groups. Further, the estimated annual rate of decline of creatinine clearance in patients in each dose group is consistent with age related decline (~1ml/min per year). Once again, the frequency of such declines and category shifts are similar to the incidence in the placebo treatment patients included in previous fracture studies.

Therefore, it is concluded that treatment with ibandronate doses of 2.5 mg orally daily, or ibandronate doses of 12 mg annually administered as 2 mg every 2 months IV, or 3 mg every 3 months IV, did not have any detrimental effect on renal function.

The applicant has proposed a SPC text that contains appropriate precautionary statements concerning the use of ibandronate in patients with confounding conditions or who are taking other medications with potential for adverse effects on renal function. This advice should ensure that the good renal safety profile noted in study BM16550 is maintained in clinical practice.

As anticipated, acute phase reaction (APR)-like events were reported following the use of IV ibandronate. These events were most frequently observed following the first injection, and the percentage of patients reporting such events decreased with each subsequent injection. Over the two years of the study, the overall incidence of patients with APR-like symptoms remains higher in the groups that received active drug IV (15.6% in 2 mg q 2 months IV group and 10% in 3 mg q 3 months IV group) than in the 2.5 mg oral daily treatment group that received placebo IV (4.3%). These events were also more likely to lead to early withdrawal from IV treatment during the study. However, the events themselves are not medically serious, are readily manageable with the use of simple antipyretic/analgesic medications, and provided that patients are appropriately informed of possible reactions and given instructions on effective management, these should not detract from the effective use of the product in practice.
Most of these AEs were observed following the first i.v. injection and decreased with each subsequent injection [Fig. 1]. It was stated that in all treatment groups, the majority of the events were mild to moderate in intensity.

Fig. 1: BM16550 - Proportion of Patients Reporting Symptoms Starting ≤ 3 Days Following IV injection and Lasting ≤ 7 Days (Safety Population)



Relative to the one-year study report, 10 new patient reports of APR-like symptoms appear in the two year analysis (two patients in the 2.5 mg daily treatment group, six patients in the 2 mg/2 months i.v. treatment group, and two patients in the 3 mg/3 months i.v. treatment group). Of these 10 patients only seven represented new cases recorded during the second year of the study. Three of the 10 patients, all in the 2 mg/2 months i.v. group, had reported events during the first year of trial treatment.

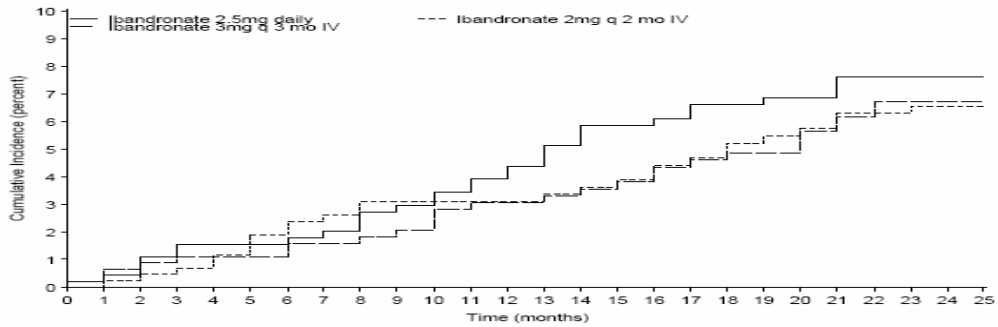
SPC and a PIL text has been proposed which contains appropriate information on the frequency and severity of the events observed and appropriate information on self-management of these conditions.

Overall, the incidence of injection site reactions was low in the three treatment groups. Injection site reactions, injection site pain, and injection site haemorrhage occurred in < 1% of patients in each treatment group. In the oral treatment group (placebo injections) these events were related to the administration technique. Injection site inflammation, swelling, or phlebitis was reported in < 1% of patients receiving IV ibandronate 2 mg every 2 months or 3 mg every 3 months.

Fractures

The incidence of clinical fractures over the two year treatment period was slightly lower in both of the IV treatment groups during both years of observation (Year 1: 2.8% to 2.9%; Year 2. 5.8% in both IV groups) compared to the 2.5 mg oral daily group (Year 1: 3.7%; Year 2: 6.9%). An analysis of the time to first occurrence of a fracture showed that after two years of trial treatment, the incidence of clinical fractures was slightly lower in both of the i.v. treatment groups (Year 2: 5.8% in both i.v. groups) compared to 6.9% in the 2.5 mg oral daily group), [Fig. 2].

Fig. 2: BM16550 - Time to First Incidence of Any Fracture (Safety Population – Year 2 Analysis)



These data support the view that the IV dose regimen will be at least as effective as the 2.5 mg daily oral dose in reducing the risk of osteoporotic fractures in postmenopausal women.

Serious adverse events
Among the 202 patients with serious adverse events, only 11 patients (<1%) had an event assessed as remotely, possibly, or probably related to treatment.
All cases of death (n=8) were judged as not treatment related. 1 patient died after study completion.
The incidence of serious AEs or drug related serious AEs were comparable between treatment groups.

Selected adverse events of special interest:

Gastrointestinal system
The most frequent possibly or probably treatment related gastrointestinal adverse events reported were abdominal pain, dyspepsia, nausea, constipation, gastritis, and diarrhea. There was a slightly lower incidence of abdominal pain, dyspepsia, and nausea in the 3 mg/3 months i.v. group compared to the 2.5 mg daily and 2 mg/2 months i.v. groups. All other frequent and possibly or probably related gastrointestinal adverse events were reported by similar percentages of patients in all treatment groups (except gastrooesophageal reflux in the 2 mg/2 months group).

Osteoarthritis/Osteonecrosis
The incidence of osteoarthritis at 2 years was 4.5 % (21/465 patients) in the oral daily treatment group, 6% (27/448 patients) in the 2 mg/2 months i.v. treatment group and 6.4% (30/469 patients) in the 3 mg/3months i.v. treatment group. The cases of osteoarthritis were apparently not classified as treatment related.
No case of osteonecrosis has been reported in women with postmenopausal osteoporosis treated with ibandronate.

Bone Biopsy Substudy
Single transiliac bone biopsies were performed in approximately 96 evaluable patients from selected centers at month 22 (3-month injection schedule) or at month 23 (2-month injection schedule). Qualitative and quantitative histomorphometric analyses were performed by a central histomorphometry evaluation. Prior to the bone biopsy, eligible patients received a bone-seeking fluorochrome (tetracycline) for bone labeling according to the schedule of the bone biopsy substudy.

A total of 109 biopsy cores were collected of which 89 were evaluable. There were 32 evaluable biopsies in the ibandronate 2.5 mg daily group, 27 in the ibandronate 2 mg/2 months i.v. group, and 30 in the ibandronate 3 mg/3 months i.v. group. Twenty biopsy specimens were not evaluable due to an inadequate biopsy sample.

The effects on the reduction in remodeling with normal quality of newly formed bone and the absence of defects in mineralization were similar in all three ibandronate treatment groups indicating that i.v. treatment does not have deleterious effects on bone quality, but causes the expected changes seen with bisphosphonates.

Overall conclusions and benefit/risk assessment

In February 2004, the European Commission provided approval of a 2.5 mg daily oral tablet formulation of ibandronate for the prevention and treatment of postmenopausal osteoporosis. This approval was based on the results of a pivotal Phase 3 study in which a reduction in the risk of new morphometric vertebral fractures and progressive increases in bone mineral density (BMD) in lumbar spine and in the hip in patients with postmenopausal osteoporosis was demonstrated. The present application is based on these results combined with the results from one single well-designed 2-year study comparing ibandronate 2.5 mg oral once daily with either intravenous injection of 2 mg every 2nd month or 3 mg every 3rd month. Dose-selection for this study is based on PK/PD-modelling of data from previously performed studies with intravenous ibandronate using biochemical markers of bone turnover and BMD as primary PD parameters.

The pivotal phase III study included in this MAA unequivocally demonstrates non-inferiority (and in many endpoints also statistical significant superiority) of either 2 mg or 3 mg intravenously every 2nd or 3rd month respectively in BMD and additional other secondary endpoints as compared to 2.5 mg oral once daily. With regard to overall safety this was found to be comparable for both intravenous regimes and the

2.5 mg once daily oral administration. In general the risk:benefit ratio for both intravenous dosing regimes are considered positive. However, since the ibandronate 3 mg every 3 months IV regimen delivers efficacy that is comparable to the 2 mg every 2 months IV ibandronate regimen, is not associated with an increase in adverse events, and offers the additional benefit of patient convenience as a result of fewer patient office visits, ibandronate 3 mg every 3 months IV is recommended for the treatment of postmenopausal women with osteoporosis.

Quality

This is a simple i.v. formulation of a very stable, soluble, well characterised and documented substance and common excipients in a pre-filled syringe. The packaging material is also well documented. The manufacturing process of the finished product is a well-validated process and stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

Efficacy

The results demonstrate that both the 2 mg every 2 months and the 3 mg every 3 months IV ibandronate dose regimens were both non-inferior and significantly increased BMD relative to the approved oral daily dose regimen. In all ibandronate treatment groups, the mean relative increase in BMD at the lumbar spine and proximal femur was greater after 2 years of treatment than after the first year. Differences between the two IV regimens in BMD change were marginal and not clinically relevant. In both Year 1 and Year 2 of this study, serum CTX levels observed post treatment were well within the pre-menopausal range in the vast majority of patients in all three treatment groups.

Since the ibandronate 3 mg every 3 months IV regimen delivers efficacy that is comparable to the 2 mg every 2 months IV ibandronate regimen, is not associated with an increase in overall adverse events, and offers the additional benefit of patient convenience as a result of fewer patient office visits, ibandronate 3 mg every 3 months IV is recommended for the treatment of postmenopausal women with osteoporosis.

Safety

The results of this study demonstrated that both IV treatment regimens were well tolerated. Over the course of the two years of follow up, study completion rates were similar (>85%) in all treatment groups. Although the early drop out rate is higher in patients receiving IV ibandronate, the related events leading to withdrawal were generally minor adverse reactions that can be effectively managed by the patient in practice. In general the safety profile in terms of AEs, SAes and drug related AEs were comparable between the IV and the daily groups.

However regarding musculoskeletal events and acute phase reactions higher proportions were observed with the IV regimens compared to the oral strategy. These events were apparently not serious in nature and were manageable and are thus, as the SPC contains adequate information addressing these topics, considered acceptable.

The incidences of possibly/probably treatment related AE such as arthralgia, bone pain, headache and gastroesophageal reflux were slightly higher in the 2mg/2months i.v. treatment group than in the 3 mg/3months i.v. group. A significant difference was only reported for bone pain. The incidence of APR-like events (remotely/possibly/probably) was also higher in the 2 mg/2 months treatment group.

The IV treatment was not associated with any changes in renal function after 2 years. The mean and median values for changes in creatinine clearance per year were -0.9 ml/min in the 3 mg/3 months treatment group (2. 5 mg/d: -1.59 ml/min; 2 mg/2 mo: -1.6 ml/min) which corresponds to the natural decrease seen with age (approximately 1 ml/min per annum).

Histomorphometric analysis of transiliac bone biopsies showed normal quality of newly formed bone, and no mineralization defects after oral or i.v. treatment with ibandronate.

The incidence of injection site reactions was low (<1%) and included injection site pain, swelling, inflammation, oedema, hemorrhage.

Overall the 2-year safety profile is considered comparable to the 1-year data and the benefit risk ratio is considered positive

Benefit/risk assessment

Based on these results the benefit/risk-ratio for use of ibandronate 3mg/3ml solution for injection once every 3 months in the treatment of postmenopausal osteoporosis is considered to be positive. The proposed indication:

"Treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established."

is in accordance with the data provided and therefore acceptable.